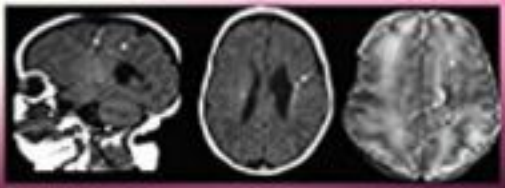
FIFTH EDITION



FETAL and NEONATAL BRAIN INJURY

EDITED BY
DAVID K. STEVENSON
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CAMBRIDGE Medicine

Fetal and Neonatal Brain Injury

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Preface

The fifth edition of this textbook incorporates all the newest information for the topics covered. The organization of the text remains fundamentally the same. We have assembled the same editors for this edition but have included many new authors so that the topics are addressed by the most up-to-date experts, in particular, individuals with not only detailed knowledge of research related to the relevant content but also a sense of clinical experience. The intent of the text remains to ensure that anyone who is responsible for providing care to fetuses and neonates at risk for brain injury have a complete compendium of knowledge content presented from a practical perspective. The content has relevance to providing the best possible care for expectant mothers and newborn infants in order to maximize potential for recovery and best possible outcome. We end the book with an updated chapter on the medicolegal issues in perinatal brain injury. This topic is one that has been included from the first edition, and it provides a valuable guide to understanding how the legal profession becomes engaged with physicians around perinatal brain injury.

We have tried to avoid overlap among the chapters, but where it might exist, the different perspectives of the authors serve to complement each other, providing emphasis on the most important points in the various topical areas. This allows once again for the integrity of the individual authors' presentations and styles and reflects their intent to communicate their many years of clinical experience as it relates to their expertise. We encouraged the authors to express their opinions and share their experiences, and sometimes variations become apparent. Nonetheless, the individual insights are informative and characterize the uncertainties that exist in our field related to perinatal brain injury. We would like to thank our contributing authors for their outstanding efforts to provide some of the best chapters in print on the selected topics, as well as the staff of Cambridge University Press for their support and expertise in preparing the text. We would like to thank, in particular, Ana Laborde for her editorial assistance and her gracious and professional engagement with contributing authors.

We would like to acknowledge the Christopher Hess Research Fund, the Charles and Ann Johnson Endowed Fund, and the L. H. M. Lui Research Fund, which provided financial assistance for the production of this textbook, including securing permissions for valuable figures, tables, and excerpts from previously published sources.

Finally, we would like to thank our spouses, Joan Stevenson, Andrea Benitz, Sara Sunshine, Elizabeth Hoffman, and Henry Rosack, for their support, encouragement, and continued patience with a cadre of aging (except for one of us) academic physicians dedicated to maternal, fetal, and neonatal health and well-being.

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Chapter 1

Neonatal Encephalopathy
Epidemiology and Overview

Matthew B. Wallenstein and Philip Sunshine

Introduction

Since publication of the first edition of this text in 1989, a great deal has been written regarding the issues of neonatal asphyxia and hypoxic-ischemic encephalopathy (HIE) in term and near-term infants. These papers have addressed the incidence, etiology, pathophysiology, treatment, and outcome, often relating outcomes to the development of cerebral palsy (CP) and/or intellectual disability in survivors [1–29]. Much of the understanding of the pathophysiology has been the result of studies carried out in laboratory animals, which have been extrapolated to the human fetus and newborn. Additional studies of complications and outcome have been population based, comparing the injured infant with carefully selected normal control individuals. These studies have added a great deal to our understanding of risk factors for brain injury and have enhanced our ability to predict and identify brain injury with increasing accuracy. This precision has become increasingly important as newer modalities of treatment have evolved that require even more precision in the early identification of these infants so that the validity of these therapies can be ascertained. Since publication of the latest edition of this text, there have also been numerous randomized trials and meta-analyses on the use of therapeutic hypothermia as treatment for neonatal encephalopathy [30–39]. As can be seen in Chapters 39, 41, and 42, early institution of treatment becomes of paramount importance if an improved outcome is to be achieved. However, neonatal encephalopathy continues to be a major cause of morbidity and mortality globally despite these new efforts to reduce its impact.

While some still believe that the major injuries in these children occur in the intrapartum period, many studies suggest otherwise and allude to the fact that many of the problems arise antenatally and may be exacerbated in the intrapartum period. Clearly, several important publications have defined specific criteria that must be present in order to establish that intrapartum events are the primary causes of the infant's difficulties, but not everyone agrees that such rigorous definitions are valid in each and every case [7,10].

Unfortunately, the terms *birth asphyxia* and *hypoxic-ischemic encephalopathy* (HIE) have been and continue to be used interchangeably to characterize the depressed infant [40]. Stanley et al. noted that "[b]irth asphyxia is a theoretical concept, and its existence in an infant is not easy to recognize accurately by clinical observation" [1]. Similarly, the description HIE may inappropriately indicate that the cause of the condition is clearly identified. Most practitioners now refer to such infants as having *neonatal encephalopathy*, a term used by Nelson and Leviton to describe "a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty in initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures" [2].

This terminology has been adopted by the International Cerebral Palsy Task Force [7] as well as by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) in their text entitled, *Neonatal Encephalopathy and Neurologic Outcome* [10].

Neonatal encephalopathy is a purely clinical description that avoids identification of the etiology or pathogenesis of the infant's condition. Unfortunately, neonatal encephalopathy does not exist as a distinct diagnostic category in the *International Classification of Diseases*, x9th Revision (ICD-9). Nevertheless, it is crucial that the caretakers of the injured infant have a more rigorous understanding of the factors that could possibly contribute to the infant's condition and that they are not unduly influenced by circumstantial evidence. As a result, some authors argue that the term *HIE* should be reserved for cases where hypoxia is the definite cause

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of encephalopathy or that the term *presumed HIE* should be used when in doubt [41–42]. Many of the events leading to the infant's presentation at birth occur long before the onset of labor. With the use of sophisticated imaging, more and more infants are being recognized as having abnormalities that have already led to significant damage prior to the intrapartum period. In addition, careful examination of the placenta has been of great value in identifying lesions that are associated with infections or other anomalies that have or can lead to fetal injury (see Chapter 20) [43–46]. Unfortunately, the incidence of completed placental examination for infants with encephalopathy is quite low [47].

We recognize that these infants are often unable to tolerate the stress of labor, may have fetal heart rate abnormalities either prior to delivery or during the early stages of labor, or have abnormal contraction stress tests or nonstress testing. These infants are often difficult to resuscitate and show neurologic features that seem excessive considering the problems that occurred during labor or the birthing process. In addition, some infants who present with neonatal encephalopathy may have suffered a significant intrauterine catastrophe, recover, and may even be able to tolerate labor well enough not to have abnormalities noted on their fetal heart rate tracings [23].

We also recognize that events leading to difficulties in the prematurely born infant may be different from those in infants born near or at term. In attempts to evaluate etiology, pathogenesis, intervention, and management, one must be aware that similar events may have different consequences depending on the infant's capacity to respond to various insults, and some of these are determined by gestational age. In addition, infants with intrauterine growth restriction (IUGR) make up a disproportionate share of infants with neonatal brain injury, suggesting that the underlying cause or causes of the growth restriction may have began in utero and continued through the intrapartum and postpartum periods.

Asphyxia

Asphyxia is defined as progressive hypoxemia and hypercapnia accompanied by the progressive development of metabolic acidosis. The definition has both clinical and biochemical components and indicates that unless the process is reversed, it will lead to cellular damage and ultimately to the death of the infant. We currently do not have the ability to routinely measure fetal cerebral activity or the neurocellular response to unfavorable conditions such as hypoxia, ischemia, or acidosis, the compensatory mechanisms that protect the brain cells, or, when such mechanisms are inadequate, the documentation of cell injury and cellular death.

Table 1.1 Acute Causes of Fetal Brain Injury (Sentinel Events)

Prolapsed umbilical cord
Uterine rupture
Abruptio placentae
Amniotic fluid embolism
Acute neonatal hemorrhage Vasa previa Acute blood loss from cord Fetal-maternal hemorrhage
Acute maternal hemorrhage
Any condition causing an abrupt decrease in maternal cardiac output and/or blood flow to the fetus

In lieu of direct measures of fetal distress, we have used indirect measurements that have been based on studies carried out in laboratory animals and extrapolated to the human fetus. In a few instances, direct measurements have been possible, but they have not been convincingly linked to outcome. Indirect assessments include the biophysical profile, electronic fetal heart rate monitoring, evidence of severe metabolic acidosis, depressed Apgar scores, abnormal newborn neurologic examination, and development of seizures. As mentioned earlier, the timing of the events is often unknown and difficult to ascertain as far as onset, duration, and severity are concerned. Based on studies in monkeys by Myers [48], and also substantiated to a great extent in fetal lambs by a group in New Zealand [49], two major types of intrauterine asphyxial conditions have been recognized. These include acute total asphyxial events and prolonged partial asphyxia.

The causes of the acute total events are listed in Table 1.1 and have been referred to as "sentinel events" by MacLennan and the International Cerebral Palsy Task Force [7]. In the acute type of asphyxia, there is a catastrophic event: the fetus is suddenly and rapidly deprived of his or her lifeline and usually does not have the opportunity to protect the brain by "invoking the diving reflex."

The conditions most commonly encountered include prolapse of the umbilical cord, placental abruption, fetal hemorrhage, and uterine rupture.

For a period of time there was an increase in the use of vaginal birth after cesarean section (VBAC), but recently, because of the risk of uterine rupture, there has been a decrease in VBAC, with many physicians and hospitals reluctant to provide such care (see Chapter 12).

Infants with acute asphyxia have damage to the deep gray matter of the brain involving the thalamus, basal ganglia, and brainstem, often with sparing of the cerebral cortex [50]. If successfully resuscitated, these infants may not have evidence of multisystem or multiorgan dysfunction. Laboratory animals develop evidence of neurologic damage as early as 8 minutes after the acute asphyxial event. Major irreversible lesions were found after 10–11 minutes, and the animals usually succumbed if not resuscitated within 18 minutes. After 20 minutes of asphyxia, some animals could be resuscitated, but they usually died of cardiogenic shock within 24–48 hours, even with intensive care [48].

Although data in humans are lacking, studies of infants following prolapsed cords or uterine rupture suggest similar time frames, and infants who have occult prolapse often have a better outcome than those with overt prolapse. However, animals used in laboratory studies are often healthy prior to asphyxia, which makes extrapolation to human fetuses difficult. A study from the Los Angeles County University of Southern California (LAC/USC) Medical Center noted that if it required greater than 18 minutes to deliver the fetus after spontaneous rupture of the uterus, neurologic sequelae would ensue [51]. Unfortunately, the long-term follow-up of the surviving infants in this study is not available. Thus the 30-minute timing of "decision to incision," as recommended by ACOG, may not fully mitigate neurologic compromise. The infants who have suffered this type of acute asphyxia will have varying degrees of neurologic injury, often manifesting extrapyramidal types of CP and varying degrees of intellectual disability depending on the severity and extent of the injury.

The second group of infants consists of those who have been subjected to prolonged partial asphyxial episodes and have involvement of the cerebral cortex in a watershed type of distribution. They often have multiorgan involvement and have pyramidal signs of CP. The incidence and severity of cognitive impairment also depend on the extent and severity of the lesion.

An acute event may also occur in a fetus that has already been subjected to a partial prolonged asphyxial condition or a preexisting neurologic insult. Such a fetus may demonstrate complications of both processes and have both pyramidal and extrapyramidal neurologic findings associated with varying degrees of auditory, visual, and/or cognitive abnormalities.

Incidence of Neonatal Encephalopathy

In 2010, an estimated 1.15 million infants developed neonatal encephalopathy worldwide compared with 1.6 million in 1990. The vast majority of these infants did not have access to skilled birthing care and were born in developing countries, where intrapartum stillbirth and neonatal mortality rates are 20 to 50 times higher than those in developed countries [52].

In industrialized nations, the incidence of neonatal encephalopathy is much lower and has continued to fall over the past three decades. Depending on the criteria used to document the incidence as well as the severity of the encephalopathy, the incidence varies from 1 to 9/1,000 live births [53–56]. Using the Sarnat score or modifications of that score, infants are classified as having mild, moderate, or severe encephalopathy [57] (see Chapter 16). In the United Kingdom [3], France [18], and Australia [19], similar declines have been noted not only in the incidence of severe encephalopathy but also in the mortality rate of infants so affected.

In Sweden, where an Apgar score of less than 7 at 5 minutes was used to identify babies with encephalopathy, the incidence increased from 5.7/1,000 live births to 8.2/1,000 over a 7-year period. Use of the Apgar score in such a fashion would identify a large group of infants who would be excluded using more stringent criteria for encephalopathy. The incidence of severe depression varied between 1.4 and 2.6/1,000 live births. However, the incidence of stillborn infants had decreased significantly [26].

Wu et al. evaluated data from the state of California from 1991 to 2000 and included 5,364,663 live-born infants and found that the incidence of neonatal asphyxia fell from 14.8 to 1.3/1,000 live births, a 91% decrease, during the study years [58]. Data from the 1996 annual summary of vital statistics also demonstrated that the infant mortality rate due to asphyxia fell 72% between 1979 and 1996 [59], and in more recent surveys, the mortality rates were 0.13/1000 in 2001 and 0.15/1000 in 2003. A recent study from Japan found the lowest incidence of HIE, which was 0.37/1,000 term infants [60].

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Table 1.2 Factors Associated with Decreased Incidence and Mortality Due to Neonatal Encephalopathy in Term and Near-Term Infants

More stringent awareness and documentation of the appropriate diagnosis of neonatal encephalopathy
Early prenatal care and recognition of mothers who are at high risk of delivering an infant with neonatal encephalopathy
Pregnancy termination when severe congenital malformations are detected
Early recognition of infants with growth restriction as well as macrosomic infants and avoidance of intrapartum complications
Improved education and training of personnel who are responsible for resuscitation and stabilization of the depressed neonate
Appropriate treatment of mothers who are carriers of group B streptococci
More liberal use of cesarean section for infants in the breech position
Improved recognition and treatment of mothers with chorioamnionitis
More appropriate induction and use of obstetrical anesthesia
Ready access to neonatal intensive care
Avoiding post-term deliveries

The reasons for the decrease in neonatal encephalopathy are not clear, but several factors have been proposed (Table 1.2). Perhaps one of the most important reasons is close adherence to a more specific diagnosis of encephalopathy. Other factors playing a significant role include early prenatal care and recognition of women with high-risk pregnancies, increased recognition and appropriate treatment of mothers who are carriers of group B *Streptococcus* early dating of pregnancy, and avoiding post-term deliveries as well as recognizing the fetus that is over- or undergrown. There has also been early termination of pregnancy where infants with significant congenital malformation are detected. Lastly, education programs have been developed to ensure that depressed infants are given appropriate resuscitation and stabilization and ready access to intensive care [58] (see Chapters 39 and 40).

Risk Factors Associated with Neonatal Encephalopathy

There are few studies that have addressed risk factors associated with neonatal encephalopathy.

Table 1.3 Risk Factors prior to Conception

Socioeconomic factors
Increased maternal age
Unemployment
Women without health insurance
Medical conditions
Family history of recurrent nonfebrile seizures
Family history of other neurologic disorders
Infertility treatment
Poorly controlled chronic illnesses

Two case-control studies from Western Australia found a predominance of antepartum, as opposed to intrapartum, risk factors that were associated with neonatal encephalopathy [5,19]. The infants were born at or near term and had moderate to severe neonatal encephalopathy as defined by strict criteria. The criteria included seizures alone or associated with abnormal consciousness, difficulty in maintaining respiration, difficulty in feeding, and abnormal tone and/or reflexes. Several recent studies have confirmed the predominance of antepartum risk factors [61,62], although other studies found that most cases of neonatal encephalopathy were characterized by a combination of both antepartum and intrapartum factors [63,64]. Undoubtedly in clinical practice it can be difficult to distinguish intrapartum from antepartum risk factors, and there often is a great deal of overlap. On review of the literature, the timing of neonatal insult continues to be an important question with therapeutic implications, and it remains the subject of ongoing studies.

Risk Factors prior to Conception

Table 1.3 lists risk factors prior to conception and includes poor socioeconomic status and advanced maternal age. The findings of a family history of seizures and/or neurologic disorders are similar to those previously described by Nelson and Ellenberg [65]. The increased incidence associated with in vitro fertilization is discussed in Chapter 6.

Risk Factors in the Antepartum Period

Risk factors in the antepartum period are delineated in Table 1.4 and include maternal and fetal characteristics. Mothers with thyroid disease were nine times more likely to have infants with neonatal

Table 1.4 Risk Factors in the Antepartum Period

Maternal conditions
Thyroid disease
Severe preeclampsia
Moderate to severe vaginal bleeding
Viral infection requiring medical attention
Late or no prenatal care
Poorly controlled diabetes
Systemic lupus erythematosus (SLE)
Infant complications
Postdatism
Intrauterine growth restriction (IUGR)
Abnormal placenta
Congenital malformations

encephalopathy compared with mothers who were euthyroid. This association has also been noted in infants with CP born to mothers with various types of thyroid diseases. Similarly, severe preeclampsia, moderate to severe vaginal bleeding, and severe viral illness were other prepartum risk factors. Growth restriction and postdates pregnancies were at increased risk as well. The impact and relative importance of each specific risk factor vary greatly among studies.

The Australian study deliberately excluded infants with birth defects and abnormal antepartum fetal heart rate tracings, but both of these findings would indicate an at-risk infant [5]. Congenital malformations involving systems other than the nervous system were found more frequently in infants with encephalopathy, suggesting that these are antepartum risk factors as well [66]. Women with chronic illnesses such as systemic lupus erythematosus (SLE) and diabetes have an increased risk of having neonates with encephalopathy.

Intrapartum Risk Factors

Intrapartum risk factors are often a continuum of the factors that placed the infant at risk in the antepartum period, such as growth restriction and preexisting congenital abnormalities. Additional factors include maternal fever, tight nuchal cord, persistent occiput posterior position, and developmental of persistent nonreassuring fetal heart rate pattern during the intrapartum period [5,6,63,64]. Prolapse of the umbilical cord, with an incidence of approximately 0.4% of pregnancies, is also associated with adverse neonatal outcomes [67]. Chorioamnionitis, a diagnosis made clinically because of maternal pyrexia, leukocytosis, and malodorous amniotic fluid, is associated with a marked increase in the incidence and severity of neonatal encephalopathy and CP [68]. In laboratory animals, the presence of various cytokines, especially interleukin 6 (IL-6), causes an increased sensitivity of the fetus to ischemia and hypoxia, as well as having a direct deleterious effect on the brain. Measurements of various cytokines in blood and cerebrospinal fluid (CSF) have been found to be significantly higher in infants with encephalopathy who were later found to have abnormal neurodevelopmental outcome [15,69,70]. More recent studies have also described a link between neuroinflammation, immunomodulation, and infection because they relate to adverse outcomes of infants with HIE [71–75]. The issue of chorioamnionitis is discussed in greater detail in Chapter 12.

Factors that are associated with sudden changes in fetal heart rate patterns leading to bradycardia that does not resolve readily have been described as sentinel events; these are listed in Table 1.1 and are highly correlative with neonatal encephalopathy.

Correlative Findings Associated with Neonatal Encephalopathy

Several findings have been correlated to some extent with the severity of encephalopathy occurring in the intrapartum period. These include a persistently low Apgar score, presence of meconium in the amniotic fluid, evidence of significant metabolic acidosis, the onset of seizures within the first 72 hours of life, the need for cardiopulmonary resuscitation, abnormal electroencephalography, evidence of multiorgan damage, corroborative findings on imaging studies, and corroborative laboratory findings.

Apgar Score

The Apgar score was designed to identify infants who were depressed at birth and who required resuscitative efforts [76]. The scoring system required an "advocate" to evaluate the infant and provide a numerical score of the infant's condition. Dr. Virginia Apgar did not design this scoring system to evaluate neurologic damage or outcome. However, a score of less than 7 at 5 minutes has been used in numerous studies to identify an infant who has suffered from intrapartum events. Unfortunately, there are many factors that influence the Apgar score, including immaturity, maternal anesthesia and/or analgesia, fetal and neonatal sepsis, and

neuromuscular abnormalities. As a result, using the Apgar score as an isolated finding is an inappropriate method for defining neonatal encephalopathy.

However, the persistence of a low Apgar score for greater than 5 minutes despite intensive and appropriate resuscitation has been associated with an increase in morbidity and mortality [27]. Perlman and Risser found that an Apgar score of 5 or less at 5 minutes in combination with significant fetal acidosis and the need for cardiopulmonary resuscitation increased the risk significantly (340-fold) for the infants to develop seizures, a marker of moderate to severe encephalopathy [4,13]. More recent studies have found that low 10-minute Apgar scores and the need for resuscitation at birth were correlated with adverse long-term neurodevelopmental outcomes [77,78]. However, other studies found that more than one-fourth of infants with an Apgar score of 0 at 10 minutes survived without neurodevelopmental impairement [79,80].

Meconium

The presence of meconium in the amniotic fluid has long been thought to indicate fetal stress. Meconium is found in 8–20% of all deliveries and is most often seen in the postterm baby [81]. If meconium is recognized in amniotic fluid of infants at 34 weeks' gestation or younger, significant intrauterine stress or intrauterine infection must be suspected. In term and post-term infants with meconium staining, the fetus and newborn are usually symptom free. However, heavy, thick meconium passed early in labor tends to have a more ominous significance than when it is passed more proximate to delivery. But even this finding has not been substantiated.

The presence of meconium per se in term infants is not predictive of neurologic outcome; in fact, Nelson and Ellenberg noted that fewer than 0.5% of infants weighing more than 2,500 g with meconium staining had neurologic sequelae [65]. In other studies, the presence of meconium-stained amniotic fluid had no predictive value in regard to outcome, the development of neurologic symptoms in the newborn period, or acidosis measured by the pH of cord blood. Even when the presence of meconium was ascertained and used in conjunction with Apgar scores and cord pH values, the finding did not alter the incidence of subsequent neurologic abnormalities (see Chapters 20 and 36). However, several other studies have found an increased risk of CP among infants with meconium-stained amniotic fluid [10], suggesting that the long-term predictive abilities of meconium may not be entirely clear.

Fetal Heart Rate Monitoring

Fetal heart rate monitoring was developed over 59 years ago, with the primary objective of decreasing the rates of neonatal encephalopathy and intrauterine fetal demise. While it has been successful in decreasing the rate of stillbirths, its use has not significantly decreased the incidence of neurologic sequelae. In one carefully controlled study comparing continuous electronic fetal heart rate monitoring with intermittent auscultation of the fetal heart rate, the incidence of seizures was reduced in the group that was continuously monitored. However, the long-term neurologic outcomes were the same in both groups, and most of the infants who developed CP did not have seizures in the newborn period [82]. A recent meta-analysis also found no effect on neurologic outcomes among 13 randomized trials of electronic fetal monitoring [83]. A more complete discussion of intrapartum monitoring is found in Chapter 15.

Fetal and Neonatal Blood Gas Evaluations

Since the mid-1960s, obstetricians have used fetal acid-base measurements as an adjunct to fetal heart rate monitoring to evaluate the well-being of fetuses. However, fetal scalp blood sampling during labor has been largely abandoned, and fetal heart rate monitoring has been used exclusively. The acid-base status of the fetus is determined immediately after delivery with arterial and venous blood gas evaluation of the umbilical cord. Initially, an arterial pH below 7.20 was considered to be abnormal, but few of these infants were found to have any neonatal or subsequent neurologic abnormalities. Correlative data identified infants with umbilical arterial pH less than 7.0 as being at risk, especially when associated with the need for resuscitation at birth. The vast majority of infants with low pH and no other findings have benign neonatal courses.

Chauhan et al. evaluated their own data as well as several large previously published studies totaling over 43,000 infants born at term who had umbilical arterial pH levels of 7.0 or less [84]. The prevalence of this low pH ranged from 0.2% to 1.6% of live births, with a mean of 0.6%. The incidence of neurologic

injury in these infants ranged from 4.3% to 30.9%, and the mortality rate ranged from 0% to 8%.

Low has noted that the threshold for significant metabolic acidosis was a base deficit between 12 and 16 mmol/L [17]. As the degree of acidosis increased, the number of neurologic abnormalities increased. In addition, the longer the acidosis persisted, the greater was the risk of neurologic defects.

The finding of a low pH in itself is of little consequence unless other abnormalities are found. Perlman reported on a total of 115 infants who were found to have an umbilical cord arterial pH of less that 7.0 [23]; 68 of the infants were cared for in the well-baby nursery and discharged home following an uneventful neonatal course. Over 80% of those who were admitted to the intensive care nursery also had benign courses.

Is there an arterial pH level that would predict an abnormal outcome in an infant who is depressed at birth? Goodwin et al. evaluated over 120 infants born at term with a cord pH of less than 7.0 [85]. Approximately 4% died, 8% had major neurologic abnormalities, 4% were suspected of having neurologic problems, 6% were lost to follow-up, and 78% were normal. The same investigators, in a follow-up study of these same infants, noted that if the arteriovenous difference in PCO_2 was greater than 25 mmHg, the infants had an increased incidence of seizures, encephalopathy, and cardiac, pulmonary, and renal dysfunction, as well as abnormal neurologic outcomes. The arteriovenous difference in PO_2 correlated to a much lesser extent [86].

Not all infants with neonatal encephalopathy will have abnormal umbilical arterial blood gases. Infants with normal gases behave as if the umbilical cord had been clamped at the onset of the asphyxial episode, with little or no blood flow between the placenta and the fetus. This would be most likely a result of cord prolapse, cord impingement, or an asystolic event. These infants are depressed, often pale, and poorly responsive. After appropriate resuscitation has been instituted and cardiopulmonary function restored, an arterial sample of the infant's blood will be found to be markedly acidemic.

Seizures

The onset of seizures within the first 2–3 days of life has been equated with the incidence and severity of neonatal encephalopathy, as well as with the quality of intrapartum care. The incidence of seizures varies from less than 1 to 3.5/1,000 live births and has decreased significantly over the past 20 years from an incidence as high as 14/1,000 live births. In a recent comprehensive study of 89 infants by Tekgul et al., the major etiologic factor was global encephalopathy, found in 40% of the children [87]. These investigators also felt that 60% of the seizures were the result of intrapartum factors, and only 25% were secondary to antepartum factors. Identification of seizures among encephalopathic infants, both clinical and subclinical, has improved with the use of amplitude-integrated electroencephalography (aEEG) in addition to video electroencephalography (vEEG). The use of aEEG may also play an important role in predicting death or disability among infants with HIE and may assist with discussions of goals of care and redirection of care [88].

The second most common cause of seizures was stroke, seen in 18% of these infants. Intracranial hemorrhage accounted for 17% of infants, with most due to extraparenchymal rather than intraparenchymal bleeding. Only 5% of the infants had developmental abnormalities, and 3% had meningitis or encephalitis. Metabolic disturbances such as hypoglycemia or hypocalcemia were encountered infrequently, although these could accompany a severe pre- or intrapartum episode as well [46].

Neonatal stroke is being encountered more frequently as the use of imaging techniques has increased. Stroke is found as frequently as 1/4000 live births and it may be associated with various types of genetic hypercoagulable states. This topic is discussed in Chapter 25.

The mortality rate associated with neonatal seizures has also fallen dramatically over the past 20 years and has been reported to be as low as 7%. Unfortunately, the prevalence of adverse long-term outcomes was 28%, with a 20% rate of seizure recurrence. With advances and improvements in perinatal care, the incidence and mortality rate associated with seizure have decreased significantly, but the long-term damage in survivors remains unchanged [89]. The seizures themselves may contribute to the already existing brain injury by impairing energy use and the integrity of the neurons. An aggressive approach to the treatment of neonatal seizures is warranted in order to mitigate further damage to an already compromised central nervous system (CNS) [90], although there continues to be controversy with regard to this aggressive approach [91] (see also Chapters 17 and 43).

Multiple Organ Dysfunction Associated with Neonatal Encephalopathy

The fetal response to an asphyxial episode is to preserve perfusion and oxygenation of the heart, brain, and adrenal gland at the expense of the other "nonvital" organs, such as the kidney, lungs, gastrointestinal tract, and musculoskeletal system. The incidence of single or multiple organ injury in association with neonatal encephalopathy has varied from 40% to almost 100% and seems to correlate with the severity of the CNS injury [7,23,25,92–94]. Most often the renal system is involved, and it is the easiest to evaluate. Findings range from mild oliguria (<1 mL/kg/h), proteinuria, and hematuria to renal tubular necrosis and acute renal failure.

Cardiac manifestations vary from minor arrhythmias, ST-segment changes on electrocardiogram (ECG), and tricuspid insufficiency to papillary muscle necrosis, poor ventricular contractions, and cardiogenic shock. Children with moderately severe or severe asphyxia may have a fixed, nonvarying rapid heart rate of 140–160 beats/minute, which may be a prelude to impending failure and cardiogenic shock.

Pulmonary manifestations of asphyxia vary from increased pulmonary vascular resistance that responds readily to correction of acidosis and hypoxia to persistent pulmonary hypertension of the newborn, severe pulmonary insufficiency, or pulmonary hemorrhage, all of which are difficult to manage.

Other organs that are involved and the manifestations of their involvement are listed in Table 1.5. One area often overlooked in the child with severe asphyxia is damage to the spinal cord. Clancy et al. described 18 severely asphyxiated newborns, 12 of whom expired [95]. On autopsy, 5 of the 12 demonstrated severe ischemic necrosis in the spinal cord gray matter. Electromyographic (EMG) studies in the six survivors were abnormal and consistent with recent injury to the lower motor neurons above the level of the dorsal root ganglion. It is often difficult to distinguish clinically between damage to the cortical motor area and damage to the spinal cord.

Phelan et al. described 57 infants with HIE, of whom 14 had no evidence of multisystem problems [96]. Six infants were delivered following uterine rupture; one had fetal exsanguination, one had a cord prolapse, and one was delivered following maternal cardiopulmonary arrest. Five fetuses had sudden and prolonged fetal heart rate decelerations, which persisted until delivery. All these infants would be classified as having an acute asphyxial or a sentinel episode and would not have had the opportunity to

Table 1.5 Effect of Asphyxia on Various Organs in the Newborn

Central nervous system injury
Hypoxic-ischemic encephalopathy (HIE)
Cerebral necrosis
Cerebral edema
Seizures
Hemorrhage
Spinal cord injury
Renal injury
Oliguria
Hematuria
Proteinuria
Acute renal failure
Pulmonary injury
Respiratory failure
Pulmonary hemorrhage
Persistent pulmonary hypertension of the newborn (PPHN)
Pulmonary edema
Meconium aspiration syndrome
Cardiovascular injury
Decreased ventricular function
Abnormalities of rate and rhythm
Tricuspid regurgitation
Papillary muscle necrosis
Hypotension
Cardiovascular shock
Gastrointestinal injury
Gastrointestinal hemorrhage
Sloughing of mucosa
Necrotizing enterocolitis (NEC)
Hepatic injury
Hyperammonemia
Elevated liver enzymes
Coagulopathies
Hematologic abnormalities
Elevated nucleated red cell count
Neutropenia or neutrophilia
Thrombocytopenia
Coagulopathy
Metabolic abnormalities
Hypoglycemia
Hypocalcemia
Sodium and potassium abnormalities
Hypo- or hypermagnesemia

Source: Modified from Carter et al. [94].

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develop the "diving reflex" necessary to protect the brain and heart at the expense of other organs.

If an infant with intrapartum asphyxia demonstrates only CNS involvement without other organ abnormalities, it may be that there was an acute hypoxic event, that the CNS damage did not occur in the intrapartum period, or that it was due to a cerebrovascular event that did not cause profound hypoxia or hypotension to affect other organs.

Biomakers of Neonatal Encephalopathy

In addition to the abnormalities in acid-base determinations that have been described previously, various metabolic parameters have also been found to be abnormal in these children. Some, but not all, have correlated to a certain degree with severe encephalopathy, but they often do not differentiate those infants from infants with mild to moderate encephalopathic states [29].

Urinalysis will usually detect proteinuria and hematuria. Elevations of serum and hepatic enzymes document renal and liver involvement but may not correlate well with the degree of CNS damage. Elevation of serum ammonia is usually found when severe neurologic damage has occurred. Elevations of creatine kinase (CK) in serum and CSF are often found, and both resolve quickly over a 1- to 2-day period. The level of urinary lactate/creatine ratio, measured within the first 6 hours of life, has been correlated with the severity of encephalopathy and adverse neurologic sequelae at 1 year of age. Follow-up data on this measurement have not been forthcoming, and many encephalopathic infants fail to pass urine within the first 6 hours of life.

Elevation of erythropoeitin levels in serum and CSF have been found to be excellent markers of severe encephalopathy. When erythropeitin production is stimulated under hypoxic conditions, elaboration of immature red blood cells ensues. Within 48 hours, increased numbers of immature red blood cells are found in the fetus and newborn. Thus the elevation of nucleated red blood cells would suggest that the intrauterine hypoxic episode may have been present for a significant period of time prior to the birth of the infant.

Recently, other biomakers for HIE have been identified in an effort to predict severity, outcome, and timing of the insult. Increased levels of troponin T [97] and S100B protein [98] in serum and IL-6 in serum and CSF have been found to correlate with the severity of the encephalopathy [15]. Troponin T has been used as a marker of myocardial damage and has been correlated with the degree of encephalopathy as well. Additional studies, including a recent meta-analysis [70], have found associations between neurologic outcomes and CSF neuron-specific enolase, IL-1β, neuronal glial fibrillary acidic protein, and ubiquitin carbosyl-terminal hydrolase L1, in addition to the biomarkers listed earlier [99–104]. Most of the reports, however, are based on a small number of children. As a result, there is insufficient evidence to recommend clinical use of these biomarkers as predictors of poor outcome [105]. Measurement and interpretation of these markers are discussed in Chapter 21.

If abnormalities are encountered, they should be reevaluated frequently in order to assess the evolution of the injury. Table 1.6 lists the various laboratory determinations that have been used to evaluate the extent of CNS injury in affected infants. Some of these measurements are not readily available in many clinical laboratories, and samples of sera or CSF have to be sent to specialized laboratories for assay.

In cases where the diagnosis is uncertain, it is important to do a lumbar puncture in encephalopathic individuals to obtain fluid for biomarker assays as well as to rule out meningitis and encephalitis as causes of the infant's encephalopathy [29].

Clinical Manifestations of Neonatal Encephalopathy

If significant damage has occurred to the CNS, the infant should demonstrate neurologic abnormalities in the neonatal period or as described by Volpe as the "neonatal neurologic syndrome" [29]. It is often difficult to appreciate such abnormalities in preterm infants, especially those who have cardiopulmonary abnormalities and who are being treated with assisted ventilation. Often these infants cannot be distinguished from other prematurely born infants with similar cardiopulmonary abnormalities. However, in the term or near-term infant, signs of encephalopathy are readily discernible. Sarnat and Sarnat developed an infant scoring system that categorizes these infants into three stages of "postasphyxial encephalopathy," identifying mild, moderate, and severe [57]. More recently, a

Table 1.6 Laboratory Studies Used to Support the Diagnosis and Severity of Neonatal Encephalopathy

Study	Body fluid
Ammonia	Serum
Lactate	Serum
Creatine kinase BB (CK-BB)	Serum, CSF
Erythropoietin [106]	Serum, CSF
Neuron-specific enolase	CSF
Myelin basic protein	CSF
Glutamate	CSF
Troponin T	Serum
S100B protein	Serum
Neuronal glial fibrillary acidic protein	Serum
Ubiquitin carboxyl-terminal hydrolase L1	Serum
Interleukin 6	Serum, CSF
Interleukin 1β	Serum, CSF

Source: Modified from Volpe [29].

numerical scoring system was developed and was shown to correlate with abnormal outcome [107]. The criteria that have been established for use of therapeutic hypothermia among infants with HIE are shown in Table 1.7 [108]. Note that there are slight variations to these inclusion criteria in various randomized trials. Although they correlated many of the findings with electroencephalographic (EEG) changes, one can use their classification even if the EEG changes are not evaluated. The clinical manifestation and the gradation of severity of the encephalopathy are discussed in Chapter 16. Similarly, the EEG abnormalities found in these infants are discussed in Chapter 17.

Neuroimaging of the Infant with Encephalopathy

With the increased use of neuroimaging in the encephalopathic infant, investigators have been able to more clearly define the extent of the injury and have, to some degree, been able to determine the timing of the insult [109,110]. A recent paper found that MRI scans of encephalopathic infants treated with hypothermia do not differ between 4 and 11 days of life [111]. Magnetic resonance spectroscopy is also of help in evaluating the extent of damage, as well as the

Table 1.7 Criteria for Initiation of Therapeutic Hypothermia

Gestational age ≥ 36 weeks
Age ≤ 6 hours of life
pH ≤ 7.0 or base deficit ≥ 16 mmol/L[a]
Moderate or severe encephalopathy on examination or seizures

[a] Cord blood or blood gas from the infant within first hour of life. Infants with no cord or postnatal gas, pH of 7.01–7.15, or base deficit of 10–15.9 must meet one of the following to qualify: acute perinatal event, Apgar score ≤ 5 at 10 minutes, or need for assisted ventilation at birth and for beyond 10 minutes of life.

Source: Committee on Fetus and Newborn (2014).

timing of the insult. Some experts recommend that the term *hypoxic-ischemic encephalopathy* be reserved for cases where specific neuroimaging findings correlate with clinical suspicion for encephalopathy [41]. These aspects are discussed in detail in Chapter 18.

How Much of Neonatal Encephalopathy Is Due to Intrapartum Events?

In evaluating all the factors that have been associated with neonatal encephalopathy, it is obvious that no one factor taken by itself can identify the infant who will have neurologic injury. The Apgar score by itself is a poor marker for encephalopathy and is generally not predictive of long-term outcome.

In his excellent review of intrapartum asphyxia and its relationship to CP, Perlman noted that "a single marker of in utero stress provided little useful information regarding the asphyxial process or the fetal adaptive responses, and thus the relationship to neonatal brain injury or subsequent cerebral palsy" [23]. He noted that there had to be a "constellation of markers" in linking intrapartum events to neonatal encephalopathy and then to CP. The infants with severe encephalopathy, including seizures, could be identified by using a 5-minute Apgar score of 5 or less, the need for intubation or cardiopulmonary resuscitation (CPR), and an umbilical cord arterial pH of 7.0 or less [23].

For years it was postulated that a depressed infant who developed seizures within the first 72 hours of life had suffered from an adverse intrapartum event. Currently, there is disagreement as to the correlation of intrapartum events with the development of neonatal encephalopathy. Case-control studies from

Australia found that 69% of infants with encephalopathy had only antepartum risk factors, 25% had both antepartum and evidence of intrapartum markers, 4% had evidence of intrapartum issues only, and 2% had no recognizable causes [5]. Others favor a more even balance between antepartum and intrapartum risk factors [63,64].

Volpe, drawing from his vast experience in evaluating encephalopathic infants, noted that 20% had insults related primarily to antepartum events, 56% had intrapartum disturbances, 14% had both intra- and antepartum events, and 10% had issues in the postpartum period. The latter was encountered primarily in prematurely born infants [29].

The International Cerebral Palsy Task Force developed a template enumerating the criteria used to define an intrapartum event sufficient to cause CP [7]. This template was modified by the ACOG and the AAP and revised in 2014 [10]. These criteria, which are listed in Table 1.8, include both essential criteria and criteria that collectively denote intrapartum timing. Not all investigators have agreed with the ACOG or the Task Force regarding these criteria.

Cowan et al. evaluated 351 infants with neonatal encephalopathy and/or seizures who were referred to two large intensive care units and who were evaluated with MRIs and/or postmortem examinations [11]. The infants were divided into two groups: 261 infants with neonatal encephalopathy and 90 who had seizures without encephalopathy. Imaging of the brain showed an acute insult in 80% of the encephalopathic infants and did not show evidence of prior injuries or atrophy. In the group with seizures only, focal damage (stroke) was found in 69%, and 2% had evidence of antenatal injury. Among the encephalopathic group, 66 infants died and 85 had neurologic sequelae. This study was not population based or case controlled, as were the studies from Australia, but was based on findings from tertiary referral centers that treated the most severely affected infants.

As noted previously, if the fetus has suffered from an acute intrapartum event and there is not enough time to invoke the "diving reflex," the infant may not show multiorgan damage. Similarly, if the umbilical cord is acutely impinged, prolapsed, or tightly wound around the fetus's neck, the cord blood gas may be normal and may not accurately reflect the fetal condition at the time of birth.

Table 1.8 Criteria to Define an Acute Intrapartum Event Sufficient to Cause CP

Essential criteria (must meet all four)
1. Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7.00 and base deficit ≥ 12 mmol/L)
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 weeks or more of gestation
3. CP of the spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders
Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g., 0 to 48 hours) but are nonspecific to asphyxial insults
1. A sentinel (signal) hypoxic event occurring immediately before or during labor
2. A sudden and sustained fetal bradycardia or absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal
3. Apgar scores of 0–3 beyond 5 minutes
4. Onset of multisystem involvement within 72 hours of birth
5. Early imaging study showing evidence of a nonfocal cerebral abnormality

Source: Reproduced from [7] with permission from BMJ.

In other situations, the fetus may have suffered an acute or subacute intrauterine asphyxial event prior to the onset of labor, followed by a period of recovery, and at the time of delivery may show no overt signs of injury. Such infants were often sent to the well-baby nursery, but within hours, they developed signs of encephalopathy, often with seizures, and had the neuroimaging findings that have been associated with an acute intrapartum asphyxial episode. Perlman noted that in his experience this group of infants makes up 50% of infants with encephalopathy [23]. In addition, these same infants may not tolerate labor, may have poor cardiopulmonary reserve, and may develop nonreassuring fetal heart rate tracings. Even though they are delivered expeditiously, they demonstrate all the findings associated with "intrapartum asphyxia" and have neuroimaging that is compatible with an intrapartum injury.

As techniques such as therapeutic hypothermia have been developed and used to treat encephalopathic infants, it behooves the physician to be as precise as possible in identifying the infants with intrapartum injury quickly and effectively in order to provide the most appropriate treatment. Therapuetic hypothermia must be initiated within 6 hours of birth, prior to secondary energy failure, to be effective. Many infants enrolled in these trials may not have had a "true" intrapartum injury, for which therapeutic hypothermia was originally developed, and as a result may not respond to treatment [112]. These infants must be identified in a retrospective manner, if possible, and evaluated as a separate group from those who had a true intrapartum injury.

Conditions Causing Neonatal Depression that Mimic or Are Associated with the Encephalopathic Infant

Nelson and Leviton were among the first to question whether all infants with neonatal encephalopathy suffered from intrapartum asphyxia [2]. One of the more common problems that can present in this fashion is the infant with neonatal sepsis. Currently, group B *Streptococcus* is the most common organism involved. After the initation of intrapartum antibiotic treatment for mothers with group B *Streptococcus* colonization, the incidence of early-onset neonatal sepsis declined, but neonates with presumed sepsis were also less likely to have positive blood or CSF cultures as a result. In these cases, indirect evidence of infection may be present, including an abnormally low or elevated white blood cell count, an elevated C-reactive protein concentration, and/or evidence of severe maternal chorioamnionitis. These infants may have severe lactic acidosis and pulmonary hypertension or hemorrhage and can be very difficult to manage in the neonatal period. Even with the use of nitric oxide, high-frequency ventilation, and extracorporeal membrane oxygenation (ECMO), the mortality and morbidity rates are high.

Similarly, neonates exposed to intrapartum chorioamnionitis may also behave like infants with intrapartum asphyxia. Placental perfusion has been shown to be decreased in such pregnancies, further subjecting the fetus to increased risk of injury (see Chapters 12 and 20).

Although most infants with congenital infections such as cytomegalovirus, herpes, or toxoplasmosis are asymptomatic at birth and later develop clinical manifestations of their diseases, a few will be symptomatic in the neonatal period and behave as if they had suffered from intrapartum asphyxia. Infants with congenital parvoviral infection are often born with generalized edema, are difficult to resuscitate, and have significant rates of morbidity and mortality. Newborns with neuronal migration disorders and those with early-onset myotonic disease have also been mislabeled as infants suffering from intrapartum encephalopathy. The infant with an intrauterine stroke may also be depressed in addition to having seizures. Too often, without substantiating evidence, it is assumed that the stroke has been caused by an adverse intrapartum hypoxic event. Lastly, infants with metabolic disorders can also present in the immediate newborn period with signs suggesting intrapartum asphyxia (see Chapters 23 and 34).

Table 1.9 Conditions Causing Neonatal Depression and/or Neonatal Encephalopathy that Mimics Intrapartum Asphyxia

Neonatal sepsis
Chorioamnionitis without documented neonatal sepsis
Congenital infections Viral Toxoplasmosis
Neuronal migration disorders
Congenital myotonic disorders, including congenital and transient myasthenia gravis
Metabolic conditions causing lactic acidosis
Genetic disorders associated with thrombotic or thrombophilic abnormalities, including protein C and protein S deficiencies Factor V Leiden deficiency Anticardiolipin antibodies

Table 1.9 lists some of these conditions, and clinicians must be aware that not all infants with encephalopathy have their insult due to an intrapartum asphyxial event.

Outcome of Infants with Neonatal Encephalopathy

Although the incidence and mortality rates of infants with encephalopathy have decreased markedly, the complication rates found in the survivors did not change appreciably prior to the implementation of therapeutic hypothermia [11], which has

Table 1.10 Potential Therapies for HIE Currently under Investigation

Erythropoetin
Noble gases (e.g., xenon)
Melatonin
Stem cell–based therapy
Autologous umbilical cord blood cells
Oxygen free-radical inhibition
Growth factor administration
Allopurinol

been shown to improve survival and long-term outcome (see Chapter 48). In a recent meta-analysis of 11 randomized, controlled trials, therapeutic hypothermia was found to reduce death or neurodevelopmental impairment at 18–24 months of age, with number needed to treat to prevent one death or major neurodevelopmental impairment between five and ten [39]. Other outcomes were also improved in the hypothermia group, including CP, neuromotor delay, and developmental delay. As a result, therapeutic hypothermia has become standard treatment for HIE [113]. Recent data suggest that prolonged duration of cooling and/or lower target temperatures are not more beneficial and may be dangerous as well [114].

It is anticipated that with the development and optimization of techniques such as hypothermia and erythropoietin delivery, among other interventions, the outcome of the encephalopathic infants will improve. Table 1.10 lists some of the potential therapies for HIE that are currently under investigation [115–126]. Preliminary data suggest that some of these novel therapies are proving to be beneficial, especially in the moderately severe group of infants (see Chapter 42).

Cerebral Palsy (CP)

The relationship of neonatal encephalopathy and CP with and without cognitive impairment continues to be elusive and often difficult to ascertain [127] (see Chapter 46). The incidence of CP varies and depends on the type of injury present and the cause, if it can be identified. The incidence of CP in the United States is 3.6/1,000 live births [128]. Data from European studies, especially from Scandinavia, are slightly lower but similar, ranging from 1.04–2.52/1,000 live births, and these figures have not changed significantly over the past two decades [129–132]. The rates of CP rose in the early 1970s and remained constant during the early 1980s, primarily due to increased numbers of very low-birth-weight infants surviving, some of whom developed CP. Himmermann et al., however, noted that the subsequent reduction in neonatal mortality has resulted in far more healthy children surviving without CP than with CP [130]. Despite this, prematurely born infants still make up at least 25–50% of the total number of infants with CP, and the risk of CP increases with decreasing gestational age and birth weight. Neonatal encephalopathy has been found in as few as 12% and as many as 24% of infants born at term who develop CP [29]. Neuroimaging has been helpful in identifying not only the area of the brain involved but also the timing of the insult. Malformations of the brain tend to occur primarily during the first and second trimesters of pregnancy, lesions in the white matter occur between the twentieth and the thirty-fourth weeks of gestation, and gray matter lesions and injuries to the striatum occur after the thirty-fourth week of pregnancy [133,134].

In a recent study from Sweden, the prevalence of CP was 2.18/1,000 live births. Neuroimaging demonstrated maldevelopment in 13%, white matter lesions in 36%, cortical/subcortical lesions in 23%, and basal ganglia lesions in 14% [132]. The etiology was deemed to be prenatal in 35%, perinatal/neonatal in 46%, and unclassified in 18%. The perinatal/neonatal group included premature infants as well.

A disproportionate number of infants with intrauterine growth restriction are found with increasing frequency to have CP in childhood [135]. Investigators have also reported an association of CP with noncerebral birth defects, particularly cardiac defects, which has added further evidence that many of the antecedents of CP occur in the antepartum period [66].

Neonatal encephalopathy was found in as few as 12% to as many as 24% of the term infants with CP reported from Australia, 22% of those from Canada, and 31% of those from Norway [19,136].

CP found in children following neonatal encephalopathy is associated with severe cognitive impairment and epilepsy compared with children with CP who were not encephalopathic. In addition, the mortality rate is almost four times greater (19% versus 5%) in the encephalopathic infants [11,19].

The rate of CP following neonatal encephalopathy likely will decrease as treatment options are optimized. In a recent meta-analysis of seven clinical trials of therapeutic hypothermia, the number needed to treat to prevent one case of CP was eight [39]. However, some authors point out that a minority of cases of CP are directly related to asphyxial events at birth [112]. Other causes, such as prematurity, thyroid disease, maternal fever, heavy alcohol consumption, multiple births, or genetic predisposition, may account for a significant number of children [137–142]. Furthermore, a recent study found that the majority of infants with CP and neonatal encephalopathy did not meet criteria for therapeutic hypothermia [143].

Is It Possible to Decrease the Incidence of CP?

The most important approach would be to decrease the incidence of preterm births because this group contributes at least 25–50% of children to the CP population [144]. This would be a formidable task and would require a multipronged attack if it were to be successful. There has been a significant increase in the number of multiple births, which has increased the number of preterm infants. In addition to being born early, these infants have an increased risk of in utero complications such as twin-to-twin transfusion and the in utero death of one of the infants. Multiple births are frequently the result of fertility-enhancing techniques, which often are used in older women. Hopefully, improved techniques, careful counseling, and the implantation of a single rather than multiple fertilized eggs will mitigate this problem to some extent.

Early recognition and treatment of women who have or are at risk of having chorioamnionitis could be a factor in decreasing the incidence of prematurity, and it may be an important factor in decreasing the incidence of CP in the term infant as well. Similarly, careful monitoring of pregnant women with chronic illnesses, especially systemic lupus erythematosus, diabetes, and thyroid disease, would be another approach [145,146].

Electronic fetal heart rate monitoring was hailed as a method to decrease the incidence of CP. This technique has helped to reduce the number of stillbirths but has had little, if any, effect on the incidence of CP. While the rate of cesarean sections in response to abnormalities noted in fetal heart rate tracings has increased almost fivefold, the incidence of CP and adverse neurologic outcomes has remained unchanged [83,147]

Infants who are growth restricted in utero contribute significantly to the number of children with neonatal encephalopathy, seizures, and CP. Infants with symmetric growth restriction may be at risk for encephalopathy due to association with congenital abnormalities, and those with asymmetric growth restriction are also at risk due to limited reserve and placental insufficiency. Improving the early recognition and earlier intervention in these pregnancies could potentially enhance the outcome for these infants.

A question that has lingered for years is whether the increased rate of cesarean section births has decreased the incidence of CP. Overall, the answer has been a resounding "No." However, if an infant is delivered by elective cesarean section, is the incidence of CP decreased? Gaffney et al. studied 141 infants with CP in the United Kingdom and found seven infants delivered by elective cesarean section who did not have neonatal encephalopathy but did have CP [3].

Badawi et al. reported that infants delivered by cesarean section without labor had an 83% reduction in the risk of having moderate or severe encephalopathy [5]. Landon et al., evaluating perinatal outcome associated with a trial of labor after a prior cesarean birth, encountered no infants with HIE in mothers who had elective repeat cesarean sections [148]. Although elective cesarean birth could decrease the incidence of neonatal encephalopathy, it may not decrease the birth of infants who would develop CP [149].

Epidemiology of Intellectual Disability (ID)

Epidemiologists define moderate to profound intellectual disability (ID) as an IQ score below 50 and mild ID as an IQ score between 50 and 69. The prevalence of severe ID has been remarkably constant, varying between 3 and 4/1,000 school-aged children. The cognitive delays are often associated with motor handicaps and seizures. These children are generally found with equal frequency in all socioeconomic classes and most commonly have cognitive delays as a result of a "biologic insult to the brain" [150].

Children with mild ID most commonly come from the most disadvantaged socioeconomic classes,

have learning problems, and may require special education services in order to reach their ultimate levels of achievement. Associated neurologic handicaps may be found in as many as 30% of these children, epilepsy being the most common finding.

Aberrant perinatal events, including intrapartum difficulties, account for 10% of the children with severe and mild ID, and postnatal difficulties account for another 10% with both types of ID.

In most of the children, the origin of severe ID lies in prenatal problems, including chromosomal abnormalities (40%), biochemical inborn errors of metabolism (3–5%), and intrauterine infections (5%). In approximately 30% of children with severe ID, the cause is unknown.

For many years it has been stated that if an infant or child has severe ID without severe CP, the ID is not due to intrapartum asphyxial issues. Initially, Robertson challenged this premise when she identified a group of children with severe ID but without severe CP [151]. Children were found to have abnormal imaging studies that corresponded to the abnormalities seen in children who had a severe intrapartum asphyxial event. Gonzalez and Miller have reported similar findings in their review of the literature and in evaluating children for whom they cared [152]. Survivors of neonatal encephalopathy were at risk of having cognitive abnormalities even in the absence of functional motor deficits and frequently demonstrated watershed lesions of the cerebral cortex (see Chapter 48).

Conclusion

Over the past two decades, a great deal of improvement has taken place in reducing the incidence, morbidity, and mortality rates of neonatal encephalopathy. We are more cognizant of the factors that place the fetus and newborn at risk for such problems. We have improved our diagnostic capabilities so that we have become more precise in evaluating the cause and timing of the events leading to the injury, and we have increased and improved our use of neuroimaging technology to assist us in doing so. We continue to improve our ability to successfully resuscitate the depressed newborn through educational programs for pediatricians, obstetricians, nurses, and respiratory therapists.

We have demonstrated the benefit of therapeutic hypothermia in multiple randomized trials and meta-analyses, and we continue to evaluate additional therapies to mitigate the adverse outcomes of the encephalopathic infant. Hopefully, over the coming two decades, we will continue to make significant progress and markedly decrease the number of children with motor and intellectual disabilities not only in the United States but worldwide as well.

References

1. Stanley F, Blair E, Alberman E. *Cerebral Palsies: Epidemiology and Causal Pathways* (Clinics in Developmental Medicine 151). London: MacKeith Press, 2000.
2. Nelson KB, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? *Am J Dis Child* 1991; **145**: 1325–31.
3. Gaffney G, Flavell V, Johnson A, et al. Cerebral palsy and neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1994; **70**: F195–200.
4. Perlman JM, Risser R. Can asphyxiated infants at risk for neonatal seizures be rapidly identified by current high-risk markers? *Pediatrics* 1996; **97**: 456–62.
5. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factor for newborn encephalopathy: the Western Australian case control study. *BMJ* 1998; **317**: 1554–8.
6. Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. *Am J Obstet Gynecol* 1998; **179**: 507–13.
7. MacLennan A. A template for defining a causal relationship between acute intrapartum events and cerebral palsy: international consensus statement International Cerebral Palsy Task Force. *BMJ* 1999; **319**: 1054–9.
8. Phelan JP, Kim JO. Fetal heart rate observations in the brain damaged infant. *Semin Perinatol* 2000; **24**: 221–9.
9. Hankins GDV, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet Gynecol* 2003; **102**: 628–36.
10. American College of Obstetricians and Gynecologists, American Academy of Pediatrics. *Neonatal Encephalopathy and Neurologic Outcome*, 2nd edn. Washington, DC: ACOG, 2014.
11. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.
12. Shevell, MI. The "Bermuda Triangle" of neonatal neurology: cerebral palsy, neonatal encephalopathy, and intrapartum asphyxia. *Semin Pediatr Neurol* 2004; **11**: 24–30.
13. Perlman JM. Brain injury in the term infant. *Semin Perinatol* 2004; **28**: 415–24.

14. Ferriero DM. Neonatal brain injury. *N Engl J Med* 2004; **351**: 1985–95.
15. Bartha AI, Foster-Barber A, Miller SP, et al. Neonatal encephalopathy: association of cytokines and MR spectroscopy and outcome. *Pediatr Res* 2004; **56**: 960–6.
16. Becher JC, Bell JE, Keeling JW, et al. The Scottish perinatal neuropathology study: clinicopathological correlation in early neonatal deaths. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F399–407.
17. Low JA. Determining the contribution of asphyxia to brain damage in the neonate. *J Obstet Gynaecol Res* 2004; **30**: 276–86.
18. Pierrat V, Haouari N, Liska A, et al. Prevalence, causes, and outcome at 2 years of age of newborn encephalopathy: population-based study. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F257–61.
19. Badawi N, Felix JF, Kurinczuk JJ, et al. Cerebral palsy following term newborn encephalopathy: a population-based study. *Dev Med Child Neurol* 2005; **47**: 293–8.
20. Foley ME, Alarab M, Daly L, et al. Term neonatal asphyxial seizures and peripartum deaths: lack of correlation with a rising cesarean delivery rate. *Am J Obstet Gynecol* 2005; **192**: 102–8.
21. Haider BA, Bhutta ZA. Birth asphyxia in developing countries: current status and public health implications. *Curr Probl Pediatr Adolesc Health Care* 2006; **36**: 178–88.
22. Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. *Obstet Gynecol* 2006; **108**: 1499–505.
23. Perlman JM. Intrapartum asphyxia and cerebral palsy: is there a link? *Clin Perinatol* 2006; **33**: 335–53.
24. Bercher JC, Stenson B, Lyon A. Is intrapartum asphyxia preventable? *BJOG* 2007; **114**: 1442–4.
25. Flidel-Rimon O, Shinwell ES. Neonatal aspects of the relationship between intrapartum events and cerebral palsy. *Clin Perinatol* 2007; **34**: 439–49.
26. Milsom I, Ladfors L, Thiringer K, et al. Influence of maternal, obstetric and fetal risk factors on the prevelance of birth asphyxia at term in a Swedish urban population. *Acta Obstet Gynecol Scand* 2002; **81**: 909–17.
27. Hogan L, Ingemarsson I, Thorngren-Jerneck K, et al. How often is a low 5-min Apgar score in term infants due to asphyxia? *Eur J Obstet Gynecol Reprod Biol* 2007; **130**: 169–75.
28. Rennie JM, Hagmann CF, Robertson NJ. Outcome after intrapartum hypoxic ischemia at term. *Semin Fetal Neonatal Med* 2007; **12**: 398–407.
29. Volpe JJ. Hypoxic-ischemic encephalopathy. In Volpe JJ, ed., *Neurology of the Newborn*, 5th edn. Philadelphia: Saunders/Elsevier, 2008: 400–80.
30. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatr Neurol* 2005; **32**: 11–17.
31. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**: 663–70.
32. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–84.
33. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; **361**: 1349–58.
34. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy. *Pediatrics* 2010; **126**: e771–8.
35. Zhou WH, Cheng GQ, Shao XM, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. *J Pediatr* 2010; **157**: 367–72.
36. Tagin MA, Woolcott CG, Vincer MJ, et al. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2012; **166**: 558–66.
37. Takenouchi T, Iwata O, Nabetani M, Tamura M. Therapeutic hypothermia for neonatal encephalopathy: JSPNM&MHLW Japan Working Group Practice Guidelines Consensus Statement from the Working Group on Therapeutic Hypothermia for Neonatal Encephalopathy, Ministry of Health, Labor and Welfare (MHLW), Japan, and Japan Society for Perinatal and Neonatal Medicine (JSPNM). *Brain Dev* 2012; **34**: 165–70.
38. Jacobs SE, Morley CJ, Inder TE. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized, controlled trial. *Arch Pediatr Adolesc Med* 2011; **165**: 692–700.
39. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013; **1**: CD003311.
40. Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. ACOG Committee Opinion. Number 326, December 2005. Inappropriate use of the terms fetal distress and birth asphyxia. *Obstet Gynecol* 2005; **106**: 1469–70.
41. Volpe JJ. Neonatal encephalopathy: an inadequate term for hypoxic-ischemic encephalopathy. *Ann Neurol* 2012; **72**: 156–66.
42. Wu Y. Brain injury in newborn babies: we can't afford to get it wrong. *Ann Neurol* 2012; **72**: 151.

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43. Harteman JC, Nikkels PGJ, Benders MJNL, et al. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. *J Pediatr* 2013; **163**: 968–75.
44. Chang KT. Examination of the placenta: medico-legal implications. *Semin Fetal Neonatal Med* 2014; **19**: 279–84.
45. Nasiell J, Papadogiannakis N, Lof E, et al. Hypoxic ischemic encephalopathy in newborns linked to placental and umbilical cord abnormalities. *J Matern Fetal Neonatal Med* 2015; **5**: 1–6.
46. Lachapelle J, Chen M, Oskoui M, et al. Placental pathology in asphyxiated newborns treated with therapeutic hypothermia. *J Neonatal Perinatal Med* 2015; **8**: 33–40.
47. Clarke P, Gardner D, Venkatesh V, et al. Investigation of neonatal encephalopathy: the oft-lost placental "black box." *Pediatr Dev Pathol* 2015; **18**: 343–4.
48. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol* 1972; **112**: 246–76.
49. Mallard EC, Williams CE, Johnston BM, et al. Repeated episodes of umbilical cord occlusion in fetal sheep lead to preferential damage to the striatum and sensitize the heart to further insults. *Pediatr Res* 1995; **37**: 707–13.
50. Ghei SK, Zan E, Nathan JE, et al. MR imaging of hypoxic-ischemic injury in term neonates: pearls and pitfalls. *Radiographics* 2014; **34**: 1047–61.
51. Leung AS, Leung EK, Paul RH. Uterine rupture after previous cesarean delivery: maternal and fetal consequences. *Am J Obstet Gynecol* 1993; **169**: 945–50.
52. Lee ACC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatr Res* 2013; **74**: 50–72.
53. Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. *Acta Paediatr* 1995; **84**: 927–32.
54. Graham EM, Ruis KA, Hartman AL, et al. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008; **199**: 587–95.
55. Lee AC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatr Res* 2013; **74**: 50–72.
56. American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol* 2014; **123**: 896–901.
57. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; **33**: 696–705.
58. Wu YW, Backstrand KH, Zhao S, et al. Declining diagnosis of birth asphyxia in California: 1991–2000. *Pediatrics* 2004; **114**: 1584–90.
59. Martin JA, Kochanek KD, Strobino DM, et al. Annual summary of vital statistics: 2003. *Pediatrics* 2005; **115**: 619–34.
60. Hayakawa M, Ito Y, Saito S, et al. Incidence and prediction of outcome in hypoxic-ischemic encephalopathy in Japan. *Pediatr Int* 2014; **56**: 215–21.
61. Locatelli A, Incerti M, Paterlini G, et al. Antepartum and intrapartum risk factors for neonatal encephalopathy at term. *Am J Perinatol* 2010; **27**: 649–54.
62. Nelson KB, Bingham P, Edwards EM, et al. Antecedents of neonatal encephalopathy in the Vermont Oxford Network Encephalopathy Registry. *Pediatrics* 2012; **130**: 878–86.
63. Hayes BC, McGarvey C, Mulvany S, et al. A case-control study of hypoxic-ischemic encephalopathy in newborn infants at >36 weeks' gestation. *Am J Obstet Gynecol* 2013; **209**: e1–29.
64. Martinez-Biarge M, Diez-Sebastian J, Wusthoff CJ, et al. Antepartum and intrapartum factors preceding neonatal hypoxic-ischemic encephalopathy. *Pediatrics* 2013; **132**: e952–9.
65. Nelson KB, Ellenberg JH. Obstetric complications as risk factors for cerebral palsy or seizure disorders. *JAMA* 1984; **251**: 1843–8.
66. Blair E, Al Asedy F, Badawi N, et al. Is cerebral palsy associated with birth defects other than cerebral defects? *Dev Med Child Neurol* 2007; **49**: 252–8.
67. Kahana B, Sheiner E, Levy A, et al. Umbilical cord prolapse and perinatal outcomes. *Int J Gynaecol Obstet* 2004; **84**: 127–32.
68. Wu YW, Escobar GJ, Grether JK, et al. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA* 2003; **290**: 2677–84.
69. Tekgul H, Yalaz M, Kutukculer N, et al. Value of biochemical markers for outcome in term infants with asphyxia. *Pediatr Neurol* 2004; **31**: 326–32.
70. Ramaswamy V, Horton J, Vandermeer B, et al. Systematic review of biomarkers of brain injury in term neonatal encephalopathy. *Pediatr Neurol* 2009; **40**: 215–26.
71. Kasdorf E, Perlman J. Hyperthermia, inflammation, and perinatal brain injury. *Pediatr Neurol* 2013; **49**: 8–14.

72. Jenster M, Bonifacio SL, Ruel T, et al. Maternal or neonatal infection: association with neonatal encephalopathy outcomes. *Pediatr Res* 2014; **76**: 93–9.
73. Nelson KB, Penn AA. Is infection a factor in neonatal encephalopathy? *Arch Dis Child Fetal Neonatal Ed* 2015; **100**: F8–10.
74. O'Hare FM, Watson RWG, O'Neill A, et al. Persistent systemic monocyte and neutrophil activation in neonatal encephalopathy. *J Matern Fetal Neonatal Med* 2016; **29**: 582–9.
75. Hagberg, H, Mallard C, Ferriero DM, et al. The role of inflammation in perinatal brain injury. *Nat Rev* 2015; **11**: 192–208.
76. Apgar VA. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953; **32**: 260–7.
77. Odd DE, Lewis G, Whitelaw A, Gunnell D. Resuscitation at birth and cognition at 8 years of age: a cohort study. *Lancet* 2009; **373**: 1615–22.
78. Natarajan G, Hankaran S, Laptook AR, et al. Apgar scores at 10 min and outcomes at 6–7 years following hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F473–9.
79. Shah P, Anvekar A, McMichael J, Rao S. Outcomes of infants with Apgar score of zero at 10 min: the West Australian experience. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**: F492–4.
80. Kasdorf E, Laptook A, Azzopardi D, et al. Improving infant outcome with a 10 min Apgar of 0. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**: F102–5.
81. Dijxhoorn MJ, Visser GHV, Touwen BC. Apgar score, meconium and acidemia at birth in small to gestational age infants born at term, and their relationship to neonatal neurological morbidity. *Br J Obstet Gynaecol* 1987; **94**: 873–9.
82. Grant A, O'Brien W, Joy MT, et al. Cerebral palsy among children born during the Dublin randomised trial of intrapartum monitoring. *Lancet* 1989; **2**: 1233–6.
83. Alfirevic Z, Devane D, Gyte, GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring for fetal assessment during labour. *Cochrane Database Syst Rev* 2013; CD006066.
84. Chauhan SP, Hendrix NW, Magann EF, et al. Neonatal organ dysfunction among newborns at gestational age ≥ 34 weeks, and umbilical arterial pH < 7.00. *J Matern Fetal Neonatal Med* 2005; **17**: 261–8.
85. Goodwin TM, Belai I, Hernandez P, et al. Asphyxial complications in the term newborn with severe umbilical acidemia. *Am J Obstet Gynecol* 1992; **167**: 1506–12.
86. Belai Y, Goodwin TM, Durand M, et al. Umbilical arteriovenous PO_2 and PCO_2 differences and neonatal morbidity in term infants with severe acidosis. *Am J Obstet Gynecol* 1998; **178**: 13–19.
87. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics* 2006; **117**: 1270–80.
88. Bonifacio SL, deVries LS, Groenendaal F. Impact of hypothermia on predictors of poor outcome: how do we decide to redirect care? *Sem Fetal Neonatal Med* 2015; **20**: 122–7.
89. Shetty J. Neonatal seizures in hypoic-ischaemic encephalopathy: risks and benefits of anticonvulsant therapy. *Dev Med Child Neurol* 2015; **57**: 40–3.
90. Silverstein FS, Jensen FE. Neonatal seizures. *Ann Neurol* 2007; **62**: 112–20.
91. Miller SP, Weiss J, Barnwell A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology* 2002; **58**: 542–8.
92. Hankins GDV, Koen S, Gei F, et al. Neonatal organ system injury in acute birth asphyxia sufficient to result in neonatal encephalopathy. *Obstet Gynecol* 2002; **99**: 688–91.
93. Shah P, Riphagen S, Beyene J, et al. Multiorgan dysfunction in infants with post-asphyxial hypoxic–ischemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F152–5.
94. Carter BS, Haverkamp AD, Merenstein GB. The definition of acute perinatal asphyxia. *Clin Perinatol* 1993; **20**: 287–304.
95. Clancy RR, Sladky JT, Rorke LB. Hypoxic-ischemic spinal cord injury following perinatal asphyxia. *Ann Neurol* 1989; **25**: 185–9.
96. Phelan JP, Ahn MO, Korst L, et al. Intrapartum fetal asphyxial brain injury with absent multi-organ system dysfunction. *J Matern Fetal Med* 1998; **7**: 19–22.
97. Trevisanuto D, Picco G, Golin R, et al. Cardiac troponin I in asphyxiated neonates. *Biol Neonate* 2006; **89**: 190–3.
98. Thorngren-Jerneck K, Alling C, Herbst A, et al. S100 protein in serum as a prognostic marker for cerebral injury in term newborn infants with hypoxic ischemic encephalopathy. *Pediatr Res* 2004; **55**: 406–12.
99. Douglas-Escobar M, Yang C, Bennett J, et al. A pilot study of novel biomarkers in neonates with hypoxic-ischemic encephalopathy. *Pediatr Res* 2010; **68**: 531–6.
100. Ennen CS, Huisman TA, Savage WJ, et al. Glial fibrillary acidic protein as a biomarker for neonatal hypoxic-ischemic encephalopathy treated with whole-body cooling. *Am J Obstet Gynecol* 2011; **205**: e1–7.

.002

101. Massaro AN, Chang T, Kadom N, et al. Biomarkers of brain injury in neonatal encephalopathy treated with hypothermia. *J Pediatr* 2012; **161**: 434–40.

102. Massaro AN, Jeromin A, Kadom N, et al. Serum biomarkers of MRI brain injury in neonatal hypoxic ischemic encephalopathy treated with whole-body hypothermia: a pilot study. *Pediatr Crit Care Med* 2013; **14**: 310–7.

103. Chalak LF, Sanchez PJ, Adams-Huet B, et al. Biomarkers for severity of neonatal hypoxic-ischemic encephalopathy and outcomes in newborns receiving hypothermia therapy. *J Pediatr* 2014; **164**: 468–74.

104. Ferriero DM, Bonifacio SL. The search continues for the elusive biomarkers of neonatal brain injury. *J Pediatr* 2014; **164**: 438–9.

105. Bennet L, Booth L, Gunn AJ. Potential biomarkers for hypoxic-ischemic encephalopathy. *Semin Fetal Neonatal Med* 2010; **15**: 253–60.

106. Phelan JP, Kirkendall C, Korst LM, et al. Nucleated red blood cell and platelet counts in asphyxiated neonates sufficient to result in permanent neurological impairment. *J Matern Fetal Neonatal Med* 2007; **20**: 377–80.

107. Thompson CM, Puterman As, Linley LL, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta Paediatr* 1997; **86**: 757–61.

108. Committee on Fetus and Newborn, Papile LA, Baley JE, et al. Hypothermia and neonatal encephalopathy. *Pediatrics* 2014: **133**: 1146–50.

109. Nanavati T, Seemaladinne N, Regier M, et al. Can we predict functional outcome in neonates with hypoxic ischemic encephalopathy by the combination of neuroimaging and electroencephalography? *Pediatr Neonatol* 2015; **56**: 307–16.

110. Hayes BC, Ryan S, McGarvey C, et al. Brain magnestic resonance imaging and outcome after hypoxic ischaemic encephalopathy. *J Matern Fetal Neonatal Med* 2016; **29**: 777–82.

111. Skranes JH, Cowan FM, Stiris T, et al. Brain imaging in cooled encephalopathic neonates does not differ between four and 11 days after birth. *Acta Paediatr* 2015; **104**: 752–8.

112. McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869–77.

113. Perlman J, Davis P, Wyllie J, Kattwinkel J. Therapeutic hypothermia following intrapartum hypoxia-ischemia: an advisory statement from the Neonatal Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2010; **81**: 1459–61.

114. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic-ischemic encephalopathy. *JAMA* 2014; **312**: 2629–39.

115. Gunes T, Ozturk MA, Koklu E, et al. Effect of allopurinol supplementation on nitric oxide levels in asphyxiated newborns. *Pediatr Neurol* 2007; **36**: 17–24.

116. Glass HC, Ferriero DM. Treatment of hypoxic-ischemic encephalopathy in newborns. *Curr Treat Options Neurol* 2007; **9**: 414–23.

117. Zhu C, Kang W, Xu F, et al. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 2009; **124**: e218–26.

118. Li J, McDonald CA, Fahey MC, et al. Could cord blood cell therapy reduce preterm brain injury? *Front Neurol* 2014; **5**: 200.

119. Cotton MC, Murtha AP, Goldberg RN, et al., Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. *J Pediatr* 2014; **164**: 973–9.

120. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *JAMA* 2014; **312**: 2629–39.

121. Rogers EE, Bonifacio SL, Glass HC, et al. Erythropoietin and hypothermia for hypoxic-ischemic encephalopathy. *Pediatr Neurol* 2014; **51**: 657–62.

122. Kasdorf E, Perlman JM. Strategies to prevent reperfusion injury to the brain following intrapartum hypoxia-ischemia. *Semin Fetal Neonatal Med* 2013; **18**: 379–84.

123. Van Velthoven CTJ, Gonzalez F, Vexler ZS, Ferriero DM. Stem cells for neonatal stroke- the future is here. *Front Cell Neurosci* 2014; **8**: 207.

124. Rangarajan V, Juul SE. Erythropoietin: emerging role of erythropoietin in neonatal neuroprotection. *Pediatr Neurol* 2014; **51**: 481–8.

125. Shea KL, Palanisamy A. What can you do to protect the newborn brain? *Curr Opin Anesthesiol* 2015 (epub ahead of print).

126. Aly H, Elmahdy H, El-Dib M, et al. Melatonin use for neuroprotection in perinatal asphyxia: a randomized, controlled pilot study. *J Perinatol* 2015; **35**: 186–91.

127. Ellenberg JH, Nelson KB. The association of cerebral palsy with birth asphyxia: a definitional quaqmire. *Dev Med Child Neurol* 2013; **55**: 210–16.

128. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, et al. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics* 2008; **121**: 547–54.

129. Oskoui M, Coutinho F, Dykeman J, et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2013; **55**: 509–19.

130. Himmelmann K, Hagberg G, Beckung E, et al. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth year period 1995–1998. *Acta Paediatr* 2005; **94**: 287–94.

131. Himmelmann K. Epidemiology of cerebral palsy. In *Handbook Clinical Neurology,* vol. III: *Pediatric Neurology Part I*, d. OF Duke, M Lassonde, HB Sarnat. New York: Elsivier, 2013: 163–7.

132. Himmelmann K, Uvebrant P. The panorama of cerebral palsy in Sweden. XI. Changing patterns in the birth-year period 2003–2006. *Acta Paediatr* 2014; **103**: 618–24.

133. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. *JAMA* 2006; **296**: 1602–8.

134. Wu YW, Croen LA, Shah SJ, et al. Cerebral palsy in a term population: risk factors and neuroimaging findings. *Pediatrics* 2006; **118**: 690–7.

135. Blair EM, Nelson KB. Fetal growth restriction and risk of cerebral palsy in singletons born after at least 35 weeks' gestation. *Am J Obstet Gynecol* 2015; **520**: e1–7.

136. Himmelmann K, Hagberg G, Wiklund LM, et al. Dyskinetic cerebral palsy: a population-based study of children born between 1991 and 1998. *Dev Med Child Neurol* 2007; **49**: 246–51.

137. Tollanes MC, Wilcox AJ, Lie RT, Moster D. Familial risk of cerebral palsy: population based cohort study. *BMJ* 2014; **349**: 4294–301.

138. Hirvonen M, Ojala R, Korhonen P, et al. Cerebral palsy among children born moderately and late preterm. *Pediatrics* 2014; **134**: e1584–93.

139. Nelson K. infection in pregnancy and cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 252–5.

140. Nelson KB, Penn AA. Is infection a factor in neonatal encephalopathy? *Arch Dis Child Fetal Neonatal Ed* 2015; **100**: F8–10.

141. O'Leary CM, Watson L, D'Antoine H, et al. Heavy maternal alcohol consumption and cerebral palsy in the offspring. *Dev Med Child Neurol* 2012; **54**: 224–30.

142. Nelson KB. Preventing cerebral palsy: paths not (yet) taken. *Dev Med Child Neurol* 2009; **51**: 765–6.

143. Garfinkle J, Wintermark P, Shevell MI, et al. Cerebral palsy after neonatal encephalopathy: how much is preventable. *J Pediatr* 2015; **167**: 58–63.

144. Nelson KB. Can we prevent cerebral palsy? *N Engl J Med* 2003; **349**: 1765–9.

145. Nelson KB. The epidemiology of cerebral palsy in term infants. *Ment Retard Dev Disabil Res Rev* 2002; **8**: 146–50.

146. Blair E, Watson L. Epidemiology of cerebral palsy. *Semin Fetal Neonatal Med* 2006; **11**: 117–25.

147. Clark SL, Hankins GDV. Temporal and demographic trends in cerebral palsy: fact and fiction. *Am J Obstet Gynecol* 2003; **188**: 628–33.

148. Landon MB, Haut JC, Leveno KJ, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *N Engl J Med* 2004; **351**: 2581–9.

149. Hankins GDV, Clark SM, Munn MB. Cesarean section on request at 39 weeks: impact on shoulder dystocia, fetal trauma, neonatal encephalopathy, and intrauterine demise. *Semin Perinatol* 2006; **30**: 276–87.

150. Hagberg B, Kyllerman M. Epidemiology of mental retardation: a Swedish survey. *Brain Dev* 1983; **5**: 441–9.

151. Robertson CMT. Can hypoxic-ischemic encephalopathy (HIE) associated with term birth asphyxia lead to mental disability without cerebral palsy? *Can J Neurol Sci* 1999; **26**: S36.

152. Gonzalez FF, Miller SP. Does perinatal asphyxia impair cognitive function without cerebral palsy? *Arch Dis Child Fetal Neonatal Ed* 2006; **91**: F454–9.

Chapter 2

Neuronal Cell Death Mechanisms Relevant to Humans

Rethinking Modeling Neonatal Hypoxic-Ischemic Encephalopathy

Lee J. Martin

Introduction

Hypoxia-ischemia (HI) and asphyxia due to umbilical cord prolapse, delivery complications, airway obstruction, asthma, drowning, and cardiac arrest are significant causes of brain damage, mortality, and morbidity in infants and young children [1]. Systemic asphyxia resulting from a disruption in placental gas exchange occurs perinatally in two to four babies per 1,000 term infants [2,3]. The reports are highly variable, but ~80% of infants who experience HI during the newborn period survive, and ~25% of survivors exhibit permanent neurologic disabilities [4,5]. Brain injury after neonatal cardiopulmonary bypass can occur in up to 11% of cases [6].

Term infants that experience episodes of asphyxia can have damage in the brainstem and forebrain, with the basal ganglia, particularly the striatum, and somatosensory system showing severe vulnerability [7]. Infants surviving with hypoxic-ischemic encephalopathy (HIE) can have long-term neurologic disability, including disorders in movement, vision, learning, and cognition and epilepsy [8]. Some of these neurologic disabilities are contributors to the complex clinical syndrome of cerebral palsy [8]. Neuroimaging studies of full-term neonates [7] and experimental studies on animal models [9–11] suggest that this pattern of selective vulnerability is related to brain regional metabolism and interconnections that instigate and propagate the damage within specific neural systems [10,11]. The idea that brain regions that are interconnected and have high metabolism dictate selective vulnerability in the newborn brain has been called the *metabolism-connectivity concept* [9,10].

The brain damage of HIE appears to occur in at least three phases [1,8]. Acute cell death is caused by abrupt mitochondrial metabolic failure and acidosis [11]. A second subacute phase is associated with reperfusion and reoxygenation. A third phase is delayed and is associated with remote neurodegeneration. The early neurodegeneration of HIE is partly triggered by excitotoxic mechanisms resulting from extracellular glutamate accumulation and excessive activation of excitatory glutamate receptors, failure of osmotic and volume control, and oxidative stress [1,12–14]. The ion channel *N*-methyl-D-aspartate (NMDA) glutamate receptor, transient receptor potential channels, and intracellular signaling networks involving calcium, nitric oxide synthase, mitochondria, and production of cytotoxic reactive oxygen species (ROS) such as superoxide, nitric oxide (NO), peroxynitrite, hydrogen peroxide (H_2O_2), and hydroxyl radical and elevations in free iron appear to have instrumental roles in the acute and subacute neuronal cell death leading to perinatal HIE in model systems [12–15]. The Fenton reaction and excessive ROS can damage macromolecules, including cell membrane lipids, proteins, and DNA [16]. The third phase appears to involve target deprivation-driven neuronal apoptosis in brain regions remote from the early primary sites of acute injury [17].

Despite considerable progress in the epidemiologic understanding and clinical management of HI, as

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well as much preclinical research on mechanisms of injury in cell and perinatal animal models of HIE, treatments for preventing the evolution of neural damage and the ensuing neurologic disabilities in infants and children are very limited. Various pharmacologic interventions designed to minimize excitotoxicity and oxidative stress mechanisms have been attempted, but the results have been unsuccessful [18]. Mild hypothermia is currently the only therapy used with potential benefit. Hypothermia is beneficial in some neonates with mild to moderate HI insults [19], but the protection is only partial, and only one baby in six babies with encephalopathy will benefit from therapeutic hypothermia [20]. Nearly half of infants treated with hypothermia still die or survive with significant neurologic morbidity. Furthermore, therapeutic hypothermia failed in providing benefit to children with out-of-hospital cardiac arrest [21].

It is not clear whether the brain tissue in newborns salvaged by hypothermia is intact structurally and functionally; moreover, the complex mechanisms of hypothermic neuroprotection are unresolved. Hypothermia is likely to influence many processes in brain, including cellular bioenergetics and mitochondrial function, protein and RNA synthesis, glutamate release and uptake, oxidative stress, and DNA damage and repair. Mild hypothermia decreases brain damage, including severe ischemic neuronal necrosis, in neonatal piglet models of HIE [22,23]. In neonatal rodent models of HI, hypothermia attenuates apoptosis [24] and mitigates inflammation [25]. It is unclear whether hypothermia completely occludes the acute ischemic necrotic cellular degeneration or delays or prevents cellular necrosis only to permit other forms of cell degeneration to emerge, as would be predicted by the concept of the cell death continuum [16,26,27]. Alternatively, hypothermia might inhibit cell death in general and all its potential forms. Major concerns of therapeutic hypothermia are possible off-target effects of hypothermia and effects of rewarming. Rewarming from therapeutic hypothermia induces cortical neuron apoptosis [28] and white matter oligodendrocyte apoptosis [29] in a piglet model of neonatal HIE. Adjunct therapies have not been forthcoming. Pharmacologic clinical trials using putative mechanism-based drugs in newborns and adults have failed disappointingly in translation from animal studies of cerebral ischemia [18,30]. The failure to identify drug and biologic therapies for acute and chronic neurologic injuries in humans can be attributed to a lack of reliable diagnostic biomarkers enabling detection of brain injury and disease early in its evolution, the implementation timing of the therapeutic intervention relative to injury and disease onset (clinical trial design), the lack of complete and comprehensive understanding of brain pathobiology and its timing, and failure to identify human-relevant cell and molecular mechanism-based targets in human neurons for drug discovery so that effective therapeutics can be implemented at appropriate times.

This chapter will summarize a few specific mechanisms of neuron degeneration related to neonatal HIE that involve DNA damage and DNA damage response (DDR) and will introduce an idea that basic research on brain injury may be too reliant on rodent models and animal cell models of injury. With the advent of human stem cell–derived neurons, human-relevant mechanisms of cell injury and human neuron-relevant therapeutics can be investigated directly.

DNA Damage: Types and Formation

DNA damage is a suspected trigger for neuronal death in a many neurologic disorders occurring throughout life [31]. DNA damage has been implicated in the mechanisms of neurodegeneration in newborn and childhood neurologic disorders, age-related disease, cerebral ischemia, and brain trauma. In the developing brain, migrating newborn neurons can sustain oxidative DNA damage and, if not repaired, undergo apoptosis [32]. Childhood human diseases link more definitely DNA damage and causal mechanisms for neurodegeneration. A connection between defective repair of DNA damage, cancer, and neurologic disease is seen in children with xeroderma pigmentosum (XP) [33,34]. The neurologic phenotype of XP patients includes ataxia, microcephaly, deafness, learning disability, peripheral neuropathy with loss of large sensory fibers and dorsal root ganglion neurons, cerebellar/cerebral atrophy, and neuronal degeneration [33]. Mutations in genes involved in the DNA nucleotide excision repair (NER) pathway cause most forms of XP [33]. Other human infant- and childhood-onset diseases associated with abnormalities in NER genes and neurodegeneration are Cockayne syndrome and trichothiodystrophy [33]. Another human childhood neurologic disorder with prominent neurodegeneration is ataxia telangiectasia (AT) caused by inactivating

mutations in the gene encoding the protein kinase ATM [35]. ATM is a major regulator of DDR [36]. Patients with AT develop progressive ataxia and have extensive degeneration of cerebellar Purkinje and granule neurons and brainstem and spinal cord neuron degeneration [37].

DNA damage has been studied in animal models of hypoxia and neonatal HIE. Hypoxia (4% O_2) alone induces nuclear and mitochondrial DNA damage in postmitotic differentiated neurons [38]. DNA fragmentation as double-stand breaks (DSBs), detected by the terminal transferase-mediated dUTP nick-end labeling (TUNEL) assay, has been found by 2–12 hours in neonatal rat brain after HI [39–41] and excitotoxic insults [42]. The morphologic appearance of the dying neurons is consistent with apoptosis [39–41] or combined apoptosis and necrosis in individual cells typifying a cell death continuum [27,42]. An elegant DNA gel electrophoresis study by MacManus [43] revealed that most DNA fragments found in neonatal rat brain after HI have staggered ends with a 3' recess of ~8–10 nucleotides. This pattern of DNA fragmentation is different from the blunt-ended DNA fragments produced in classical apoptosis, and thus the DNA endonucleases activated in the immature rodent brain after HI and during programmed cell death are probably different. After stroke in adult mice, DNA SSBs accumulate very quickly, within 15 minutes, in cerebral cortex at levels 20-fold higher than baseline [44]. Gel electrophoresis has shown that after excitotoxicity in neonatal rat brain, DNA DSBs can accumulate within 15 minutes [45]. Accumulation of DNA DSBs is incompatible with cell viability; thus these DNA lesions could be early sentinel events in the pathogenesis of brain damage. The effect of whole-body therapeutic hypothermia on DNA damage in term babies with probable HIE has been assessed and found to reduce DNA damage in blood leukocytes [46]. Much more work is needed to decipher the role of DNA damage as an upstream cause of neuron degeneration or a consequence of the degeneration following neonatal HI.

The likely causal role of DNA damage in human pathobiology and disease treatment is pervasive [47,48]. DNA damage has been implicated in the mechanisms of aging [48] and in the pathogenesis of many human illnesses, including cancer and neurologic disorders ranging from neonatal HIE to chronic neurodegenerative diseases [31]. Spontaneous DNA damage is a constant threat to cells by producing gene mutations and triggering programmed cell death. Endogenous and environmental agents can cause DNA damage in cells [48]. Endogenous agents are ROS and reactive nitrogen species (RNS) generated by cellular metabolism and other factors such as body temperature, errors in DNA replication and repair, and DNA alkylation. The genotoxic actions of ROS (e.g., hydroxyl radical and H_2O_2) and RNS (e.g., peroxynitrite [$ONOO^-$]) are dramatic [49,50]. Intrinsically generated DNA lesions occur as mismatched base pairs, base structure alterations such as tautomeric shifts and deamination, base adducts (e.g., hydroxylation), and base deletions causing apurinic/apyrimidinic (AP or abasic) sites, DNA single-strand breaks (SSBs), and DNA DSBs [34]. Metabolism-generated ROS can cause ~10,000 lesions/day in the genome of human nonneuronal cells, and purine base turnover in DNA, resulting from hydrolytic depurination and subsequent repair, is ~2,000–10,000 bases/day [34]. In nonproliferating, long-living cells such as neurons, $\sim 10^8$ purines are estimated to be lost because of spontaneous depurination during a lifespan [34]. Other estimates indicate the presence of 50,000–200,000 AP sites/mammalian cell; brain cells contain the most AP sites [34]. In some organs, the levels of AP sites appear to be age dependent, with higher levels found in older animals [34]. The estimated frequency of occurrence of spontaneous (endogenous) DNA SSBs in a mammalian cell is ~20,000–40,000 and can be much higher depending on diet, lifestyle, and tissue type. The neuronal genome is very sensitive to ROS and RNS because they induce the formation of AP sites, SSBs, and DSBs [50]. The different forms of DNA damage can be converted from one form to another. Hydroxyl radical and $ONOO^-$ attack on DNA induces base adducts and then strand breaks because AP sites are converted into SSBs if not repaired. Hydroxyl radical and $ONOO^-$ are also potent mutagens in human cells [49]. In addition to the intrinsically generated lesions to DNA, dietary mutagenic chemicals, ultraviolet and ionizing radiation, and free heavy metals are environmental agents that damage the genome, causing DNA cross-links, adducts, and oxidative cleavage. Iron is also an endogenous heavy metal that on liberation from macromolecules after tissue injury can cause catalysis of DNA damage. Free iron is believed to have a role in brain tissue injury in neonatal HI [8,12,15].

DDR Signaling

Cells that have sustained irreparable DNA damage from ROS/RNS and other genotoxic agents undergo

apoptosis by engaging molecular cascades involving expression or activation of p53, Bax, and caspases [51]. However, the signal transduction mechanisms in neurons that link DNA damage to apoptosis are not well characterized, particularly in human neurons. It is possible that neurons are particularly sensitive to specific DNA lesions, thereby activating signals for apoptosis or programmed necrosis [16,31]. DNA damage sensor mechanisms in postmitotic cells such as neurons are largely unknown.

DNA damage sensor proteins have been studied in nonneuronal cells [52]. DNA DSBs are recognized and bound by the heterodimeric regulatory subunits of DNA-dependent protein kinase (DNA-PK, Ku70/80), thereby recruiting the catalytic DNA-PK that phosphorylates p53 [53]. The *ATM* gene product, the causative mutant gene in AT, and ATM/Rad3-related kinase (ATR) are other protein kinases that become activated in response to DNA damage [52]. DNA-PK, ATM, and ATR are members of the phosphatidylinositol 3-kinase family [53,54]. Identified substrates for ATM and ATR are $p53^{Ser15}$, murine double-minute-2 $(Mdm2)^{Thr417}$, and $Rad17^{Ser645}$. ATM is required for the phosphorylation of p53 at serine-15 and serine-20. This relationship exists in the developing rodent nervous system because ATM-dependent apoptosis requires p53 phosphorylation and caspase-3 activation [55]. DDR can also be linked to c-Abelson protein kinase (c-Abl) [56]. c-Abl is a nonreceptor tyrosine kinase that is found in many tissues and is distributed in the nucleus and cytoplasm of cells. c-Abl appears to function in the regulation of cell proliferation, differentiation, and apoptosis. Phosphorylation of c-Abl at Tyr245 activates its kinase activity. Several in vitro studies have shown that the activity of c-Abl is upregulated after exposure to genotoxic agents in a process independent of DNA-PK. c-Abl, in turn, activates mitogen-activated protein kinase kinase kinase (MEKK1) in response to DNA damage. ATM and DNA-PK pathways can also converge through c-Abl because c-Abl can downregulate the activity of DNA-PK [53].

An important question is what are the mechanisms that activate DDR protein kinases in neurons? A DNA damage sensor that has been studied in nonneuronal cells is the meiotic recombination 11 homolog A protein (Mre11)-Rad50–Nijmegen breakage syndrome-1 protein (Nbs1) complex [57]. The multiprotein Mre11-Rad50-Nbs1 (MRN) complex is required for DNA damage signaling via ATM activation. Indeed, the MRN complex is required for full activation of ATM and ATR. The MRN complex is composed of two heterodimers of Mre11-Rad50 associated with a single Nbs1 (also called *nibrin* and *p95*). The MRN complex, due to Mre11, possesses DNA single-strand endonuclease activity and DNA double-strand-specific 3'-5' exonuclease activity. Rad50 binds DNA ends to hold them in close proximity. Nbs1 functions in recruiting ATM and ATR (and possibly DNA-PK) to the DNA damage sites and activating their functions. Nbs1 also recruits Mre11 and Rad50 to the DNA break site by interaction with the histone H2AX. MRN proteins migrate and localize to discrete nuclear foci in nonneural cells in response to genotoxic agents [58]. Scant information is available on the expression and localization of DDR proteins in human brain. Postmortem studies have found that ATM and the MRN complex are concentrated in the nucleus of cerebellar Purkinje neurons in human children [59].

Functions and Regulation of p53

The tumor suppressor p53 has been in the spotlight of human cancer biology for a long time, and it now is known to have a critical role in neurodegeneration and neuronal death. Substantial preapoptotic accumulation of phosphoserine-p53 occurs in cultured mouse cortical neurons treated with a DNA-damaging stress [60]. In animal models, p53 mediates apoptosis of neurons in rat and mouse spinal cord and thalamus after trauma [61–64]. p53 links DNA damage to apoptosis in rodent neurons [60,64]. Genetic and pharmacologic inactivation of p53 is neuroprotective in culture [60] and in the acutely injured central nervous system (CNS) [61–64]. However, p53 signaling mechanisms in immature and differentiated mouse neurons appear to be different [60]. p53-regulated mechanisms of growth arrest and cell death have been studied extensively in human nonpostmitotic cells, but these mechanisms have not been studied well in human neurons.

p53 has been found to be activated in postmortem human infant cortical neurons with HIE [65], and it appears to have a role in brain injury caused by HI in neonatal rats [66]. p53 functions in DDR, growth control, and senescence [67–69]. p53 is activated by genotoxic stress and can trigger the onset of DNA repair or apoptosis. The ability of p53 to induce apoptosis is accepted unequivocally. Genetic overexpression of p53 alone causes neurodegeneration in cultures of rodent sympathetic ganglion neurons [70] and immature cerebellar granule neurons [71]. The intricacies of p53 in

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DNA repair are less well known. Genetically null $p53^{-/-}$ mice exhibit an increase in chromosomal abnormalities and a deficiency in global genomic DNA repair [67]. Both NER and base excision repair pathways can involve p53 via its ability to interact with components of the repair machinery (e.g., apurinic/apyrimidinic endonuclease and DNA polymerase β) [47].

p53 is a short-lived protein with a half-life of ~5–20 minutes in most types of cells studied [69]. It is regulated by posttranslational modifications (phosphorylation and acetylation) and is modulated by intracellular redox state [67]. Protein levels of p53 can rapidly increase several-fold after DNA damage, mainly by post-translational mechanisms. The elevation in p53 protein levels occurs through stabilization that is stimulated by its phosphorylation. Phosphorylation of serine-15 is a key response to DNA damage. The signal for DNA damage is transduced to p53 by DNA-PK, ATM, and ATR [53,54]. In an in vitro system, DNA-PK-mediated phosphorylation of p53 at serine-15 alleviates the inhibition by Mdm2 (and thus p53 degradation) and correlates with the stabilization of p53 and its activation as a transcription factor [67]. Other in vitro studies have shown that DNA DSBs result in serine-15 phosphorylation of p53 and stabilization through a process mediated by ATM [54]. Phosphorylation also regulates the interactions of individual p53 monomers. p53 can form homotetramers and must be in tetrameric form for sequence-specific DNA binding and transcriptional activation [67]. Tetramerization is stimulated by phosphorylation of serine-392. This phosphorylation increases 10-fold the association constant for the formation of p53 tetramers that bind DNA for its transcriptional regulation.

p53 is degraded rapidly in a ubiquitination-dependent proteasomal pathway. Mdm2 has a crucial role in this degradation pathway [53]. Mdm2 appears to function in a feedback loop to limit the duration or magnitude of the p53 response to DNA damage. Expression of the *Mdm2* gene is controlled by p53 through promoter regulation. Mdm2 binds to the N-terminal transcriptional activation domain of p53 and regulates the transactivation activity and stability of p53 by direct association. Mdm2 appears to possess ubiquitin ligase activity for p53 through the ubiquitin-conjugating enzyme E2. Stabilization of p53 is achieved through phosphorylation of serine-15, resulting in inhibition of formation of Mdm2-p53 complexes. ATM also regulates the stabilization of p53 through Mdm2 phosphorylation, thus preventing Mdm2-dependent p53 degradation and favoring p53 accumulation.

p53-mediated apoptosis is known to be induced by DNA SSBs [72], while the MRN-ATM network is usually associated with DNA DSB signaling [55]. There is exciting information on Xrcc1 activating polynucleotide kinase at sites of DNA SSBs, but this pathway functions in stimulating DNA repair [73]. Replication protein A (RPA) [74] might also have a role as a DNA SSB sensor leading ATM/ATR-p53-instructed apoptosis in mouse cortical neurons. RPA is nuclear protein known to be a single-strand DNA binding protein. RPA recruits ATR to the site of single-stranded DNA by binding to ATR-interacting protein, which forms a heterodimer complex with ATR [75]. The involvement of ATM and ATR in human neurons in response to DNA DSBs and SSBs has not been studied.

DNA Topoisomerase and Modeling DNA Damage-Induced Neuronal Death

The genotoxins camptothecin (CPT) and etoposide (ETOP) are used commonly to inhibit DNA topoisomerase 1 (Topo1) and DNA Topo2, respectively, as a stimulus for apoptosis. Derivatives of CPT and ETOP are used clinically as chemotherapeutic agents; their use is likely to become more frequent [76]. DNA topoisomerases remove torsional stress in the DNA double helix by introducing transient protein-bridged DNA breaks in one or both DNA strands during DNA replication and transcription [76,77]. CPT is thought to be an S-phase-specific anticancer agent that binds irreversibly to the DNA-Topo1 complex. This binding inhibits the re-ligation of DNA after cleavage by Topo1 and traps the enzyme in a covalent linkage with DNA [78]. In proliferating cells, CPT is thought to generate DNA strand breaks during DNA synthesis, suggesting that CPT should not be toxic to non-dividing cells such as neurons. However, CPT can also cause premature termination of transcription and depletion of cellular Topo1 through its ubiquitination and proteasomal degradation [77].

Topoisomerase inhibitors (e.g., CPT and ETOP) are potent inducers of apoptosis in cultured neurons [60,79,80,81] and in the neonatal mouse brain [60]. Sadly, in children and adults, a disconcerting side effect of anticancer chemotherapy protocols containing these compounds is cognitive impairment [82]. The biochemical and molecular pathways that mediate neuronal apoptosis induced by topoisomerase inhibition are

not well understood. Little is known about the effects of CPT and ETOP in neurons on DNA trapping, DNA strand break formation [60], and RNA synthesis [79]. CPT-induced neuronal death appears to involve caspase-3, cell cycle proteins, and p53 [60,80,81,83], but the details of the upstream signaling mechanisms (DNA damage signal transduction to p53) are unknown or sketchy at best, and possible brain maturity–related neuronal death mechanisms associated with vulnerability to these drugs are unknown completely.

Topo1 can be trapped onto DNA, inducing DNA SSBs by events other than CPT exposure, particularly by ROS, mitochondrial dysfunction, and cytoskeletal perturbations [84] – all events implicated in neonatal brain injury after HI. Topo1-DNA trapping is meaningful endogenously because a specific enzyme, tyrosyl-DNA phosphodiesterase 1 (TDP1), has evolved that functions specifically to release Topo1 from DNA [85]. This DNA repair enzyme is critical for facilitating DNA SSB repair and preventing the conversion of SSBs to DSBs [86]. Work on TDP1 shows that inefficient repair of DNA SSBs can cause human neuron degeneration [85]. TDP1 appears to be important in some neuron types because loss-of-function mutations in *TDP1* cause spinocerebellar ataxia with axonal neuropathy in humans [85]. TDP1 overexpression counteracts DNA-Topo1 cross-linking damage mediated by Topo1 inhibition in human embryonic kidney-293 cells [86] and by ROS-mediated DNA damage in yeast [87]; thus Topo1 and TDP1 may be targets for neuroprotection in neonatal HIE.

Molecular Regulation of Cortical Neuron Apoptosis Induced by DNA Damage

Neurons in the prenatal and newborn cerebral cortex are highly vulnerable to HIE. Exposure of rodent neurons to CPT and ETOP is described frequently as a DNA-damaging insult [88,89], and it has been believed that CPT and ETOP trigger the apoptosis in neurons by activation of DDR [79,89,90]. The nature of the mechanisms of CPT and ETOP toxicity in neurons has not been identified clearly, and comparisons in the DDR–cell death signaling pathways in immature and well-differentiated neurons are important for efficient neuroprotection [60,81].

p53 drives apoptosis of immature and differentiated cortical neurons through its rapid and prominent activation stimulated by DNA strand breaks induced by Topo1 and Topo2 inhibition [60]. Blocking p53-DNA transactivation with α-pifithrin protects very immature neurons; blocking p53-mitochondrial functions with pifithrin-μ protects differentiated neurons [60]. Mitochondrial death proteins are upregulated in apoptotic immature and differentiated neurons and have nonredundant proapoptotic functions; Bak is more dominant than Bax as an apoptosis effector in differentiated neurons. p53 phosphorylation is mediated by ATM kinase in mouse cortical neurons [60]. ATM inactivation is antiapoptotic, particularly in differentiated neurons, while inhibition of the nonreceptor tyrosine kinase c-Abl protects immature neurons but not differentiated neurons [60]. Cell death protein expression patterns in developing mouse forebrain are mostly similar to differentiating cortical neurons in culture. In developing mouse brain, DNA damage induces prominent p53 activation and apoptosis in cerebral cortex [60]. Thus DNA strand breaks in cortical neurons induce rapid p53-mediated apoptosis through the actions of upstream ATM and c-Abl kinases and downstream mitochondrial death proteins. This molecular network operates via variations depending on neuron maturity. The relevance of a neuron culture system for precisely identifying the molecular regulation of cortical neuron apoptosis is strengthened by the finding that CPT induces fulminant apoptosis in neonatal mouse cerebral cortex in vivo [60].

Apoptosis of Mouse and Human Neurons Is Morphologically and Biochemically Different

Preclinical data on drug mechanism–based ischemic neuroprotection repeatedly fails to translate in clinical trials, or the positive effects in humans are not nearly as robust as those seen in experimental settings [18,23,30]. For neonatal HIE, even therapeutic hypothermia has a far less robust effectiveness compared to rodent models in which the interanimal variability in the injury can be high and gender related [91]. One explanation for this translational problem is that neurodegeneration in the rodent CNS is not representative of neurodegeneration in the human CNS [92,93].

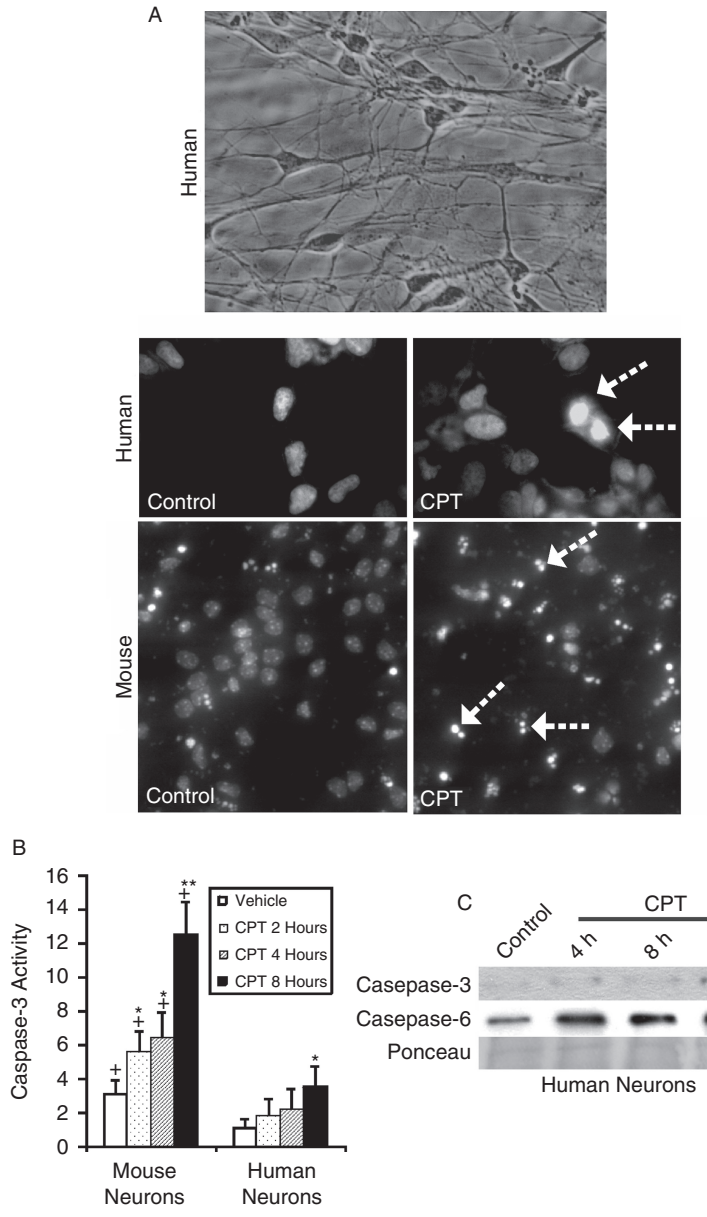


Figure 2.1 Human neurons and mouse neurons degenerate and die differently in cell culture. (A, top) Phase contrast microscopy of live human neurons generated by culturing human neural stem cells derived from the H9 human embryonic stem cell line. The human neurons are well differentiated and healthy and form a network with elaborate dendrites. (A, bottom) Differentiated human and mouse neurons were treated with 10 μM DNA-damaging agent camptothecin (CPT, a DNA topoisomerase 1 inhibitor) or vehicle (control) and then fixed after 24 hours and stained with DNA dye Hoechst 33258. The degenerating human neurons treated with CPT have a uniformly bright nonfragmented nucleus (arrows), while the degenerating mouse neurons treated with CPT have a nucleus that is fragmented into two or three round masses indicative of apoptosis (arrow).

(B) Caspase-3 activity, determined by biochemical colorimetric assay, is increased abruptly and robustly in mouse cortical neurons in a time-related manner after 10 μM CPT exposure. In contrast, human neurons have significantly less activation of caspase-3 activity than similarly cultured mouse neurons. Values (in units $\times 10^{-1}$) are mean ± SD ($n = 3$ different cultures). Significantly greater $^{*}P < 0.05$, $^{**}P < 0.001$ than control (same species comparison); $^{+}P < 0.01$ and $^{++}P < 0.001$ (time-matched comparison of mouse versus human neurons).

(C) Western blot for cleaved caspase-3 and cleaved caspase-6 in cell lysates of differentiated human neurons treated with DNA-damaging agent (10 μM CPT). Degenerating human neurons display only a modest increase in cleaved caspase-3, while cleaved caspase-6 accumulates abruptly and robustly by 4–8 hours, and the accumulation progresses through 16 hours. Ponceau S (protein-binding dye)–stained blot is shown as a loading control to verify equivalent protein lysate input per lane.

It is now possible to directly test the hypothesis that human and mouse neurodegeneration is different. Robust and healthy differentiated human neurons can be generated from human neuroprogenitors derived from human embryonic H9 stem cells (Figure 2.1A). When similarly cultured human cortical neurons and mouse cortical neurons (also derived from neural stem cells) are challenged with identical doses of DNA-damaging insult such as CPT, the nuclear morphology in the degenerating neurons is quite different in the human and mouse cells. In this paradigm, mouse neurons stereotypically die with classically apoptotic nuclear morphology (Figure 2.1A). In contrast, in human neurons, the nuclear chromatin condensation fails to form discrete round chromatin clumps (Figure 2.1A). This feature of degenerating human neurons has also been seen in vivo in postmortem adult spinal cord and midbrain [16,94] and in newborns with HIE [65]. Furthermore, caspase activation is different in human and mouse neurons exposed to CPT (Figure 2.1B). Mouse neurons typically respond

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to a lethal DNA-damaging insult by strongly activating caspase-3 (Figure 2.1B) [60,80,81]. In contrast, human neurons respond to a lethal DNA-damaging insult by strongly activating caspase-6 rather than caspase-3 (Figure 2.1B, C). Of additional importance, human neurons responding to a DNA-damaging insult rapidly and strongly activate the MRN complex, as seen by Nbs1 (nibrin) phosphorylation, while mouse neurons do not activate the MRN complex (Figure 2.2A).

The DNA Damage and Repair Responses in Neurons Are Species Dependent: Pig Neurons Are More Similar to Human Neurons than Are Mouse Neurons

It is also possible to test the hypothesis that DNA damage and DNA repair responses in human and animal (small and large) neurons are different. Mouse and pig neural stem cells can be isolated as described previously [95,96]. Human, mouse, and pig forebrain neuroprogenitors then can be cultured to differentiation under similar conditions and then exposed to identical insults, including DNA damage, excitotoxicity, and oxidative stress (Figure 2.2). These insults are thought to contribute to the pathogenesis of HIE [8,12,14,15]. A readout can be DNA SSB formation based on single-cell gel electrophoresis (comet assay) (Figure 2.2B, C).

The comet assay can profile the emergence of genomic DNA damage in neurons. The feasibility and innovative utility of the comet assay have been demonstrated in neuronal systems [97–99]. This assay is the only known method to track specific types of DNA lesions and DNA repair at the single-cell level (Figure 2.2C) because the DNA elutes out of the nucleus and appears, after staining for DNA, as a tail extending from the nucleus (Figure 2.2C). The assay is based on the fundamental principle that single-strand DNA elutes rapidly under alkaline conditions from cells onto filters [100]. This principle was then extended to the analysis of DNA damage in individual cells using gel electrophoresis [101]. The comet assay detects DNA SSBs at pH ~ 12, DNA DSBs at neutralized conditions, and DNA-DNA or DNA-protein cross-linking, and alkali-labile sites that cause SSBs under alkali conditions (pH > 12.6) and damage to purine and pyrimidine bases (AP sites) [98,99]. At pH conditions of 12.6 or higher, alkali-labile sites are converted SSBs, and thus a pH ≥ 13 maximizes the detection of alkali-labile sites as SSBs [100]. The sensitivity of the comet assay is exquisite, detecting one DNA strand break per 2×10^{10} Da of DNA in lymphocytes [97].

Mouse neurons have greater vulnerability than human and pig neurons to different types of physiologic challenges mimicking the insults seen in HI brain injury. After exposure to the DNA Topo1 inhibitor CPT, mouse neurons exhibit more DNA damage than human and pig neurons (Figure 2.2C, D). Similarly, mouse neurons show more DNA damage accumulation than human and pig neurons after exposure to NMDA glutamate receptor excitotoxicity, while human and pig neurons show similar responses (Figure 2.2E). Human and pig neurons also show similar responses to oxidative stress induced by H_2O_2, NO donors (sodium nitropruside and NONOate), and peroxynitrite (ONOO), while mouse neurons display the greatest injury (Figure 2.2F–H).

DNA repair activity in cells also can be evaluated using the comet assay. To this end, human, mouse, and pig neurons can be subjected to a low-dose DNA-damaging insult and then permitted to recover (Figure 2.3). The *comet moment* represents a calculation of the number of DNA SSBs in the comet tail. Human neurons displayed highly efficient DNA repair, as evidenced by a lower comet moment (Figure 2.3A). Comparatively, mouse neurons did not have efficient DNA repair in this paradigm (Figure 2.3B). Pig neurons had DNA repair efficiency closer to that of human neurons (Figure 2.3C). While these observation relate only to a small part of the comprehensive neuronal injury response, they allow for a critical rethinking of fundamental aspects of how neuronal injury and degeneration in neonatal HIE is modeled.

Corroborating Evidence for Human-Specific Neuronal Cell Death/Injury Mechanisms

Other independent evidence supports the premise that human neuron DDR and cell death could be different from neurons in other species such as rodents. For example, major differences exist in cell death–related genes. Murine and human *Bax, Fas*, and *Caspase-6* gene promoter activities are regulated

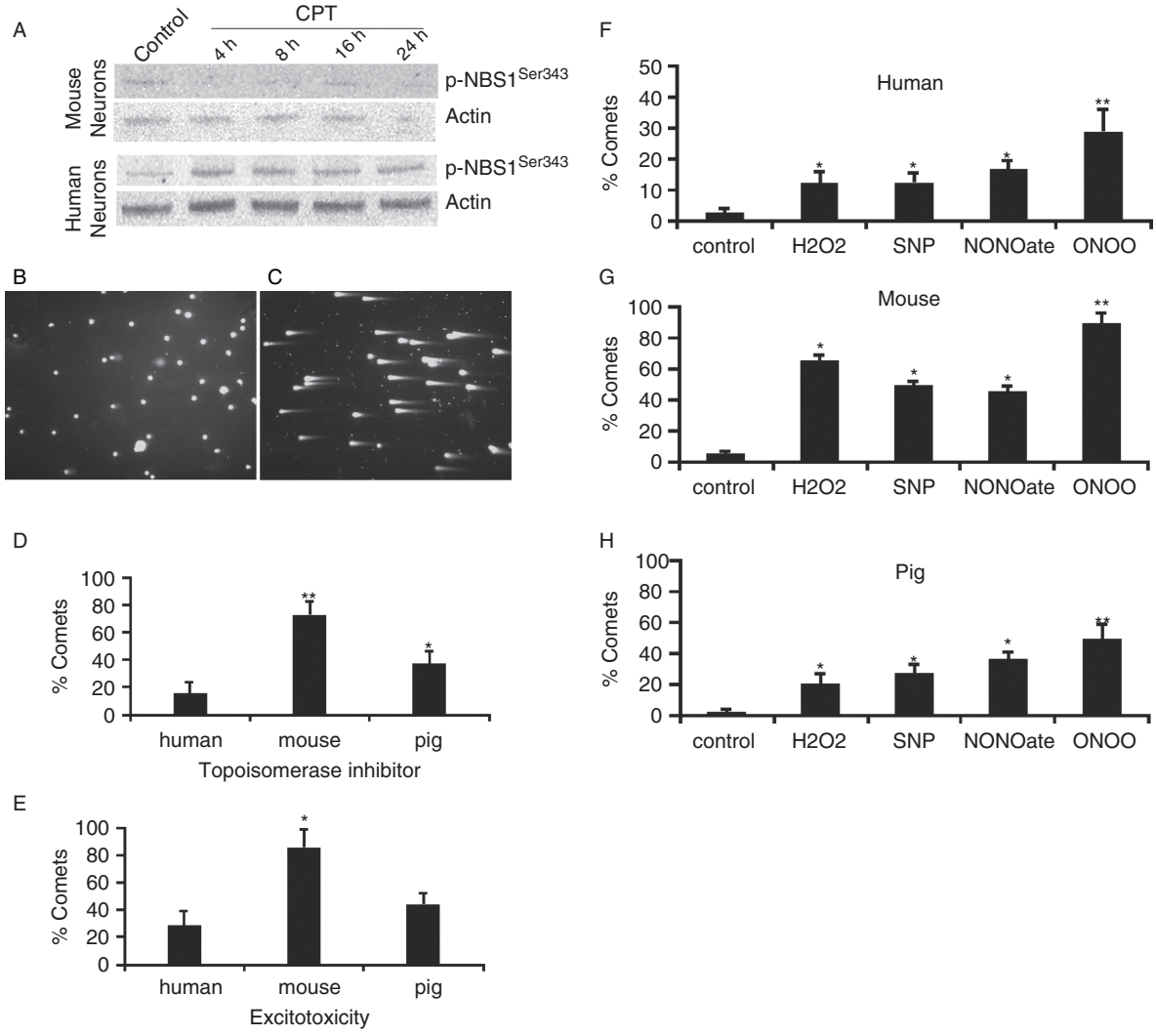


Figure 2.2 Human, mouse, and pig neurons respond differently to insults mimicking pathophysiologic events in neonatal HIE. (A) Differentiated human and mouse neurons treated with 10 μM DNA-damaging agent camptothecin (CPT) show different DNA-damaged sensor activation patterns, assessed by Western blotting for phosphorylated Nbs1 (nibrin). Mre11-Rad50-Nbs1 activation, shown by the phosphorylation of Nbs1, occurs in human neurons but not in mouse neurons. Western blots for β-actin are shown as loading controls to verify equivalent protein lysate input per lane. (B,C) Mouse neurons without (B) and with (C) DNA damage (DNA SSBs) as visualized by single-cell gel electrophoresis (the comet assay). Living, differentiated mouse cortical neurons were treated with vehicle (B) or 10 μM CPT (C) and subjected to alkaline comet assay and DNA staining with SYBR Green. Normal neurons with intact nuclear DNA appear to have round nuclei with no tails (B). In neurons with DNA SSBs (C), some of the DNA elutes out of the nucleus and appears as a tail, which gives the appearance of a comet. (D) Human, mouse, and pig neurons respond differently to DNA-damaging insults. Cultured differentiated neurons were challenged with 10 μM CPT for 8 hours and then harvested for comet assay. Values are mean ± SD.

The percentage of mouse neurons with DNA damage was significantly greater (**$P < 0.01$) than the percentages for human and pig neurons. Pig neurons were also significantly different from human neurons, but the level of significance was less (* $P < 0.05$) than for mouse neurons. (E) Human, mouse, and pig neurons respond differently to excitotoxicity by forming different levels of DNA damage. Cultured differentiated neurons were challenged with 75 μM NMDA for 30 minutes and then subjected to comet assay. Values are mean ± SD. The percentage of mouse neurons with DNA damage was significantly greater (*$P < 0.01$) than the percentages for human and pig neurons. Pig neuron response was not different from the human neuron response. (F–H) Human, mouse, and pig neurons respond differently to oxidative and nitrative stress. Cultured differentiated neurons were challenged with hydrogen peroxide (H_2O_2), nitric oxide donors (sodium nitroprusside [SNP] and NONOate), and peroxynitrite (ONOO) for 30 minutes and then subjected to comet assay. Values are mean ± SD. Human neurons (F), mouse neurons (G), and pig neurons (H) all developed DNA damage after exposures to ROS and RNS. All types of neurons were most sensitive to ONOO because more DNA damage was found in these groups. DNA damage accumulation in human and pig neurons was similar with exposure to H_2O_2, SNP, and NONOate (*$P < 0.05$), while mouse neurons had more severe DNA damage accumulation (*$p < 0.01$) than human and pig neurons.

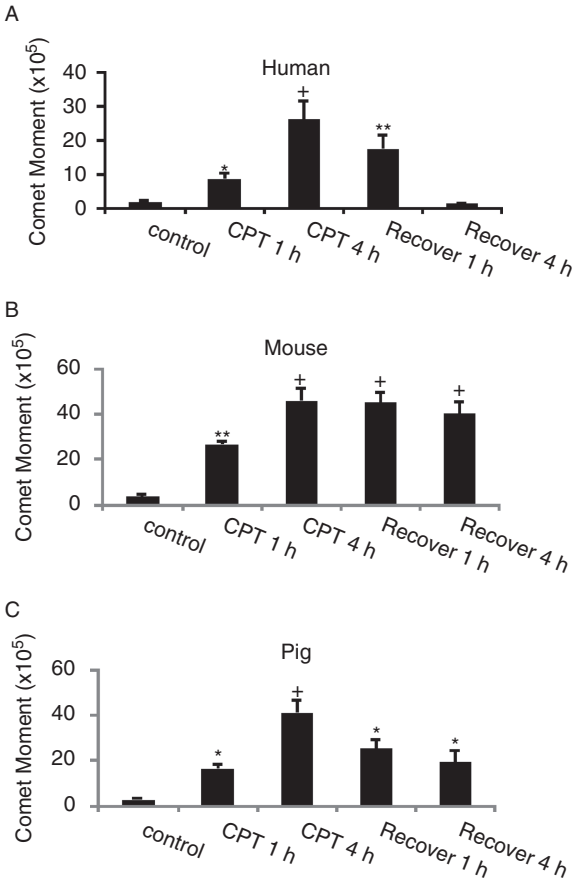


Figure 2.3 Human neurons have more efficient DNA SSB repair than mouse and pig neurons. Cultured human neurons (A), mouse neurons (B), and pig differentiated neurons (C) were challenged with 10 μM CPT for 1 or 4 hours, washed, allowed to recover for 1 or 4 hours, and then subjected to comet assay to determine levels of DNA SSB break repair as calculated by the comet moment (DNA intensity$_{tail}$ × tail area) [50,98]. Values are mean ± SD. Differentiated human neurons (A) accumulated significant levels of DNA damage (*$P < 0.05$, $^{+}P < 0.001$ compared to control) and showed efficient time-related repair of DNA SSBs (**$P < 0.01$). In contrast, mouse neurons suffered greater amounts of DNA damage than human neurons (**$P < 0.01$, $^{+}P < 0.001$ compared to control) and were not successful at repairing DNA damage over a 4-hour recovery period. Pig neurons also accumulated significant levels of DNA damage (*$P < 0.05$, $^{+}P < 0.001$ compared to control) and were significantly less successful at repairing DNA (*$P < 0.05$).

differently by p53 [102–104]. Other transcription factor (e.g., FOXA, HNF1A, HNF4A, and HNF6) DNA-binding events are 41–89% species specific for mouse versus human [105]. In rodent cells, the *Caspase-12* gene product functions in apoptosis induced by endoplasmic reticulum stress, but in human cells, the *Caspase-12* gene is a pseudogene or produces a truncated, protease-inactive protein [106]. Caspase substrates, for example, c-Abl, are also known to be species specific [107]. Moreover, human and mouse caspase-3 activation pathways are different [108], consistent with observations that caspase-3 activation is different in apoptotic human and mouse neurons (Figure 2.1). A number of major differences among mouse and human cells exist in chromatin vulnerability and DDR. There is almost no conservation of functional response elements for genes involved in DNA repair and DNA metabolism among human and rodents [109]. Also, the alternative splicing of the p53 C-terminus is different in human and mouse cells [110]. Repair of radiation-induced DNA SSBs is different in mouse and human cells [111]. Of additional significance to neonatal HIE, mouse and human fibroblasts have major differences in the ability to handle oxidative stress [112]. There is now evidence that human and mouse neurons manage oxidative stress, excitotoxicity, and DNA damage burden differently and that human neurons have a superior ability to repair DNA damage compared to mouse neurons (Figure 2.3). The capacity of pig neurons to manage oxidative stress, excitotoxicity, and DNA damage is far more similar to that of human neurons than this capacity of mouse neurons. The argument for human-specific neuronal injury and degeneration is strengthened by observations that mice with homozygous null mutations in *Atm* do not develop neuropathologic features consistent with human AT [113] and mice with human XP- and Cockayne syndrome–causing inactivating mutations in NER genes do not develop neuropathologic features of XP and Cockayne syndrome [114,115]. Lastly, mice harboring human gene mutations in *TDP1* causing spinocerebellar ataxia with axonal neuropathy do not develop a neurodegenerative disorder as in humans [116].

Implications for Human-Specific Neuronal Cell Injury and Death Mechanisms for Neonatal HIE

Uniquely hominid neural cell injury response, DDR, and cell death mechanisms would have major ramifications for experimental neuropathology and human CNS injury and disease modeling. It would confound translational studies and contribute to the lack of success of costly clinical trials. Vigilance and cynicism would be needed in extrapolating neuroprotection from model organisms to humans. While perhaps difficult to accept by some, this concept would provide needed incentive to move away from the status quo to make room for a

paradigm shift. The design of preclinical studies would need to be changed fundamentally. The preponderant reliance on mouse and rat as preclinical model organisms would need to be superannuated for more work on large animal models such as pig and macaque monkeys or other advanced nonhuman primates that likely have neuronal injury and neuropathologic outcomes more similar to those of humans [9–11,117] as well as similar DDR (Figures 2.2 and 2.3). In addition, drug candidates would need to be screened for neuroprotection in cultured human neurons derived from neural stem cells and induced pluripotent stem cells. Alternatively, chimeric rodents with major CNS cellular constituents humanized by human neural stem cells and human genes could be developed. If this concept of human-specific neurodegeneration is correct, then specific cellular mechanism–based therapeutics derived from rodent work is not likely to translate efficiently to humans.

The idea that neuronal injury and degenerative mechanisms could be specific for cells intended for long life, such as human neurons, ties into the concept of the cell death continuum [16,26,27,65] and adds a higher level of complexity to therapeutic strategies for neuroprotection. Cell viability during and after a human neuron sustains an insult is best interpreted as a complex balance between compensatory mechanisms (e.g., cell volume control, intracellular Ca^{2+} and Na^{+} management, metabolic activity, ion channel regulation, protein quality control, RNA stability, and DNA repair) and coincident cascades leading to cellular necrosis and apoptosis. The fate of the injured neuron will be determined by the relative contributions, efficiencies, and kinetics of a particular process. A human neuron that is designed and sculpted by evolution to have extended longevity (~80 years) is likely to invest extraordinary measures for cellular repair and conservation of viability. Rodent neurons, in contrast, are designed to live only about 2 years, and in terms of population biology, the individual organism is expendable. Thus measures for neuronal repair and conservation may be less propitious. Factors influencing neuron decision making are numerous, including, but not limited to, type of neuron, metabolic activity, mitochondrial biology, propinquity to cell cycle exiting, intrinsic programs for cell senescence, cell maturity, ion channel expression signatures, neurotropin dependence, and efficiency of DNA repair and unfolded protein response [16,27,65]. A single mechanism-based drug therapeutic intervention may modulate one process without influencing other pathways or having opposing actions on other pathways. Interestingly, the reason for the efficacy of therapeutic hypothermia might be because it is a very broad-spectrum and pleiotropic intervention that is not likely to be reliant on a single mechanistic target for therapeutic activity.

References

1. Volpe JJ. *Neurology of the Newborn*, 4th ed. Philadelphia: Saunders, 2001: 912.
2. Wu TW, Backstrand KH, Zhao S, et al. Declining diagnosis of birth asphyxia in California: 1991–2000. *Pediatrics* 2004; **114**: 1584–90.
3. Johnston MV, Hoon AH. Cerebral palsy. *NeuroMolecular Med* 2006; **8**: 435–50.
4. Dilenge M-E, Majnemer A, Shevell MI. Long-term developmental outcome of asphyxiated term neonates. *J Child Neurol* 2001; **16**: 781–92.
5. Graham EM, Ruis KA, Hartman AL, et al. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008; **199**: 587–95.
6. Hsia T-Y, Gruber PJ. Factors influencing neurologic outcome after neonatal cardiopulmonary bypass: what we can and cannot control. *Ann Thorac Surg* 2006; **81**: S2381–88.
7. Maller AI, Hankins LL, Yeakley JW, Butler IJ. Rolandic type cerebral palsy in children as a pattern of hypoxic-ischemic injury in the full-term neonate. *J Child Neurol* 1998; **13**: 313–21.
8. Ferriero DM. Neonatal brain injury. *N Engl J Med* 2004; **351**: 1985–95.
9. Martin LJ, Brambrink A, Koehler RC, Traystman RJ. Primary sensory and forebrain motor systems in the newborn brain are preferentially damaged by hypoxia-ischemia. *J Comp Neurol* 1997; **377**: 262–85.
10. Martin LJ, Brambrink A, Koehler RC, Traystman RJ. Neonatal asphyxic brain injury is neural system preferential and targets sensory-motor networks. In Stevenson DK, Sunshine P, eds., *Fetal and Neonatal Brain Injury: Mechanisms, Management, and the Risks of Practice*, 2nd edn. New York: Oxford University Press, 1997: 374–99.
11. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol* 1972; **12**: 246–76.
12. Johnston MV, Nakajima W, Hagberg H. Mechanisms of hypoxic neurodegeneration in the developing brain. *Neuroscientist* 2002; **8**: 212–20.
13. Martin LJ. Mechanisms of brain damage in animal models of hypoxia-ischemia in newborns. In Stevenson

DK, Benitz WE, Sunshine P, eds., *Fetal and Neonatal Brain Injury: Mechanisms, Management, and the Risks of Practice*, 3rd edn. New York: Oxford University Press, 2003: 30–57.

14. McQuillen PS, Ferriero DM. Selective vulnerability in the developing central nervous system. *Pediatr Neurol* 2004; **30**: 227–35.
15. Blomgren K, Hagberg H. Free radicals, mitochondria, and hypoxia-ischemia in the developing brain. *Free Rad Biol Med* 2006; **40**: 388–97.
16. Martin LJ. Mitochondrial and cell death mechanisms in neurodegenerative diseases. *Pharmaceuticals* 2010; **3**: 839–915.
17. Northington FJ, Graham EM, Martin LJ. Apoptosis in perinatal hypoxic-ischemic brain injury: how important is it and should it be inhibited? *Brain Res Rev* 2005; **50**: 244–57.
18. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy. *Cochrane Database of Systematic Reviews* 2012; **7**: CD006817. doi:10.1002/14651858.CD006817.pub3
19. Shah PS. Hypothermia: a systemic review and meta-analysis of clinical trials. *Semin Fetal Neonatal Med* 2010; **15**: 238–46.
20. Wachtel EV, Hendricks-Munzo KD. Current management of the infant who presents with neonatal encephalopathy. *Curr Probl Adolesc Health Care* 2011; **4**: 132–53.
21. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med* 2015; **372**: 1898–1908.
22. Haaland K, Loberg EM, Steen PA, Thoresen M. Posthypoxic hypothermia in newborn piglets. *Pediatr Res* 1997; **41**: 505–12.
23. Agnew DM, Koehler RC, Guerguerian AM, et al. Hypothermia for 24 hours after asphyxic cardiac arrest in piglets provides striatal neuroprotection that is sustained 10 days after rewarming. *Pediatr Res* 2003; **54**: 1–10.
24. Xiong M, Cheng GQ, Ma SM, et al. Post-ischemic hypothermia promotes generation of neural cells and reduces apoptosis by Bcl-2 in the striatum of neonatal rat brain. *Neurochem Int* 2011; **58**: 625–33.
25. Fukui O, Kinugasa Y, Fukuda A, et al. Post-ischemic hypothermia reduced IL-18 expression and suppressed microglial activation in the immature brain. *Brain Res* 2006; **1121**: 35–45.
26. Martin LJ, Al-Abdulla NA, Brambrink AM, et al. Neurodegeneration in excitotoxicity, global cerebral ischemia, and target deprivation: a perspective on the contributions of apoptosis and necrosis. *Brain Res Bull* 1998; **46**: 281–89.
27. Martin LJ. Neuronal cell death in nervous system development, disease, and injury. *Int J Mol Med* 2001; **7**: 455–78.
28. Wang B, Armstrong JS, Lee J-H, et al. Rewarming from therapeutic hypothermia induces cortical neuron apoptosis in a swine model of neonatal hypoxic-ischemic encephalopathy. *J Cereb Blood Flow Metab* 2015; **35**: 781–93.
29. Wang B, Armstrong JS, Reyes M, et al. White matter apoptosis is increased by delayed hypothermia and rewarming in a neonatal piglet model of hypoxic ischemic encephalopathy. *Neuroscience* 2016; **316**:296–310.
30. Besancon E, Guo S, Lok J, et al. Beyond NMDA and AMPA glutamate receptors: emerging mechanisms for ionic imbalance and cell death in stroke. *Trends Pharmacol Sci* 2008; **29**: 268–75.
31. Martin LJ. DNA damage and repair: relevance to mechanisms of neurodegeneration. *J Neuropathol Exp Neurol* 2008; **67**: 377–87.
32. Narasimhaiah R, Tuchman A, Lin SL, Naegele JR. Oxidative damage and defective DNA repair is linked to apoptosis of migrating neurons and progenitors during cerebral cortex development in Ku70-deficient mice. *Cerebral Cortex* 2005; **15**: 696–97.
33. Kraemer KH, Patronas NJ, Schiffmann R, et al. Xeroderma pigmentosum, trichothiodystrophy and cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience* 2007; **145**: 1388–96.
34. Rao KS. Genomic damage and its repair in young and aging brain. *Mol Neurobiol* 1993; **7**: 23–48.
35. Shiloh Y. ATM and related protein kinases: safeguarding genome integrity. *Nat Rev Cancer* 2003; **3**: 155–68.
36. McKinnon PJ. ATM and the molecular pathogenesis of ataxia telangiectasia. *Annu Rev Pathol* 2012; **7**: 303–21.
37. Verhagen MMM, Martin J-J, van Deuren M, et al. Neuropathology in classical and variant ataxia telangiectasia. *Neuropathology* 2012; **32**: 234–44.
38. Englander EW, Greeley GH, Wang G, et al. Hypoxia-induced mitochondrial and nuclear DNA damage in rat brain. *J Neurosci Res* 1999; **58**: 262–69.
39. Ferrer I, Tortosa A, Macaya A, et al. Evidence of nuclear DNA fragmentation following hypoxia-ischemia in the infant rat brain, and transient forebrain ischemia in the adult gerbil. *Brain Pathol* 1994; **4**: 115–22.
40. Hill IE, MacManus JP, Rasquinha I, Tuor UI. DNA fragmentation indicative of apoptosis following

unilateral cerebral hypoxia-ischemia in the neonatal rat. *Brain Res* 1995; **676**: 398–403.

41. de Torres C, Munell F, Ferrer I, et al. Identification of necrotic cell death by the TUNEL assay in the hypoxic-ischemic neonatal rat brain. *Neurosci Lett* 1997; **230**: 1–4.
42. Portera-Cailliau C, Price DL, Martin LJ. Excitotoxic neuronal death in the immature brain is an apoptosis-necrosis morphological continuum. *J Comp Neurol* 1997; **378**: 70–87.
43. MacManus JP, Fliss H, Preston E, et al. Cerebral ischemia produces laddered DNA fragments distinct from cardiac ischemia and archetypal apoptosis. *J Cereb Blood Flow Metab* 1999;**19**: 502–10.
44. Huang D, Shenoy A, Cui J, et al. In situ detection of AP sites and DNA strand breaks bearing 3'-phosphate termini in ischemic mouse brain. *FASEB J* 2000; **14**: 407–17.
45. Lok J, Martin LJ. Rapid subcellular redistribution of bax precedes caspase-3 and endonuclease activation during excitotoxic neuronal apoptosis. *J Neurotrauma* 2002; **19**: 815–28.
46. Gane BD, Bhat V, Rao R, et al. Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled trial. *J Trop Pediatr* 2014; **60**: 134–40.
47. Norbury CJ, Hickson ID. Cellular responses to DNA damage. *Annu Rev Pharmacol Toxicol* 2001; **41**: 367–401.
48. Lindahl T. Instability and decay of the primary structure of DNA. *Nature* 1993; **362**: 709–15.
49. Juedes MJ, Wogen GN. Peroxynitrite-induced mutation spectra of pSP189 following replication in bacteria and in human cells. *Mutat Res* 1996; **3349**: 51–61.
50. Martin LJ, Liu Z. DNA damage profiling in motor neurons: a single-cell analysis by comet assay. *Neurochem Res* 2002; **27**: 1093–1104.
51. Polyak K, Xia Y, Zweier JL, et al. A model for p53-induced apoptosis. *Nature* 1997; **389**: 300–5.
52. Kastan MB, Lim D-S. The many substrates and functions of ATM. *Nat Rev Mol Cell Biol* 2000; **1**: 179–86.
53. Shangary S, Brown KD, Adamson AW, et al. Regulation of DNA-dependent protein kinase activity by ionizing radiation-activated Abl kinase is an ATM-dependent process. *J Biol Chem* 2000; **275**: 30161–68.
54. Nakagawa K, Taya Y, Tamai K, Yamaizumi, M. Requirement of ATM in phosphorylation of the human p53 protein at serine 15 following DNA double-strand breaks. *Mol Cell Biol* 1999; **19**: 2828–34.
55. Lee Y, Chong MJ, McKinnon PJ. Ataxia telangiectasia mutated-dependent apoptosis after genotoxic stress in the developing nervous system is determined by cellular differentiation status. *J Neurosci* 2001; **21**: 6687–93.
56. Kharbanda S, Pandey P, Yamauchi T, et al. Activation of MEK kinase 1 by the c-Abl protein tyrosine kinase in response to DNA damage. *Mol Cell Biol* 2000; **20**: 4070–89.
57. Lee J-H, Paull TT. Direct activation of the ATM protein kinase by the Mre11/Rad50/Nbs1 complex. *Science* 2004; **304**: 93–96.
58. Shiloh Y. The ATM-mediated DNA-damage response: taking shape. *Trends Biochem Sci* 2006; **31**: 402–10.
59. Gorodetsky E, Calkins S, Ahn J, Brooks PJ. ATM, the Mre11/Rad50/Nbs1 complex, and topoisomerase 1 are concentrated in the nucleus of Purkinje neurons in the juvenile human brain. *DNA Repair* 2007; **6**: 1698–1707.
60. Martin LJ, Liu Z, Pipino J, et al. Molecular regulation of DNA damage-induced apoptosis in neurons of cerebral cortex. *Cerebral Cortex* 2009; **19**: 1273–93.
61. Martin LJ, Kaiser A, Yu JW, et al. Injury-induced apoptosis of neurons in adult brain is mediated by p53-dependent and p53-independent pathways and requires Bax. *J Comp Neurol* 2001; **433**: 299–311.
62. Martin LJ, Liu Z. Injury-induced spinal motor neuron apoptosis is preceded by DNA single-strand breaks and is p53- and Bax-dependent. *J Neurobiol* 2002; **50**: 181–97.
63. Martin LJ, Price AC, McClendon K, et al. Early events in target deprivation/axotomy induced neuronal apoptosis in vivo: oxidative stress, DNA damage, p53 phosphorylation, and subcellular redistribution of death proteins. *J Neurochem* 2003; **85**: 234–47.
64. Martin LJ, Chen K, Liu Z. Adult motor neuron apoptosis is mediated by nitric oxide and Fas death receptor linked to DNA damage and p53 activation. *J Neurosci* 2005; **25**: 6449–59.
65. Northington F, Chavez-Valdez R, Martin LJ. Neuronal cell death in neonatal hypoxia-ischemia. *Ann Neurol* 2011; **69**: 743–58.
66. Nijboer CH, Heijnen CJ, van der Kooij MA, et al. Targeting the p53 pathway to protect the neonatal ischemic brain. *Ann Neurol* 2011; **70**: 255–64.
67. Giaccia AJ, Kastan MB. The complexity of p53 modulation: emerging patterns from divergent signals. *Genes Dev* 1998; **12**: 2973–83.
68. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell* 1997; **88**: 323–31.
69. Vogelstein B, Kinzler KW. p53 function and dysfunction. *Cell* 1992; **70**: 523–36.

70. Slack RS, Belliveau DJ, Rosenberg M, et al. Adenovirus-mediated gene transfer of the tumor suppressor, p53, induces apoptosis in postmitotic neurons. *J Cell Biol* 1996; **135**: 1085–96.
71. Cregan SP, Arbour NA, MacLaurin JG, et al. p53 activation domain 1 is essential for PUMA upregulation and p53-mediated neuronal cell death. *J Neurosci* 2004; **24**: 10003–12.
72. Hsiang YH, Hertzberg R, Hecht S, Liu LF. Camptothecin induced protein-linked DNA breaks via mammalian DNA topoisomerase I. *J Biol Chem* 1985; **260**: 14873–78.
73. Whitehouse CJ, Taylor RM, Thisthlethwaite A, et al. XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair. *Cell* 2001; **104**: 107–17.
74. Binz SK, Sheehan AM, Wold MS. Replication protein A phosphorylation and the cellular response to DNA damage. *DNA Repair* 2004; **3**: 1015–24.
75. Zou L, Elledge SJ. Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science* 2003; **300**: 1542–48.
76. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions – colorectal cancer and beyond. *Oncologist* 2001; **6**: 66–80.
77. Nieves-Neira W, Pommier Y. Apoptotic response to camptothecin and 7-hydroxystaurosporine (UCN-01) in the 8 human breast cancer cell lines of the NCI anticancer drug screen: multifactorial relationships with topoisomerase 1, protein kinase C, Bcl-2, p53, MDM-2 and caspase pathways. *Int J Cancer* 1999; **82**: 396–404.
78. Bendixen C, Thomsen B, Alsner J, Westergaard O. Camptothecin-stabilized topoisomerase I-DNA adducts cause premature termination of transcription. *Biochemistry* 1990; **29**: 5613–19.
79. Morris EJ, Geller HM. Induction of neuronal apoptosis by camptothecin, an inhibitor of DNA topoisomerase-I: evidence for cell cycle-independent toxicity. *J Cell Biol* 1996; **134**: 757–70.
80. Lesuisse C, Martin LJ. Long term culture of mouse cortical neurons as a model for neuronal development, aging, and death. *J Neurobiol* 2002; **51**: 9–23.
81. Lesuisse C, Martin LJ. Immature and mature cortical neurons engage different apoptotic mechanisms involving caspase-3 and the MAP kinase pathway. *J Cereb Blood Flow Metab* 2002; **22**: 935–50.
82. Riva D, Massimino M, Giorgi C, et al. Cognition before and after chemotherapy alone in children with chiasmatic-hypothalamic tumors. *J Neurooncol* 2009; **92**: 49–56.
83. Stefanis L, Park DS, Friedman WJ, Greene LA. Caspase-dependent and -independent death of camptothecin-treated embryonic cortical neurons. *J Neurosci* 1999; **19**: 6235–47.
84. Sordet O, Khan QA, Pommier Y (2004) Apoptotic topoisomerase I-DNA complexes induced by oxygen radicals and mitochondrial dysfunction. *Cell Cycle* 2004; **3**: 1095–97.
85. Takashima H, Boerkoel CF, Johns J. Mutation of TDP1, encoding a topoisomerase I-dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. *Nat Genet* 2002; **32**: 267–72.
86. Barthelmes HU, Habermeyer M, Christensen MO, et al. TDP1 overexpression in human cells counteracts DNA damage mediated by topoisomerase I and II. *J Biol Chem* 2004; **279**: 55618–25.
87. Hassine SB, Arcangioli (2009) Tdp1 protects against oxidative DNA damage in non-dividing fission yeast. *EMBO J* 2009; **28**: 632–40.
88. Keramaris E, Stefanis L, MacLaurin J, et al. Involvement of caspase 3 in apoptotic death of cortical neurons evoked by DNA damage. *Mol Cell Neurosci* 2000; **15**: 368–79.
89. Park DS, Morris EJ, Padmanabhan J, et al. Cyclin-dependent kinases participate in death of neurons evoked by DNA-damaging agents. *J Cell Biol* 1998; **143**: 457–67.
90. Endokido Y, Araki T, Tanaka K, et al. Involvements of p53 in DNA strand break-induced apoptosis in postmitotic CNS neurons. *Eur J Neurosci* 1996; **8**: 1812–21.
91. Burnsed JC, Chavez-Valdez R, Shanaz-Hossain M, et al. Hypoxia-ischemia and therapeutic hypothermia in the neonatal mouse brain- a longitudinal study. *PLoS One* 2015;**10**(3): e0118889. doi:10.1371/journal.pone.0118889.
92. Martin LJ, Liu Z. Opportunities for neuroprotection in ALS using cell death mechanism rationales. *Drug Discov Today Dis Models* 2004; **1**: 135–43.
93. Institute of Medicine. *Neurodegeneration: Exploring Commonalities across Diseases. Workshop Summary*. Washington, DC: National Academies Press, 2013: 93.
94. Martin LJ. Neuronal death in amyotrophic lateral sclerosis is apoptosis: possible contribution of a programmed cell death mechanism. *J Neuropathol Exp Neurol* 1999; **58**: 459–71.
95. Liu Z, Martin LJ. The olfactory bulb core is a rich source of neural progenitor and stem cells in adult rodent and human. *J Comp Neurol* 2003; **459**: 368–91.
96. Martin LJ, Katzenelson A, Koehler PC, Chang Q. The olfactory bulb in newborn piglet is a reservoir of neural stem and progenitor cells. *PLoS One* 2013; **8**(11): e81105. doi: 10.1371/journal.pone

97. Lai H, Singh NP. Acute low-intensity microwave exposure increased DNA single-strand breaks in rat brain cells. *Bioelectromagnetics* 1995; **16**: 207–10.

98. Liu Z, Martin LJ. Isolation of mature spinal motor neurons and single cell analysis using the comet assay of early low-level DNA damage induced in vitro and in vivo. *J Histochem Cytochem* 2001; **49**: 957–72.

99. Martin LJ, Liu Z. DNA damage profiling in motor neurons: a single-cell analysis by comet assay. *Neurochem Res* 2002; **27**: 1093–1104.

100. Kohn KW. Principles and practice of DNA filter elution. *Pharmacol Ther* 1991; **49**: 55–77.

101. Ostling O, Johanson KJ. Microelectrophoretic study of radiation-induced DNA damage in individual mammalian cells. *Biochem Biophys Res Commun* 1984; **123**: 291–98.

102. Schmidt T, Korner K, Karsunky H, et al. The activity of the murine Bax promoter is regulated by Sp1/3 and E-box binding proteins but not by p53. *Cell Death Diff* 1999; **6**: 873–82.

103. Igata E, Inoue T, Ohtani-Fujita N, et al. Molecular cloning and functional analysis of the murine bax gene promoter. *Gene* 1999; **238**: 407–15.

104. Horvath MM, Wang X, Resnick MA, Bell DA. Divergent evolution of human p53 binding sites: cell cycle versus apoptosis. *PLoS Genet* 2007; **3**(7): e127. doi10.1371/journal.pgen.0030127

105. Odom DT, Dowell RD, Jacobsen ES, et al. Tissue-specific transcriptional regulation has diverged significantly between human and mouse. *Nat Genet* 2007; **39**: 730–32.

106. Fischer H, Koenig U, Eckhart L, Tschachler E. Human caspase 12 has acquired deleterious mutations. *Biochem Biophys Res Commun* 2002; **293**: 722–26.

107. Ussat S, Werner U-E, Adam-Klages SA. Species differences in the usage of several caspase substrates. *Biochem Biophys Res Commun* 2002; **297**: 1186–90.

108. Kerr LE, Birse-Archbold J-LA, Simon A, et al. Differential regulation of caspase-3 by pharmacological and developmental stimuli as demonstrated using humanized caspase-3 mice. *Apoptosis* 2004; **9**: 739–47.

109. Jegga AG, Inga A, Menendez D, et al. Functional evolution of the p53 regulatory network through its target response elements. *Proc Natl Acad Sci USA* 2008; **105**: 944–9.

110. Laverdiere M, Beaudoin J, Lavigueur A. Species-specific regulation of alternative splicing in the C-terminal region of the p53 tumor suppressor gene. *Nucleic Acids Res* 2000; **28**: 1489–97.

111. Banuelos CA, Banath JP, MacPhail SH, et al. Mouse but not human embryonic stem cells are deficient in rejoining of ionizing radiation-induced DNA double-strand breaks. *DNA Repair* 2008; **7**: 1471–83.

112. Parrinello S, Samper E, Krtolica A, et al. Oxygen sensitivity severely limits the replicative lifespan of murine fibroblasts. *Nat Cell Biol* 2003; **5**: 741–47.

113. Barlow C, Hirostune S, Paylor R, et al. ATM-deficient mice: a paradigm of ataxia telangiectasia. *Cell* 1997; **86**: 159–71.

114. van der Horst GTJ, van Steeg H, Berg RJW, et al. Defective transcription-coupled repair in Cockayne syndrome B mice is associated with skin cancer. *Cell* 1997; **89**: 425–35.

115. Jaarsma D, van der Pluijm I, de Waard MC, et al. Age-associated neuronal degeneration: complementary roles of nucleotide excision repair and transcription-coupled repair in preventing neuropathology. *PLoS Genet* 2011; **7**(12): e1002405. doi:10.1371/journal.pgen.1002405

116. Hirano R, Interthal H, Huang C. et al. Spinocerebellar ataxia with axonal neuropathy: consequence of a Tdp1 recessive neomorphic mutation? *EMBO J* 2007; **26**: 4732–43.

117. Yang H, Wang G, Sun H, et al. Species-dependent neuropathology in transgenic SOD1 pigs. *Cell Res* 2014; **24**: 464–81.

Chapter 3

Cellular and Molecular Biology of Hypoxic-Ischemic Encephalopathy

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Introduction

Acute hypoxic-ischemic brain injury occurring around the time of birth is a major cause of death and disability. The exact timing and the preceding course of events are often not known but play a crucial role in the pathogenesis, regional susceptibility, and injury severity in humans [1,2], requiring different treatment approaches. The dynamic nature of the developing brain requires the use of age-appropriate models to advance our understanding of both the injurious mechanisms and the means to ameliorate injury and enhance repair.

Several aspects of injury to the immature brain caused by experimental hypoxia-ischemia (HI) [3] or focal stroke [4,5] in animals have been reviewed extensively, including the role of age [6–8], blood flow regulation and energy metabolism [9], inflammation [7,10], and intracellular injury mechanisms and neuronal death [10,11]. We will review emerging concepts in the cellular and molecular basis of injury, including the status of the neurovascular unit and blood-brain barrier, neuroinflammation, adaptive intracellular mechanisms, neuroprotection, and brain repair.

Energy Failure and Early Intracellular Injury

The role of disruption of cerebral blood flow and failure of mitochondrial ATP production in initiating injury after HI has been reviewed by Vannucci [12] and Perlman [13]. Extracellular accumulation of excitatory amino acids (EAAs) and overactivation of EAA receptors and calcium (Ca^{2+})–mediated intracellular injury, which depends in part on failure of ATP-dependent processes, are important factors in early injury progression [14,15]. Recent studies have demonstrated the importance of the link between the *N*-methyl-D-aspartate (NMDA) receptor, postsynaptic density (PSD)–93 and PSD-95 membrane-associated guanylate kinases (MAGUKs), and neuronal nitric oxide synthase (nNOS) in HI injury and the role of Src family kinase activation [16] in neuronal injury. Oxygen free-radical generation leads to lipid peroxidation and DNA/RNA fragmentation [17]. Further studies confirming that reactive oxygen species play a major role in HI injury have been conducted in mice with manipulated CuZn-superoxide dismutase (SOD) and glutathione peroxidase (Gpx) [18] activities. Selective nNOS blockade during HI has also been shown to reduce neuronal damage in the basal ganglia of neonatal mice and fetal sheep [19,20].

Neurovascular Unit and Blood-Brain Barrier (BBB) Permeability

It has become apparent that neuronal survival depends on the microenvironment and cellular interactions leading to the concept of the "neurovascular unit." The neurovascular unit includes brain microvascular endothelium and the BBB as a whole: glia, neurons, and extracellular matrix, along with the complexities of cell-cell communication within the brain and the cross-talk between the systemic circulation and the brain. The BBB, which is a primary mechanism for the maintenance of brain homeostasis and a critical mediator of brain injury after stroke, is controlled by a number of different and partially independent components, including the extracellular matrix, tight junctions, pericytes, and astrocyte endfoot processes [21–23].

In adults, the BBB is disrupted after stroke, with the temporal-spatial extent depending on both the systemic and local inflammatory reactions [24]. Peripheral leukocytes contribute to the opening of the BBB [24], the release of toxic mediators [25], and basal lamina degradation [26]. Leukocyte extravasation occurs through several discrete steps and depends on a number of integrins, adhesion molecules, and chemokine gradients in the brain (reviewed in Vexler et al. [10]). Microglia, locally and systemically produced cytokines,

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and matrix metalloproteinase activation also potentiate damage to BBB constituents [26–28].

The early postnatal BBB is not as permeable as once thought. Entrance of proteins is restricted by tight junctions early in embryonic development [29]. By birth, the BBB is functional with no fenestrations [30]. Regulation of the BBB is age dependent but does not change linearly with brain maturation. The BBB is more permeable in P21 than in P1 pups following intrastriatal injections of the inflammatory cytokines interleukin 1β (IL-1β) or tumor necrosis factor α (TNF-α) [31]. The mechanisms that keep the BBB relatively preserved are not well understood but may be related to the very limited transmigration of neutrophils [32,33] and monocytes [34] in the injured parenchyma during the neonatal period. Extracellular matrix degradation and matrix metallopeptidase 9 (MMP-9) activation are injurious acutely after HI in P9 pups [35], but inhibition of metalloproteinases after neonatal rodent HI has had inconsistent effects [36].

Neuroinflammation

Microglial Cells and Astrocytes

Microglial cells are the resident macrophages of the central nervous system (CNS), primarily responsible for maintenance of the microenvironment; production of cytokines, chemokines, and growth factors; and removal of debris. For a long time activated microglial cells were viewed as uniformly injurious in acute and chronic neurodegenerative conditions [37]. They were also believed to adversely affect repair in adult stroke [38]. This view is being reconsidered based on accumulating data regarding the ability of these cells to support neurogenesis in vitro and in vivo [39] and minimize (rather than enhance) neurodegeneration [40].

Microglia, which populate the developing brain by birth, can provoke the death of neurons during the period of synaptogenesis rather than clear the debris of neurons dying by caspase-3-dependent mechanisms [41]. Microglial activation is rapid in neonates and is seen after transient focal ischemia [34,42], hypoxia-ischemia [33,43] and excitotoxic injury [44]. A broad range of anti-inflammatory drugs that target various intracellular inflammatory pathways in microglial cells, such as minocycline [45], iminobiotin [46], chloroquine [44], and aminoguanidine [47], show varying degrees of protection against acute injury in neonates. In a growing number of cases, protection by anti-inflammatory drugs occurs through antiapoptotic mechanisms without directly affecting inflammatory pathways [48].

Astrocytes contribute to neuronal homeostasis and function, play an immune-modulating role in the brain, and are an important part of the BBB [49]. After cerebral ischemia, activated astrocytes have the potential to harm the ischemic brain [50] as a major source of inflammatory mediators such as cytokines, chemokines [51,52], and inducible nitric oxide synthase (iNOS) [52,53]. At the same time, death of astrocytes in the ischemic core following cerebral ischemia may have important implications for excitotoxicity, antioxidative defenses, and the status of the BBB. This is evidenced by larger cortical infarct volumes in glial fibrillary acidic protein (GFAP)–null mice compared with their wild-type littermates, suggesting a beneficial role of GFAP during ischemia [54]. While mechanisms of astrocytic death in the immature postischemic brain are not well understood, at least a subpopulation of these cells is dying in a caspase-3-dependent way. Caspase-3-dependent death of GFAP-immunoreactive astrocytes is seen early after permanent middle cerebral artery (MCA) occlusion and transient central cerebral artery (CCA) occlusion in P7 rats [55,56] and is associated with increased Bax expression cytochrome c release from mitochondria, DNA fragmentation, and poly(ADP-ribose) polymerase (PARP-1) cleavage [57,58].

Other Inflammatory Cells

Infiltration of T and B cells following neonatal HI and focal stroke may be less profound [33] or more transient [55] than in adult stroke. There is, however, increasing evidence for the injurious role of mast cells after neonatal HI [59], excitotoxic injury [60], and focal stroke [61]. Agents that inhibit histamine release and degranulation of mast cells have been shown to diminish brain injury following ischemic insults [59] and after intracerebral injections of the glutamatergic analogue ibotenate [60]. Mast cell–deficient neonatal mice have smaller injury size [62]. The injurious effects of mast cells have been shown to depend on transforming growth factor β (TGF-β) and IL-9 [63].

Cytokines and Chemokines

Cytokines are polypeptides that affect long-term developmental events such as proliferation, differentiation, and cell survival, as well as short-term events

such as modulation of synaptic activity and inflammatory responses. They are expressed by cells in the immune system and also by resident brain cells, including glia and neurons. Cytokines are upregulated rapidly in the neonatal brain after HI and focal stroke. IL-1β, IL-6, and TNF-α exacerbate local inflammation by activating astrocytes and microglia and inducing a number of other cytokines and chemokines in neonatal models of HI [64], excitotoxicity [65], and focal ischemia [66]. Pretreatment with inflammatory Th1 cytokines IL-1β, IL-6, and TNF-α or a Th2 cytokine IL-9 prior to an excitotoxic stimulus in P5 rats significantly exacerbates injury severity and increases the density of activated microglia [60,65]. A pleotropic Th2 cytokine IL-10, in turn, can reverse injury caused by IL-1β and IL-6 if administered after HI [67]. Our study using minocycline suggested that attenuation of the elevated levels of circulating cytokines without reduction in the elevated cytokine levels in ischemic-reperfused brain provides only short-term protection [66].

Chemoattractant cytokines, chemokines, and their receptors exert a variety of physiologic functions, including control of cell migration, proliferation, differentiation, and angiogenesis in normal and disease states [68]. The breakdown of inflammatory genes by functional category in a microarray analysis has shown that chemokines are the first family of molecules to increase following HI in P7 rats [69]. Accumulation of multiple chemokines, including a CC chemokine monocyte chemoattractant protein-1 (MCP-1), is rapid following HI in P7 rats. The role of MCP-1 as a mediator of acute excitotoxic brain injury has become apparent from exacerbation of NMDA-induced excitotoxic injury by direct coadministration of recombinant MCP-1 together with NMDA and the reversal of the injury by coadministration of a neutralizing anti-MCP-1 antibody [70]. The rapidity of the HI-induced inflammatory response is also evident from accumulation of another CC chemokine, macrophage inflammatory protein-1α (MIP-1α) as well as from complement activation [71,72].

Mechanisms of Ischemic Neuronal Death and Sex Differences

Several concepts have emerged regarding the complexity of the apoptotic machinery. HI causes a pattern of activation and leakage of pro- and antiapoptotic proteins, as well as caspase-3 expression. Expression of many of the key components of apoptosis declines with age in normal brain [73–76]. Therefore, it is not surprising that apoptotic pathways are more readily activated in the immature brain after injury. This results in up to 100-fold increases in caspase-3-dependent apoptosis after HI [74,76], focal ischemia-reperfusion [77], and brain trauma [78]. While pharmacologic inhibition of caspase-3 protects the neonatal brain against HI [74,79], a lack of caspase-3 exacerbates injury via amplification of necrosis and caspase-3-independent injury pathways [80], suggesting that complete abolishment of caspase-3 activity can be injurious rather than purely beneficial. Second, data on the central role of mitochondria in apoptosis after HI and the ability to attenuate mitochondrial response by counteracting oxidative stress via modulation of expression of proteins within the apoptotic pathways continue to accumulate [81,82]. Permeabilization of mitochondrial membranes and release of apoptogenic factors into the cytosol affect the response to the injurious event. The failure to complete apoptosis may result in the "continuum" or "hybrid" cell death, an intermediate form of cell death that exhibits features of both necrosis and apoptosis (reviewed in Northington et al. [11] and Blomgren et al. [83]). The insufficient clearance of apoptotic cells also enhances necrosis [80,84] and inflammation (reviewed in Vexler and Ferriero [14]), exacerbating injury. Another form of cell death recently implicated in neonatal brain injury is *necroptosis*, or programmed necrosis [85]. There is a clear overlap of programmed death pathways, and many of the components of the signaling pathway regulating necroptosis have been studied previously in models of neonatal HI. Receptor interacting protein-1 (RIP-1) is at the crossroads between these pathways of cellular death and survival, and RIP-1 kinase activity appears to trigger formation of the necrosome (in complex with RIP-3) leading to this programmed necrosis.

Many CNS diseases display sexual dimorphism, specifically affecting one sex. Cerebral palsy (CP) and related developmental disorders are more common in males than in females (reviewed in Johnston and Hagberg [86]), but the reasons for this disparity are uncertain. Males born very preterm also appear to be more vulnerable to white matter injury and intraventricular hemorrhage than females. Sex hormones

can provide protection against ischemic injury, but the neonatal brain may not be as influenced by these hormones as the adult brain. Recent experimental data demonstrate single-sex predominance in the mechanisms of excitotoxic cell death and intracellular calcium regulation[87], apoptotic death [88–90], and the ability of antiapoptotic drugs to protect immature brain from ischemia [91]. Inhibition or lack of the gene for PARP-1 protected male but not female mouse pups from HI [88]. The existence of intrinsic sex-specific differences in cell death pathways in the fetal or neonatal periods seems likely.

Data are emerging that the effects of therapeutics can be sex specific. As an example, 2-iminobiotin (2-IB), an inhibitor of iNOS, can reduce long-term brain damage (6 weeks) in female but not male P7 rats, likely through inhibition of the HI-induced increase in cytosolic cytochrome c and caspase-3 activation. Activation of apoptosis inhibitory factor (AIF) has been observed in males only and is not affected by 2-IB [92]. Similarly, in P3 rats, neuroprotection after HI is observed in female rats only [93]. Protection is associated with reversal of HI-induced elevated HSP70 protein expression and cytochrome c release from the mitochondria in female but not male rats [92]. Therefore, sex-specific effects of therapeutics are important for the design of future clinical trials of potential neuroprotective strategies.

Adaptive Response of Cells to Injury

In addition to injurious responses to hypoxia ischemia, the cell also exhibits protective mechanisms. Innate responses to HI include upregulation of the hypoxia inducible factor-1 (HIF-1) cascade and many downstream targets, including erythropoietin (EPO), vascular-derived growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and insulin-like growth factor 1 (IGF-1).

Hypoxia-Inducible Factor 1 (HIF-1)

HIF-1 is a heterodimeric transcription factor that consists of an inducible α subunit and a constitutive β subunit [94]. It is found in both neurons and glia [95,96]. Under normoxic conditions, HIF-1α is expressed but rapidly hydroxylated and ultimately degraded via the ubiquitin pathway by the oxygen-dependent EGLN family of HIF prolyl hydroxylases [97]. Following hypoxia, HIF-1α is stabilized and upregulated by inhibition of these prolyl hydroxylases. The phosphorylated form of HIF-1α dimerizes with the constitutive β subunit, forming the active complex that binds to the transcriptional coactivator p300/CBP and to the hypoxia response element (HRE) in the promotor region of a variety of genes, including EPO, glucose transporters, glycolytic enzymes, VEGF, and other growth factors [98] (Figure 3.1). These HIF-1 target

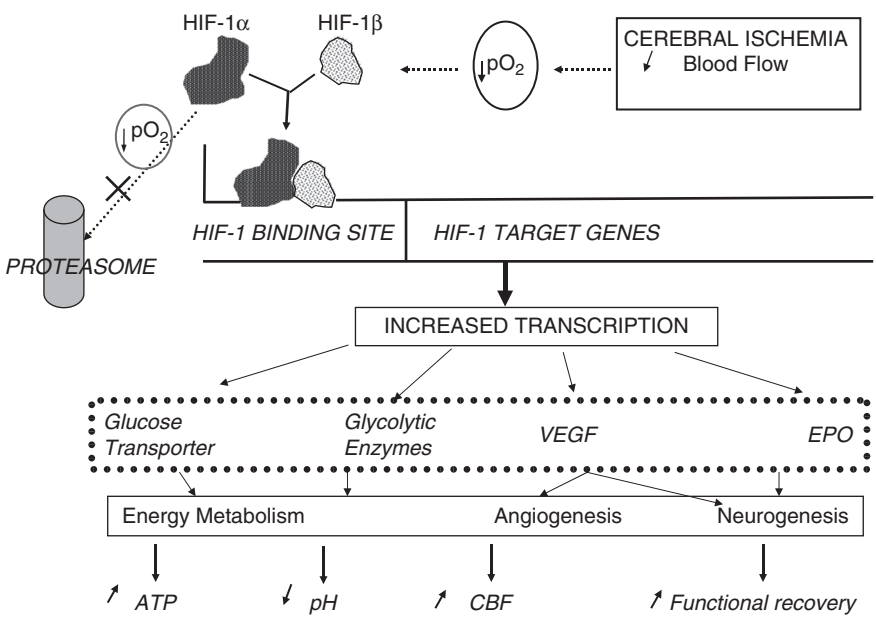


Figure 3.1 The mechanisms of HIF-1-mediated protection from HI. (A) A diagram of HIF-1α-induced neuroprotection. Ischemia in neonatal rats rapidly induces HIF-1α and EPO expression. Administration of rhEPO significantly reduces sensorimotor deficit 2 weeks after injury.

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genes, which maintain energy metabolism, angiogenesis, and neurogenesis, contribute to protection and recovery after stroke in adults, as demonstrated by exacerbation of injury in neuron-specific HIF-1α conditional knockouts [95,99] and reduction of ischemic injury in animals treated with HIF-1α stimulators [99,100]. Although HIF-1α is generally considered neuroprotective, it has also been shown to induce various pro-death proteins (such as bNIP3) [101] and caspase-3 activation [102], interfering with protective responses in the hippocampus in a model of global hypoxia [103]. The exact mechanisms of these opposing effects of HIF-1α on ischemic injury are not clear, but the extent of temporal-spatial HIF-1α-dependent induction of genes such as EPO and VEGF after ischemic injury and the balance between pro-survival and pro-death proteins seem to play a major role in HIF-1α-dependent outcomes [95,99,103].

In neonatal models, HIF-1α is induced by HI [104], focal ischemia-reperfusion [105,106], and desferoxamine (DFO) administration [104], which acts in both a HIF-dependent and -independent manner. Increased HIF-1α expression occurs as early as 4 hours, peaks at 8 hours, and returns to baseline by about 24 hours following a transient middle cerebral artery occlusion (MCAO) in P10 rats (Figure 3.1) and is followed by increases in both VEGF and EPO expression [105,106]. HIF-1α upregulation is mediated in part by the PI3 K/AKT and ERK1/2 pathways, as evidenced by attenuation of HIF-1α upregulation by inhibitors of proteins in these pathways [107,108]. HIF-1 is also believed to contribute to hypoxic preconditioning in neonatal rat brain [109] likely via induction of a variety of HIF-1-inducible genes, including VEGF, EPO, GLUT-1, adrenomedullin, and propyl 4-hydroxylase-α [110].

Erythropoietin

EPO is a pleotropic growth factor and a member of the type I superfamily of cytokines. While EPO was identified for its role in erythropoiesis [111], biological activity of EPO extends far beyond erythropoiesis. It contributes directly to brain development by supporting neural cell progenitor cells and promoting survival and proliferation of these cells, directing them toward a neurogenic outcome [112,113]. EPO knockout is embryonic lethal by E13 [114], with fetuses exhibiting severe anemia and a paucity of neural progenitor cells and neurogenesis [112].

EPO receptor (EPOR) binding results in phosphorylation of Janus-tyrosine kinase 2 (JAK-2) and MAP kinase pathways, leading to downstream activation of ERK1/2, PI3 K/AKT, and STAT-5 [115]. In neurons, EPO activates the nuclear factor κB (NFκB) [115a] and reduces glutamate release [116]. EPO administration protects against focal and global ischemia, glutamate toxicity, and kainite-induced seizures [117,118] by reducing neuronal apoptosis [119], stimulating neuronal precursors [112,113], and stimulating angiogenesis [120], partly through interactions with VEGF and other growth factors [121]. EPO also contributes to neuroprotection via attenuation of inflammation [122,123] and white matter protection/regeneration [124].

In neonatal rodents, EPO treatment reduces brain injury, apoptosis, and gliosis days after the HI insult [124a] in part by rapid EPOR upregulation [125]. It preserves auditory processing and learning/memory after HI even when administered in low doses (0.3–1 units/g) [126] and improves sensorimotor, memory, and behavioral outcomes [127,128]. However, a U-shaped dose response to the range of EPO concentrations is reported [124]. In a focal ischemia-reperfusion model in neonatal rats, we showed that EPO (5 units/g) markedly preserved hemispheric volume, decreased the expansion of the subventricular zone (SVZ) unilaterally, and significantly improved sensorimotor and memory function after MCAO [129] (Figure 3.1). The effect on tissue preservation is due in part to increased percentage of newly generated neurons versus decreased newly generated astrocytes following brain injury, suggesting that in neonatal stroke EPO may redirect cell fate toward neurogenesis and away from gliogenesis, allowing for repair and replacement of damaged tissue [130,131]. Recently, EPO administration for human hypoxic-ischemic encephalopathy (HIE) has suggested short- and long-term benefit, and studies are ongoing [132,133].

Vascular Endothelial Growth Factor

VEGF is a family of growth factors involved in vasculogenesis, neurogenesis, and angiogenesis. There are multiple VEGF isoforms that signal by binding to endothelial tyrosine kinase receptors VEGFR1, Flt-1, and VEGFR2, Flk-1 [134]. VEGFR2 has higher affinity to VEGF-A (aka VEGF) and is thought to be responsible for most biological signaling by VEGF in the CNS. Loss of a single VEGF allele is embryonic lethal [135].

VEGF-induced VEGFR2 autophosphorylation leads to binding of SH2-containing molecules, including phospholipase Cγ (PLCγ), Shb, and VEGF receptor–associated protein (VRAP) [136], and activation of several downstream signaling pathways, including the MAPK, ERK1/2, and PI3 K/AKT pathways [137,138]. VEGFR1, in turn, mediates monocyte and machrophage migration [139] and can affect the integrity of the BBB via the PI3 K/AKT pathway [140]. VEGFR1 can also modulate VEGR2 activity [141,142]. In vitro, VEGF stabilizes and promotes survival of neurons after hypoxia, nutrient deprivation, or glutamate administration [143].

In stroke, VEGF is a downstream target of the HIF cascade and is robustly upregulated by ischemia [144]. VEGF administration or overexpression results in decreased infarct volume, increased angiogenesis and neurogenesis, and improved functional outcomes 4–8 weeks after injury [145,146]. However, a rush to use VEGF as a salvage treatment following CNS injury must be tempered with caution because early administration of VEGF after stroke actually can increase BBB leakage and infarct size [147]. A U-shaped curve – protection after low, nonangiogenic doses of VEGF and increased damage and hemorrhagic transformation associated with doses high enough to stimulate angiogenesis – is reported after adult stroke [148]. Delayed administration of VEGF shows enhanced microvascular perfusion and no increase in BBB leakage [147], reinforcing the importance of the timing for VEGF biological effects for long-term outcomes.

VEGF and VEGFR2 expression are high in the developing brain in concert with developmental cerebral angiogenesis [149] and is further upregulated following HI [107,108] and focal stroke [105] in neonatal animals. The increase in VEGF (and HIF-1α) expression is blocked by the PI3/AKT and ERK inhibitors [108]. Endogenous VEGF is a necessary piece of the neuroprotection offered by hypoxic preconditioning, with exogenous VEGF augmenting the benefits of hypoxic preconditioning [150]. In an ongoing study using VEGFR2 antagonist SU5416, we showed injury exacerbation and increased gliosis after neonatal focal ischemia [151].

Other Growth Factors

Neurotrophins are a family of growth factor proteins that are important in neuronal development and function and include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line–derived neurotrophic factor (GDNF), neurotrophin-3, and neurotrophin-4. BDNF is secreted by the postsynaptic membrane and binds to ligand-specific receptor tropomysin-related kinase B (TrkB) or general neurotrophic factor receptor low-affinity nerve growth factor receptor (LNGFR, or p75 neurotrophin receptor) [152,153]. Binding to TrkB leads to neuronal survival through Ras-ERK, PI3 K, and PLCγ activation and signaling, with roles in the regulation of neuronal plasticity, signaling, and a key mediator in cell survival [154,155]. Binding to LNGFR activates intracellular signaling pathways including NFkB, Jun kinase, and sphingomyelin hydrolysis, leading to the initiation of apoptosis [49]. Thus temporal-specific expression of receptors is an important consideration for the exogenous administration of BDNF.

Insulin-like growth factor 1 (IGF-1) is a pleiotropic peptide responsible for a variety of pro-survival signaling mechanisms, acting through receptor IGF-1R [66]. After ligand-induced autophosphorylation, IGF-1R activates the PI3 K/AKT pathway and the ras-raf-MEK/ERK pathway leading to the inhibition of apoptosis and increased cell survival [67]. Progranulin is a growth factor that suppresses neutrophil recruitment in the ischemic brain, leading to a reduction in NFκB and MMP-9 activation in vivo, and suppresses neutrophil chemotaxis and ICAM-1 expression caused by TNF-α in endothelial cells [82].

New Trends in Neuroprotection: Hypothermia and Natural Ingredients

Five large multicenter randomized studies of newborn infants with hypoxic-ischemic encephalopathy demonstrate the neuroprotective potential of hypothermia using head cooling [156] or whole-body cooling [157]. The benefits may be limited to infants with moderate injury [156] and, while indicating great promise, show the need to better understand optimal depth, timing, and duration of hypothermia to maximize beneficial effects [158].

Several studies in immature rats showed that hypothermia during HI insult is protective [159] and significantly attenuates spatial learning deficits [160]. When induced immediately after HI in P7 rats, hypothermia provides protection and inhibition of caspase activation via the intrinsic pathway in the neonatal brain, thereby preventing apoptotic cell death [161]. Delayed cooling of P7 rats not only

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significantly reduces final size of cerebral infarction at 6 weeks after the insult but leads to long-lasting behavioral improvement throughout brain maturation despite the severity of the injury and delayed onset of cooling [162]. Yet other studies show that hypothermia alone do not improve long-term outcomes but is beneficial as a part of combinatory treatment [163]. In larger species (piglets), mild hypothermia reduces HI injury and neuronal apoptosis [164] and preserves sensorimotor and behavioral function [165]. The timing for hypothermia is critical for protection. Deep cooling is needed to protect between 6 and 12 hours after HI in rodents [166]. In fetal lambs, cooling protects against HI when delayed up to 5 hours [167] but not 8 hours [168] after insult. Combinatory strategies show further benefits. The long-term benefits of hypothermia can be augmented by coadministering topiramate [163], *N*-acetylcysteine [169], or xenon [170]. Recently, a phase I trial of hypothermia and EPO cotreatment demonstrated safety in human neonates with HIE [171], and efficacy studies are currently enrolling patients.

Recent studies show that pomegranate juice protects against neonatal HI when given as maternal dietary supplementation prior to subjecting newborn pups to HI [172] and when pups are drinking pomegranate juice after HI [173]. Polyphenols, which are believed to be active ingredients in the juice, and resveratrol in particular can reduce caspase-3 activation and calpain activation following neonatal HI [173], presumably via the SIRT signaling pathway. Pretreatment with grape seed extract protects against HI possibly due to its antioxidant characteristics and ability to restore regulation within the prostaglandin pathways [174].

Repair: Neurogenesis and Angiogenesis

Generation of new neurons – neurogenesis – is a critical element of repair following neurodegenerative conditions, including stroke and HI. Ischemic focal stroke gives rise to cell proliferation in the SVZ in both adult [175,176] and neonatal [129,177] brains. The newly formed neuroblasts migrate from the SVZ into the damaged striatum [175,178,179] and differentiate to become mature neurons of appropriate phenotypes. This suggests a potential for self-repair strategies after stroke [176]. However, endogenous neurogenesis is short lived and ineffective, as shown by several laboratories [180,181], including ours [129,175].

Some studies show that neonatal HI depletes the SVZ of progenitors, while other studies have demonstrated expansion of the SVZ after HI [177] and focal stroke [129]. Activated calpains and caspase-3 colocalized to regions with progenitor cell death, whereas neither enzyme was activated in the medial SVZ, which harbors the neural stem cells that are resilient to this insult [182]. Increased neocortical production was associated with increases in IGF-1 and MCP-1 but statistically insignificant production of EPO, brain-derived neurotrophic factor, glial-derived neurotrophic factor, and TGFα, suggesting that HI injury in the neonatal brain initiates a regenerative response from the SVZ [183]. HIF-1α modulates neurogenesis through increased expression of genes such as VEGF and EPO and that EPO by itself is a major inducer of neurogenesis after neonatal ischemic insults.

The formation of new blood vessels – angiogenesis – is a limiting factor in postischemic repair [184]. Angiogenesis is a complex multistep process with numerous soluble factors strictly controlling this process. [185]. The presence of newly formed blood vessels is critical in several aspects of repair, including not only ensuring the blood supply but also providing an angiogenic-neurogenic niche in the brain, because neurogenesis appears to be intimately associated with active vascular recruitment and remodeling [184]. Evidence continues to accumulate that angiogenesis is coupled with neurogenesis [184]. The VEGFR2 mediates antiapoptotic effects and supports survival of the endothelial cells that have been induced by VEGF [143].

More recent evidence from experimental models using cell-based therapies to treat brain injury is also promising. For example, beneficial effects have been observed with mesenchymal stem cells transplanted anywhere from 3 hours to 10 days after the onset of neonatal ischemic injury [186]. Apoptosis is reduced, while endogenous neurogenesis is enhanced, demonstrating a neuroprotective and neuroregenerative role based on the timing of administration. While intraventricular, intravenous, and intranasal administration show stem cells homing to different regions of the brain, these cells do not appear to survive long term, suggesting a possible paracrine effect on trophic factor release [187].

Future Directions

Considerable progress has been made into delineating the complexity of cellular injury, including

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better understanding of the network of intracellular signaling pathways and the rationale for identification of therapeutic targets and development of effective therapies. Two new aspects of thinking in the field have been acknowledgment of the integrative nature of brain injury, which evolves via communication between different cell types, and the dynamic nature of changes during brain maturation. Recent studies have begun targeting repair as the way of improving long-term recovery following HI injury during the newborn period. Currently, promising clinical studies are being conducted on the effects of hypothermia and erythropoietin following perinatal HIE, but much needs to be learned about the optimal conditions for these interventions and ways of targeting severely injured brains. Therefore, future work should address the optimal timing for modulating effects of interventions. Elucidating how to enhance the repair process, with supporting angiogenesis, neurogenesis, and preservation of function, will be the major markers of success. Emerging evidence suggests that different interventions may be necessary to accomplish improvement in males and females. Studies are also needed to determine whether proposed interventions adversely affect long-term brain development.

References

1. Volpe JJ. Brain injury in the premature infant: overview of clinical aspects, neuropathology, and pathogenesis. *Semin Pediatr Neurol* 1998; **5**(3): 135–51.
2. Ferriero DM. Neonatal brain injury. *N Engl J Med* 2004; **351**(19): 1985–95.
3. Vannucci RC, Vannucci SJ. A model of perinatal hypoxic-ischemic brain damage. *Ann NY Acad Sci* 1997; **835**: 234–49.
4. Derugin N, Ferriero DM, Vexler ZS. Neonatal reversible focal cerebral ischemia: a new model. *Neurosci Res*, 1998; **32**(4)349–53.
5. Ashwal S, et al. Core and penumbral nitric oxide synthase activity during cerebral ischemia and reperfusion. *Stroke* 1998; **29**(5)1037–46; discussion 1047.
6. McQuillen PS, Ferriero DM. Selective vulnerability in the developing central nervous system. *Pediatr Neurol* 2004; **30**(4)227–35.
7. Hagberg H, Mallard C. Effect of inflammation on central nervous system development and vulnerability. *Curr Opin Neurol* 2005; **18**(2): 117–23.
8. Vexler ZS. Glia and inflammation in neurodegenerative disease. In Yenari MA, Giffard RG, eds., *Inflammation and Ischemia in the Developing Brain*. Hauppauge, NY: Nova Science Publishers, 2006.
9. Vannucci SJ, Hagberg H. Hypoxia-ischemia in the immature brain. *J Exp Biol* 2004; **207**(18): 3149–54.
10. Vexler ZS, Tang D, Yenari M. Inflammation in adult and neonatal stroke. *Clin Neurosci Res* 2006: **6**(5): 293–313.
11. Northington FJ, et al. Failure to complete apoptosis following neonatal hypoxia-ischemia manifests as "continuum" phenotype of cell death and occurs with multiple manifestations of mitochondrial dysfunction in rodent forebrain. *Neuroscience* 2007; **149**(4)822–33.
12. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. *Semin Perinatol* 2000; **24**(2): 107–15.
13. Perlman JM. Intervention strategies for neonatal hypoxic-ischemic cerebral injury. *Clin Ther* 2006; **28** (9): 1353–65.
14. Vexler ZS, Ferriero DM. Mechanisms of ischemic cell death in the developing brain, in Chan P, ed., *Handbook of Neurochemistry and Molecular Neurobiology*. New York: Springer, 2006.
15. Rousset CI, et al. A dual role for AMP-activated protein kinase (AMPK) during neonatal hypoxic-ischaemic brain injury in mice. *J Neurochem* 2015; **133** (2)242–52.
16. Jiang X, et al. Activated Src kinases interact with NMDA receptor after neonatal brain ischemia. *Ann Neurol* 2008; **63**(5):632–41.
17. Fraser M, et al. Extracellular amino acids and lipid peroxidation products in periventricular white matter during and after cerebral ischemia in preterm fetal sheep. *J Neurochem* 2008; **105**(6): 2214–23.
18. Sheldon RA, Christen S, Ferriero DM. Genetic and pharmacologic manipulation of oxidative stress after neonatal hypoxia-ischemia. *Int J Dev Neurosci* 2007; **26**(1): 87–92.
19. Ferriero DM, et al. Neonatal mice lacking neuronal nitric oxide synthase are less vulnerable to hypoxic-ischemic injury. *Neurobiol Dis* 1996; **3**(1): 64–71.
20. Drury PP, et al. Partial neuroprotection by nNOS inhibition during profound asphyxia in preterm fetal sheep. *Exp Neurol* 2013; **250**: 282–92.
21. Bolton SJ, Anthony DC, Perry VH. Loss of the tight junction proteins occludin and zonula occludens-1 from cerebral vascular endothelium during neutrophil-induced blood-brain barrier breakdown in vivo. *Neuroscience* 1998; **86**(4)1245–57.
22. Bazzoni G, et al. Interaction of junctional adhesion molecule with the tight junction components ZO-1,

cingulin, and occludin. *J Biol Chem* 2000; **275**(27): 20520–6.

23. Kratzer I, Chip S, Vexler ZS. Barrier mechanisms in neonatal stroke. *Front Neurosci* 2014; **8**: 359.
24. Garcia JH, et al. Influx of leukocytes and platelets in an evolving brain infarct (Wistar rat). *Am J Pathol* 1994; **144**(1)188–99.
25. Hallenbeck JM. Significance of the inflammatory response in brain ischemia. *Acta Neurochir Suppl* 1996; **66**: 27–31.
26. Rosenberg GA. Matrix metalloproteinases in neuroinflammation. *Glia* 2002; **39**(3)279–91.
27. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat Rev Immunol* 2005; **5**(8): 629–40.
28. Pan W, et al. Stroke upregulates TNF-α transport across the blood-brain barrier. *Exp Neurol* 2006; **198**(1): 222–33.
29. Kniesel U, Risau W, Wolburg H. Development of blood-brain barrier tight junctions in the rat cortex. *Brain Res Dev Brain Res* 1996; **96**(1–2): 229–40.
30. Engelhardt B. Development of the blood-brain barrier. *Cell Tissue Res* 2003; **314**(1): 119–29.
31. Blamire AM, et al. Interleukin-1β -induced changes in blood-brain barrier permeability, apparent diffusion coefficient, and cerebral blood volume in the rat brain: a magnetic resonance study. *J Neurosci* 2000; **20**(21): 8153–9.
32. Palmer C, Roberts RL, Young PI. Timing of neutrophil depletion influences long-term neuroprotection in neonatal rat hypoxic-ischemic brain injury. *Pediatr Res* 2004; **55**(4): 549–56.
33. Bona E, et al. Chemokine and inflammatory cell response to hypoxia-ischemia in immature rats. *Pediatr Res* 1999; **45**(4 Pt 1): 500–9.
34. Denker S, et al. Macrophages are comprised of resident brain microglia not infiltrating peripheral monocytes acutely after neonatal stroke. *J Neurochem* 2007; **100**(4): 893–904.
35. Svedin P, et al. Matrix metalloproteinase-9 gene knock-out protects the immature brain after cerebral hypoxia-ischemia. *J Neurosci* 2007; **27**(7): 1511–8.
36. Ranasinghe HS, et al. Inhibition of MMP-9 activity following hypoxic ischemia in the developing brain using a highly specific inhibitor. *Dev Neurosci* 2012; **34**(5): 417–27.
37. Raivich G, et al. Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res Brain Res Rev* 1999; **30**(1): 77–105.
38. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 2003; **302**(5651): 1760–5.
39. Walton NM, et al. Microglia instruct subventricular zone neurogenesis. *Glia* 2006; **54**(8): 815–25.
40. Britschgi M, Wyss-Coray T. Immune cells may fend off Alzheimer disease. *Nat Med* 2007; **13**(4): 408–9.
41. Marin-Teva JL, et al. Microglia promote the death of developing Purkinje cells. *Neuron* 2004; **41**(4): 535–47.
42. Derugin N, et al. Evolution of brain injury after transient middle cerebral artery occlusion in neonatal rat. *Stroke* 2000; **31**: 1752–61.
43. McRae A, et al. Microglia activation after neonatal hypoxic-ischemia. *Brain Res Dev Brain Res* 1995; **84**(2): 245–52.
44. Dommergues MA, et al. Early microglial activation following neonatal excitotoxic brain damage in mice: a potential target for neuroprotection. *Neuroscience* 2003; **121**(3): 619–28.
45. Tikka T, et al. Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. *J Neurosci* 2001; **21**(8): 2580–8.
46. van den Tweel ER, et al. Long-term neuroprotection with 2-iminobiotin, an inhibitor of neuronal and inducible nitric oxide synthase, after cerebral hypoxia-ischemia in neonatal rats. *J Cereb Blood Flow Metab* 2005; **25**(1): 67–74.
47. Dingman A, et al. Aminoguanidine inhibits caspase-3 and calpain activation without affecting microglial activation following neonatal transient ischemia. *J Neurochem* 2006; **96**: 1467–79.
48. Faustino JV, et al. Microglial cells contribute to endogenous brain defenses after acute neonatal focal stroke. *J Neurosci* 2011; **31**(36): 12992–3001.
49. Dong Y, Benveniste EN. Immune function of astrocytes. *Glia* 2001; **36**(2): 180–90.
50. Zhang Y, et al. Notch-1 signaling regulates astrocytic proliferation and activation after hypoxia exposure. *Neurosci Lett* 2015; **603**: 12–18.
51. Benveniste EN. Cytokine actions in the central nervous system. *Cytokine Growth Factor Rev* 1998; **9**(3–4): 259–75.
52. Teo JD, Morris MJ, Jones NM. Hypoxic postconditioning reduces microglial activation, astrocyte and caspase activity, and inflammatory markers after hypoxia-ischemia in the neonatal rat brain. *Pediatr Res* 2015; **77**(6): 757–64.
53. Iadecola C, Zhang F, Xu X. Inhibition of inducible nitric oxide synthase ameliorates cerebral ischemic damage. *Am J Physiol* 1995; **268**(1 Pt 2): R286–92.

54. Nawashiro H, et al. High susceptibility to cerebral ischemia in GFAP-null mice. *J Cereb Blood Flow Metab* 2000; **20**(7): 1040–4.

55. Benjelloun N, et al. Inflammatory responses in the cerebral cortex after ischemia in the P7 neonatal rat. *Stroke* 1999; **30**(9): 1916–23; discussion 1923–4.

56. Benjelloun N, et al. Apoptotic mitochondrial pathway in neurones and astrocytes after neonatal hypoxia-ischaemia in the rat brain. *Neuropathol Appl Neurobiol* 2003; **29**(4): 350–60.

57. Ducrocq S, et al. Poly(ADP-ribose) synthase inhibition reduces ischemic injury and inflammation in neonatal rat brain. *J Neurochem* 2000; **74**(6): 2504–11.

58. Joly LM, et al. Distribution of poly(ADP-ribosyl)ation and cell death after cerebral ischemia in the neonatal rat. *Pediatr Res* 2003; **53**(5): 776–82.

59. Jin Y, Silverman AJ, Vannucci SJ. Mast cell stabilization limits hypoxic-ischemic brain damage in the immature rat. *Dev Neurosci* 2007; **29**(4–5): 373–84.

60. Patkai J, et al. Deleterious effects of IL-9-activated mast cells and neuroprotection by antihistamine drugs in the developing mouse brain. *Pediatr Res* 2001; **50**(2): 222–30.

61. Biran V, et al. Stroke induces histamine accumulation and mast cell degranulation in the neonatal rat brain. *Brain Pathol* 2008; **18**(1): 1–9.

62. Mesples B, et al. Neuronal TGF-β1 mediates IL-9/mast cell interaction and exacerbates excitotoxicity in newborn mice. *Neurobiol Dis* 2005; **18**(1): 193–205.

63. Hedtjarn M, Mallard C, Hagberg H. Inflammatory gene profiling in the developing mouse brain after hypoxia-ischemia. *J Cereb Blood Flow Metab* 2004; **24**(12): 1333–51.

64. Szaflarski J, Burtrum D, Silverstein FS. Cerebral hypoxia-ischemia stimulates cytokine gene expression in perinatal rats. *Stroke* 1995; **26**(6): 1093–100.

65. Dommergues MA, et al. Proinflammatory cytokines and interleukin-9 exacerbate excitotoxic lesions of the newborn murine neopallium. *Ann Neurol* 2000; **47**(1): 54–63.

66. Fox C, et al. Minocycline confers early but transient protection in the immature brain following focal cerebral ischemia-reperfusion. *J Cereb Blood Flow Metab* 2005; **25**(9): 1138–49.

67. Mesples B, Plaisant F, Gressens P. Effects of interleukin-10 on neonatal excitotoxic brain lesions in mice. *Brain Res Dev Brain Res*, 2003; **141**(1–2): 25–32.

68. Gerard C, Rollins BJ. Chemokines and disease. *Nat Immunol* 2001; **2**(2): 108–15.

69. Hedtjarn M, et al. Global gene expression in the immature brain after hypoxia-ischemia. *J Cereb Blood Flow Metab* 2004; **24**(12): 1317–32.

70. Galasso JM, et al. Acute excitotoxic injury induces expression of monocyte chemoattractant protein-1 and its receptor, CCR2, in neonatal rat brain. *Exp Neurol* 2000; **165**(2): 295–305.

71. Cowell RM, et al. Hypoxic-ischemic injury induces macrophage inflammatory protein-1alpha expression in immature rat brain. *Stroke* 2002; **33**(3): 795–801.

72. Cowell RM, Plane JM, Silverstein FS. Complement activation contributes to hypoxic-ischemic brain injury in neonatal rats. *J Neurosci* 2003; **23**(28): 9459–68.

73. Hu BR, et al. Involvement of caspase-3 in cell death after hypoxia-ischemia declines during brain maturation. *J Cereb Blood Flow Metab* 2000; **20**(9): 1294–300.

74. Han BH, et al. Selective, reversible caspase-3 inhibitor is neuroprotective and reveals distinct pathways of cell death following neonatal hypoxic- ischemic brain injury. *J Biol Chem* 2002; **277**(33): 30128–36.

75. Yakovlev AG, et al. Differential expression of apoptotic protease-activating factor-1 and caspase-3 genes and susceptibility to apoptosis during brain development and after traumatic brain injury. *J Neurosci* 2001; **21**(19): 7439–46.

76. Zhu C, et al. The influence of age on apoptotic and other mechanisms of cell death after cerebral hypoxia-ischemia. *Cell Death Differ* 2005; **12**(2): 162–76.

77. Manabat C, et al. Reperfusion differentially induces caspase-3 activation in ischemic core and penumbra after stroke in immature brain. *Stroke* 2003; **34**(1): 207–13.

78. Bittigau P, et al. Apoptotic neurodegeneration following trauma is markedly enhanced in the immature brain. *Ann Neurol* 1999; **45**(6): 724–35.

79. Cheng Y, et al. Caspase inhibitor affords neuroprotection with delayed administration in a rat model of neonatal hypoxic-ischemic brain injury [see comments]. *J Clin Invest* 1998; **101**(9): 1992–9.

80. West T, Atzeva M, Holtzman DM. Caspase-3 deficiency during development increases vulnerability to hypoxic-ischemic injury through caspase-3-independent pathways. *Neurobiol Dis* 2006; **22**(3): 523–37.

81. Zhu C, et al. X chromosome-linked inhibitor of apoptosis protein reduces oxidative stress after cerebral irradiation or hypoxia-ischemia through up-regulation of mitochondrial antioxidants. *Eur J Neurosci* 2007; **26**(12): 3402–10.

82. Matsumori Y, et al. Hsp70 overexpression sequesters AIF and reduces neonatal hypoxic/ischemic brain injury. *J Cereb Blood Flow Metab* 2005; **25**(7): 899–910.

83. Blomgren K, Leist M, Groc L. Pathological apoptosis in the developing brain. *Apoptosis* 2007; **12**(5): 993–1010.

16:30:50

.004

84. Carloni S, et al. Extended role of necrotic cell death after hypoxia-ischemia-induced neurodegeneration in the neonatal rat. *Neurobiol Dis* 2007; **27**(3): 354–61.

85. Chavez-Valdez R, Martin LJ, Northington FJ. Programmed necrosis: a prominent mechanism of cell death following neonatal brain injury. *Neurol Res Int* 2012; **2012**: 257563.

86. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. *Dev Med Child Neurol* 2007; **49**(1): 74–8.

87. Zup SL, Edwards NS, McCarthy MM. Sex- and age-dependent effects of androgens on glutamate-induced cell death and intracellular calcium regulation in the developing hippocampus. *Neuroscience* 2014; **281C**: 77–87.

88. Hagberg H, et al. PARP-1 gene disruption in mice preferentially protects males from perinatal brain injury. *J Neurochem* 2004; **90**(5)1068–75.

89. Renolleau S, Fau S, Charriaut-Marlangue C. Gender-related differences in apoptotic pathways after neonatal cerebral ischemia. *Neuroscientist* 2008; **14**(1): 46–52.

90. Del Pino Sans J. et al. Microarray analysis of neonatal rat anteroventral periventricular transcriptomes identifies the proapoptotic Cugbp2 gene as sex-specific and regulated by estradiol. *Neuroscience* 2015; **303**: 312–22.

91. Renolleau S, et al. Sex, neuroprotection, and neonatal ischemia. *Dev Med Child Neurol* 2007; **49**(6): 477; author reply 477–8.

92. Nijboer CH, et al. Gender-specific neuroprotection by 2-iminobiotin after hypoxia-ischemia in the neonatal rat via a nitric oxide independent pathway. *J Cereb Blood Flow Metab* 2007; **27**(2): 282–92.

93. Nijboer CH, et al. Gender-dependent pathways of hypoxia-ischemia-induced cell death and neuroprotection in the immature P3 rat. *Dev Neurosci* 2007; **29**(4–5): 385–92.

94. Wang GL, Semenza GL. Characterization of hypoxia-inducible factor 1 and regulation of DNA binding activity by hypoxia. *J Biol Chem* 1993; **268** (29): 21513–8.

95. Bergeron M, et al. Induction of hypoxia-inducible factor-1 (HIF-1) and its target genes following focal ischaemia in rat brain. *Eur J Neurosci* 1999; **11**(12): 4159–70.

96. Chavez JC, LaManna JC. Activation of hypoxia-inducible factor-1 in the rat cerebral cortex after transient global ischemia: potential role of insulin-like growth factor-1. *J Neurosci* 2002; **22**(20): 8922–31.

97. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science* 2001; **294**(5545): 1337–40.

98. Semenza GL. Hypoxia-inducible factor 1: master regulator of O_2 homeostasis. *Curr Opin Genet Dev* 1998; **8**(5): 588–94.

99. Baranova O, et al. Neuron-specific inactivation of the hypoxia inducible factor 1 alpha increases brain injury in a mouse model of transient focal cerebral ischemia. *J Neurosci* 2007; **27**(23): 6320–32.

100. Zaman K, et al. Protection from oxidative stress-induced apoptosis in cortical neuronal cultures by iron chelators is associated with enhanced DNA binding of hypoxia-inducible factor-1 and ATF-1/CREB and increased expression of glycolytic enzymes, p21(waf1/cip1), and erythropoietin. *J Neurosci* 1999; **19**(22): 9821–30.

101. Bruick RK. Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. *Proc Natl Acad Sci USA* 2000; **97**(16): 9082–7.

102. Van Hoecke M, et al. Evidence of HIF-1 functional binding activity to caspase-3 promoter after photothrombotic cerebral ischemia. *Mol Cell Neurosci* 2007; **34**(1): 40–7.

103. Helton R, et al. Brain-specific knock-out of hypoxia-inducible factor-1alpha reduces rather than increases hypoxic-ischemic damage. *J Neurosci* 2005; **25**(16): 4099–107.

104. Bergeron M, et al. Role of hypoxia-inducible factor-1 in hypoxia-induced ischemic tolerance in neonatal rat brain. *Ann Neurol* 2000; **48**(3): 285–96.

105. Mu D, et al. Regulation of hypoxia-inducible factor 1alpha and induction of vascular endothelial growth factor in a rat neonatal stroke model. *Neurobiol Dis* 2003; **14**(3): 524–34.

106. Mu D, et al. Hypoxia-inducible factor 1alpha and erythropoietin upregulation with deferoxamine salvage after neonatal stroke. *Exp Neurol* 2005; **195**(2):407–15.

107. Li L, et al. The involvement of phosphoinositid 3-kinase/Akt pathway in the activation of hypoxia-inducible factor-1alpha in the developing rat brain after hypoxia-ischemia. *Brain Res* 2008; **1197**:152–8.

108. Li L, et al. The requirement of extracellular signal-related protein kinase pathway in the activation of hypoxia inducible factor 1alpha in the developing rat brain after hypoxia-ischemia. *Acta Neuropathol* 2008; **115**(3): 297–303.

109. Jones NM, Bergeron M. Hypoxic preconditioning induces changes in HIF-1 target genes in neonatal rat brain. *J Cereb Blood Flow Metab* 2001; **21**(9): 1105–14.

110. Bernaudin M, et al. Brain genomic response following hypoxia and re-oxygenation in the neonatal rat. Identification of genes that might contribute to hypoxia-induced ischemic tolerance. *J Biol Chem* 2002; **277**(42): 39728–38.

111. Jelkmann W. Erythropoietin: structure, control of production, and function. *Physiol Rev* 1992; **72**(2): 449–89.

112. Chen ZY, et al. Endogenous erythropoietin signaling is required for normal neural progenitor cell proliferation. *J Biol Chem* 2007; **282**(35): 25875–83.

113. Shingo T, et al. Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. *J Neurosci* 2001; **21**(24): 9733–43.

114. Wu H, et al. Generation of committed erythroid BFU-E and CFU-E progenitors does not require erythropoietin or the erythropoietin receptor. *Cell* 1995; **83**(1): 59–67.

115. Kilic E, et al. Brain-derived erythropoietin protects from focal cerebral ischemia by dual activation of ERK-1/-2 and Akt pathways. *FASEB J* 2005; **19**(14): 2026–8.

115a. Digicaylioglu M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades. *Nature* 2001; **412**(6847): 641–7.

116. Kawakami M, et al. Erythropoietin receptor-mediated inhibition of exocytotic glutamate release confers neuroprotection during chemical ischemia. *J Biol Chem* 2001; **276**(42): 39469–75.

117. Marti HH, et al. Neuroprotection and Angiogenesis: Dual Role of Erythropoietin in Brain Ischemia. *News Physiol Sci* 2000; **15**: 225–9.

118. Solaroglu I, et al. Erythropoietin prevents ischemia-reperfusion from inducing oxidative damage in fetal rat brain. *Childs Nerv Syst* 2003; **19**(1): 19–22.

119. Sola A, et al. Potential for protection and repair following injury to the developing brain: a role for erythropoietin? *Pediatr Res* 2005; **57**(5 Pt 2): 110 R–17 R.

120. Wang L, et al. Treatment of stroke with erythropoietin enhances neurogenesis and angiogenesis and improves neurological function in rats. *Stroke* 2004; **35**(7): 1732–7.

121. Ribatti D, et al. Human erythropoietin induces a pro-angiogenic phenotype in cultured endothelial cells and stimulates neovascularization in vivo. *Blood* 1999; **93**(8): 2627–36.

122. Sun Y, Calvert JW, Zhang JH. Neonatal hypoxia/ischemia is associated with decreased inflammatory mediators after erythropoietin administration. *Stroke* 2005; **36**(8): 1672–8.

123. Dzietko M, et al. Erythropoietin protects the developing brain against N-methyl-D-aspartate receptor antagonist neurotoxicity. *Neurobiol Dis* 2004; **15**(2): 177–87.

124. Xiong T, et al. Erythropoietin for neonatal brain injury: opportunity and challenge. *Int J Dev Neurosci* 2011; **29**(6): 583–91.

124a. Kellert BA, McPherson RJ, Juul SE. A comparison of high-dose recombinant erythropoietin treatment regimens in brain-injured neonatal rats. *Pediatr Res* 2007; **61**(4): 451–5.

125. Spandou E, et al. Hypoxia-ischemia affects erythropoietin and erythropoietin receptor expression pattern in the neonatal rat brain. *Brain Res* 2004; **1021**(2): 167–72.

126. McClure MM, Threlkeld SW, Fitch RH. Auditory processing and learning/memory following erythropoietin administration in neonatally hypoxic-ischemic injured rats. *Brain Res* 2007; **1132**(1): 203–9.

127. Iwai M, et al. Erythropoietin promotes neuronal replacement through revascularization and neurogenesis after neonatal hypoxia/ischemia in rats. *Stroke* 2007; **38**(10): 2795–803.

128. Kumral A, et al. Erythropoietin improves long-term spatial memory deficits and brain injury following neonatal hypoxia-ischemia in rats. *Behav Brain Res* 2004; **153**(1): 77–86.

129. Chang YS, et al. Erythropoietin improves functional and histological outcome in neonatal stroke. *Pediatr Res* 2005; **58**(1): 106–11.

130. Gonzalez F, et al. Erythropoietin enhances long-term neuroprotection and neurogenesis in neonatal stroke. *Dev Neurosci* 2007; **29**(4–5): 321–30.

131. Gonzalez FF, et al. Erythropoietin increases neurogenesis and oligodendrogliosis of subventricular zone precursor cells after neonatal stroke. *Stroke* 2013; **44**(3): 753–8.

132. Zhu C, et al. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 2009; **124**(2): e218–26.

133. Elmahdy H, et al. Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. *Pediatrics* 2010; **125**(5): e1135–42.

134. Ferrara N, Gerber HP. The role of vascular endothelial growth factor in angiogenesis. *Acta Haematol* 2001; **106**(4): 148–56.

135. Carmeliet P, et al. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature* 1996; **380**(6573): 435–9.

136. Dougher M, Terman BI. Autophosphorylation of KDR in the kinase domain is required for maximal VEGF-stimulated kinase activity and receptor internalization. *Oncogene* 1999; **18**(8): 1619–27.

137. Takahashi T, et al. A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells. *EMBO J* 2001; **20**(11): 2768–78.

138. Fujio Y, Walsh K. AKT mediates cytoprotection of endothelial cells by vascular endothelial growth factor in an anchorage-dependent manner. *J Biol Chem* 1999; **274**(23): 16349–54.

139. Shibuya M. Structure and dual function of vascular endothelial growth factor receptor-1 (Flt-1). *Int J Biochem Cell Biol* 2001; **33**(4): 409–20.

140. Vogel C, et al. Flt-1, but not Flk-1 mediates hyperpermeability through activation of the PI3-K/Akt pathway. *J Cell Physiol* 2007; **212**(1): 236–43.

141. Rahimi N, Dayanir V, Lashkari K. Receptor chimeras indicate that the vascular endothelial growth factor receptor-1 (VEGFR-1) modulates mitogenic activity of VEGFR-2 in endothelial cells. *J Biol Chem* 2000; **275**(22): 16986–92.

142. Autiero M, et al. Role of PlGF in the intra- and intermolecular cross talk between the VEGF receptors Flt1 and Flk1. *Nat Med* 2003; **9**(7): 936–43.

143. Jin KL, Mao XO, Greenberg DA. Vascular endothelial growth factor: direct neuroprotective effect in in vitro ischemia. *Proc Natl Acad Sci USA* 2000; **97**(18): 10242–7.

144. Shweiki D, et al. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992; **359**(6398): 843–5.

145. Sun Y, et al. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. *J Clin Invest* 2003; **111**(12): 1843–51.

146. Wang Y, et al. *VEGF-overexpressing transgenic mice show enhanced post-ischemic neurogenesis and neuromigration*. *J Neurosci Res*, 2007. **85**(4): p. 740–7.

147. Zhang, Z.G., et al. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. *J Clin Invest* 2000; **106**(7): 829–38.

148. Manoonkitiwongsa PS, et al. Neuroprotection of ischemic brain by vascular endothelial growth factor is critically dependent on proper dosage and may be compromised by angiogenesis. *J Cereb Blood Flow Metab* 2004; **24**(6): 693–702.

149. Ogunshola OO, et al. Neuronal VEGF expression correlates with angiogenesis in postnatal developing rat brain. *Brain Res Dev Brain Res* 2000; **119**(1): 139–53.

150. Laudenbach V, et al. Neonatal hypoxic preconditioning involves vascular endothelial growth factor. *Neurobiol Dis* 2007; **26**(1): 243–52.

151. Shimotake J, et al. Vascular endothelial growth factor receptor-2 inhibition promotes cell death and limits endothelial cell proliferation in a neonatal rodent model of stroke. *Stroke* 2010; **41**(2): 343–9.

152. Waterhouse EG, Xu B. New insights into the role of brain-derived neurotrophic factor in synaptic plasticity. *Mol Cell Neurosci* 2009; **42**(2): 81–9.

153. Zheng F, Wang H. NMDA-mediated and self-induced bdnf exon IV transcriptions are differentially regulated in cultured cortical neurons. *Neurochem Int* 2009; **54**(5–6): 385–92.

154. Chen K, et al. Creating a neurogenic environment: the role of BDNF and FGF2. *Mol Cell Neurosci* 2007; **36**(1): 108–20.

155. Rivera C, et al. BDNF-induced TrkB activation down-regulates the K+-Cl- cotransporter KCC2 and impairs neuronal Cl^- extrusion. *J Cell Biol* 2002; **159**(5): 747–52.

156. Gluckman PD, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**(9460): 663–70.

157. Shankaran S, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**(15): 1574–84.

158. Wyatt JS, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 2007; **119**(5): 912–21.

159. Yager JY, et al. Preventing hyperthermia decreases brain damage following neonatal hypoxic-ischemic seizures. *Brain Res* 2004; **1011**(1): 48–57.

160. Mishima K, et al. Effects of hypothermia and hyperthermia on attentional and spatial learning deficits following neonatal hypoxia-ischemic insult in rats. *Behav Brain Res* 2004; **151**(1–2): 209–17.

161. Zhu C, et al. Post-ischemic hypothermia-induced tissue protection and diminished apoptosis after neonatal cerebral hypoxia-ischemia. *Brain Res* 2004; **996**(1): 67–75.

162. Wagner BP, Nedelcu J, Martin E. Delayed postischemic hypothermia improves long-term behavioral outcome after cerebral hypoxia-ischemia in neonatal rats. *Pediatr Res* 2002; **51**(3): 354–60.

163. Liu Y, et al. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. *Stroke* 2004; **35**(6): 1460–5.

164. Thoresen M, et al. A piglet survival model of posthypoxic encephalopathy. *Pediatr Res* 1996; **40**(5): 738–48.

165. Bona E, et al. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome. *Pediatr Res* 1998; **43**(6): 738–45.

166. Taylor DL, et al. Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. *Pediatr Res* 2002; **51**(1): 13–9.

167. Gunn AJ, et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997; **99**(2): 248–56.

168. Gunn AJ, et al. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. *Pediatr Res* 1999; **46**(3): 274–80.

169. Jatana M, et al. Combination of systemic hypothermia and *N*-acetylcysteine attenuates hypoxic-ischemic brain injury in neonatal rats. *Pediatr Res* 2006; **59**(5): 684–9.

170. Hobbs CT, Tucker M, Aquilina A, et al. Xenon and hypothermia combine additively. offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. *Stroke* 2008; **39** (4):1307–13.

171. Wu YW, et al. Erythropoietin for neuroprotection in neonatal encephalopathy: safety and pharmacokinetics. *Pediatrics* 2012; **130**(4): 683–91.

172. Loren DJ, et al. Maternal dietary supplementation with pomegranate juice is neuroprotective in an animal model of neonatal hypoxic-ischemic brain injury. *Pediatr Res* 2005; **57**(6): 858–64.

173. West T, Atzeva M, Holtzman DM. Pomegranate polyphenols and resveratrol protect the neonatal brain against hypoxic-ischemic injury. *Dev Neurosci* 2007; **29**(4–5): 363–72.

174. Feng Y, et al. Grape seed extract given three hours after injury suppresses lipid peroxidation and reduces hypoxic-ischemic brain injury in neonatal rats. *Pediatr Res* 2007; **61**(3): 295–300.

175. Parent JM, et al. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol* 2002; **52**(6): 802–13.

176. Lindvall O, Kokaia Z. Recovery and rehabilitation in stroke: stem cells. *Stroke* 2004; **35**(11 Suppl. 1): 2691–4.

177. Plane JM, et al. Neonatal hypoxic-ischemic injury increases forebrain subventricular zone neurogenesis in the mouse. *Neurobiol Dis* 2004; **16**(3): 585–95.

178. Arvidsson A, et al. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med* 2002; **8**(9): 963–70.

179. Zhang R, et al. Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. *J Cereb Blood Flow Metab* 2004; **24**(4): 441–8.

180. Zhang R, et al. Stroke transiently increases subventricular zone cell division from asymmetric to symmetric and increases neuronal differentiation in the adult rat. *J Neurosci* 2004; **24**(25): 5810–5.

181. Ohab JJ, et al. A neurovascular niche for neurogenesis after stroke. *J Neurosci* 2006; **26**(50): 13007–16.

182. Romanko MJ, et al. Death effector activation in the subventricular zone subsequent to perinatal hypoxia/ischemia. *J Neurochem* 2007; **103**(3): 1121–31.

183. Yang Z, et al. Sustained neocortical neurogenesis after neonatal hypoxic/ischemic injury. *Ann Neurol* 2007; **61**(3): 199–208.

184. Greenberg DA, Jin K. From angiogenesis to neuropathology. *Nature* 2005; **438**(7070): 954–9.

185. Distler JH, et al. Angiogenic and angiostatic factors in the molecular control of angiogenesis. *Q J Nucl Med* 2003; **47**(3): 149–61.

186. van Velthoven CT, Kavelaars A, Heijnen CJ. Mesenchymal stem cells as a treatment for neonatal ischemic brain damage. *Pediatr Res* 2012; **71**(4 Pt 2): 474–81.

187. van Velthoven CT, et al. Stem cells for neonatal stroke: the future is here. *Front Cell Neurosci* 2014; **8**: 207.

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Chapter 4

The Pathogenesis of Preterm Brain Injury

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Introduction

Premature birth remains a major cause of morbidity and mortality. While there have been marked improvements in the survival of preterm infants, this has not been matched by a corresponding improvement in morbidity [1]. Although there is some evidence for modest improvements in survival without disability from modern cohorts [2,3], others report no apparent improvement in disability after extremely preterm birth (<25 weeks' gestation) [4].

Traditionally, brain injury in preterm infants was thought to reflect a fundamental vulnerability of the developing periventricular white matter to damage. However, recent evidence suggests a much more complex picture. In this chapter, we critically dissect the neuropathology of preterm brain injury, including the timing of injury, the association of hypoxia-ischemia and infection/inflammation with adverse outcomes, and the underappreciated importance of impaired development of both white and gray matter, and highlight key unresolved issues.

The Long-Term Problem: Neurodevelopmental Handicap

Children born preterm (<37 weeks) have high rates of disability, including visual damage, mental retardation, epileptic seizures, and cerebral palsy [5,6]. The incidence of these deficits increases steeply with decreasing gestational age and birth weight [2,6], but even "late preterm" infants (34–36 weeks' gestation) have a sevenfold or more increased risk of brain injury and disability compared with term infants [7]. Further, children who survive without apparent motor disability have a significant reduction in mean IQ and more frequent cognitive and educational difficulties [6].

In the United States, 13% of all births are preterm, costing over $26.2 billion in 2005 alone [8]. Most of this cost is related not to the need for acute care after birth, but rather to long-term costs of disability in surviving infants, particularly the loss of productive members of society [9], in addition to the considerable personal burdens on the individuals and their families. Thus, the lifelong economic impact of preterm birth has been estimated as several times greater than that of chronic neurodegenerative diseases such as Parkinson's disease [8].

Preterm Neuropathology: A Shift to Diffuse White Matter Injury

There has been a dramatic shift in the nature of preterm brain injury and the factors associated with disability in survivors. Historically, the predominant pattern of injury found on postmortem examination after preterm birth was severe necrotic white matter injury (WMI), predominantly in the periventricular tracts (periventricular leukomalacia [PVL]), with evidence of axonal degeneration and loss of cortical neurons [10,11]. This white matter necrosis, in turn, was associated with cerebral palsy (CP) [12,13].

Recent postmortem and imaging studies now suggest that with modern neonatal intensive care, the overall burden of severe cystic PVL has fallen steadily to very low levels (~1% of cases) [14] and that the majority of infants now show a pattern of less severe but widespread diffuse WMI without cystic changes [15,16]. Pathologically, this injury is characterized by diffuse myelination failure associated with reactive astrocytosis and microgliosis without major primary axonal damage [15,17–19]. Previously, selective death of preoligodendrocytes was believed to be the predominant mechanism leading to these diffuse deficits in white matter myelination [20]. Nevertheless, there is now

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strong evidence that preoligodendrocytes can rapidly regenerate in the preterm brain despite severe acute cell death. Indeed, preclinical studies have consistently found that the acute loss of oligodendrocytes in response to hypoxia-ischemia in neonatal rats [21] and preterm fetal sheep [18] rapidly recovers after a rapid proliferative response of the oligodendrocyte progenitor cell population. Similarly, the human neonatal brain exhibits vast numbers of migratory oligodendrocyte progenitors that can easily repopulate the area of injury to replace dying oligodendrocytes [22].

However, compelling human data suggest that these new preoligodendrocytes often become arrested in their maturation, likely at the O4/O1 transition stage, and thus fail to differentiate into myelin-producing cells [15,23,24]. Similarly, arrest of oligodendrocyte maturation has been reported in perinatal animal models of hypoxia-ischemia [18,21,25], chronic hyperoxia [26] or hypoxia [27,28], intrauterine growth restriction [29], and infection/inflammation [30–32]. Experimental models of neonatal WMI have also shown evidence of oligodendrocyte progenitor cell proliferation and impaired maturation in the absence of acute oligodendrocyte cell death [28,31,32].

Diffuse White Matter Injury Is Associated with Disability

It is striking that despite the marked reduction in the severity of WMI over the last decade, even less severe diffuse forms of WMI are associated with impaired brain development and disability [14]. Further, the consistent link between preterm white matter damage and neurodevelopmental impairment [33,34] seems contradictory because we think with our neurons not with white matter [35]. A recent key insight comes from quantitative MRI studies, which show that preterm birth is also associated with regionally specific long-term reductions in brain gray matter volumes in both cortical and subcortical regions, including the thalamus and hippocampus, in addition to reduced white matter volumes [33,36,37].

Use of advanced MRI-based tractography has also shown persisting alterations in connectivity between various brain regions in infants born prematurely [38]. For example, at term equivalent in preterm born infants (median gestation at birth 28 weeks), there was a significant association between frontal and temporal lobe volumes and thalamic and cortical tissue reduction and the loss of microstructural integrity in the connective white matter tracts [39]. Subsequent tractography revealed a significant reduction in connectivity between the thalamus and cortex [38]. Further, while strong resting-state networks involving the thalamus, sensorimotor cortex, brainstem, and cerebellar vermis were observed in term born infants using resting-state functional connectivity MRI, preterm infants at term-equivalent age demonstrated much more limited connectivity [40]. Supporting these findings, both early and late premature birth were associated with reduced long-term depression-like responses to noninvasive transcranial magnetic brain stimulation in adolescence [41], consistent with impaired cortical neuroplasticity. Further, prematurely born adolescents with WMI on MRI exhibited reduced magnetoencephalographic brain activation over the right parietal cortex in response to specific stimuli [42], consistent with a link between early WMI and long-term alterations in cortical function.

These reductions in gray matter volumes and connectivity are correlated with adverse neurodevelopmental outcomes, even after adjustment for the presence of PVL [33,37]. The presence of WMI was associated with greater reduction in gray matter volume [33]. However, a quantitative reduction in cortical surface area and complexity of cortical folding was observed at term equivalent in premature infants without overt parenchymal lesions [43] and in ex-preterm infants at older ages [37,44,45], which correlated with reduced IQ [37,46]. A similar correlation was seen between reduced volume of subcortical gray matter regions, including the caudate nucleus and hippocampus, and long-term functional problems in ex-preterm children, including cognitive ability and memory problems in later childhood and adolescence [47,48]. Further, after long-term follow-up of preterm infants from 4 to 6 years of age, neurocognitive impairment was associated with preceding WMI (and reductions in gray matter volumes), whereas children without WMI exhibited normal neurocognitive development [36]. It remains unclear whether this relationship reflects a direct effect of WMI on cortical development or some common mechanism affecting both the white and the gray matter.

Mechanisms of Chronic Deficits in Gray Matter Development

These persistently adverse outcomes in the setting of diffuse WMI suggest the hypothesis that primary

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neuronal disturbances may occur in multiple cortical and subcortical gray matter structures in addition to disturbances in connectivity related to cerebral WMI.

A Role for Acute Neural Injury?

There is evidence that in some infants these *chronic* anatomic deficits in gray matter partly reflect *acute* neuronal death sustained during the peripartum period, although this seems to be largely associated with evidence of severe WMI. Postmortem case series of infants dying in the early neonatal period show that at least the most severely affected infants do have significant neuronal loss [49–51]. MRI of preterm infants exposed to known severe perinatal asphyxia also demonstrated a consistent pattern of acute subcortical damage involving the thalamus and basal ganglia and cerebellar infarction combined with diffuse periventricular WMI but sparing of the cortex [52].

Moreover, although infants with cystic WMI are now uncommon, this group appears to have reduced numbers of cortical neurons compared with infants without cystic injury [11]. Further, a detailed postmortem analysis suggested that neuronal loss occurred in a third or more of cases of cystic WMI, whereas there was no apparent neuronal loss in infants with only chronic noncystic WMI [35]. Similarly, in human autopsy cases with acute noncystic diffuse WMI, few acutely degenerating cells were observed in the cerebral cortex, in contrast to the cerebral white matter. A quantitative analysis of neuroprostanes, a specific biomarker of neuronal oxidative damage, also found no evidence of acute neuronal degeneration in these patients [20]. It is unclear whether this cortical deficit represents neuronal injury or a secondary consequence of white matter damage. Regardless, the evidence that infants with diffuse WMI have minimal neuronal loss supports the fact that additional mechanisms are involved in impaired gray matter development.

Other Mechanisms of Chronic Deficits in Gray Matter Development?

The data reviewed in the preceding section provide compelling evidence that acute subcortical neuronal injury does accompany severe WMI in a subset of preterm infants. However, this does not seem to be sufficient to explain long-term impairment of brain growth in a majority of premature infants. Indeed, since the preterm gray matter, including the cerebral cortex, is consistently spared both on neuroimaging and histologically in infants with diffuse WMI [35,49,52], chronic reductions in gray matter volumes must involve additional mechanisms.

There is evidence that clinical brain injury evolves progressively. Over half of premature infants who go on to develop CP do not show white matter lesions during the first few days to weeks after birth, but have marked white matter loss on longer-term MRI and evidence of delayed myelination [33]. This is consistent with an experimental study in the postnatal day 7 rat (broadly equivalent to the preterm infant of around 32 weeks' gestation), in which no significant damage was seen during the initial 2 weeks of recovery from moderate hypoxia-ischemia, followed by the development of delayed infarction by 8 weeks [53], in contrast with rapid but nonprogressive infarction after a severe insult. Thus, a mild to moderate ischemic insult to the perinatal brain may establish a vulnerable region in which cell death develops over time. This is likely mediated by enhanced physiologic apoptosis (programmed cell death).

During normal neural development, cells that are surplus to requirement are eliminated by apoptosis [54]. Cell survival is tightly linked to extrinsic signals from neighboring cells and synaptic activity [55], and thus apoptosis is triggered when cells lose essential input from other cells, for example, due to injury elsewhere in the brain or to damage to the interconnecting axons. This ensures matching between the number of myelinating cells to the axonal surface area requiring myelination and the number of neurons to the size of their target fields [55]. Thus, loss of input from other cells can trigger secondary cell death. Indeed, there is evidence of axonal injury within and around areas of periventricular white matter necrosis [17,56,57], which may then lead to target deprivation in the cortex. For example, in a recent postmortem study, diffuse axonal injury was reported both around and distant from areas of white matter necrosis, whereas 31% of infants with WMI had thalamic damage and 15% had neuronal injury in the cerebral cortex overlying areas of PVL [17]. These data support the hypothesis that after severe HI injury, chronic neuronal loss is partly related to target degeneration secondary to damage to the corticothalamic tracts.

During late fetal human development, there is a dramatic expansion of the cerebral cortex that is

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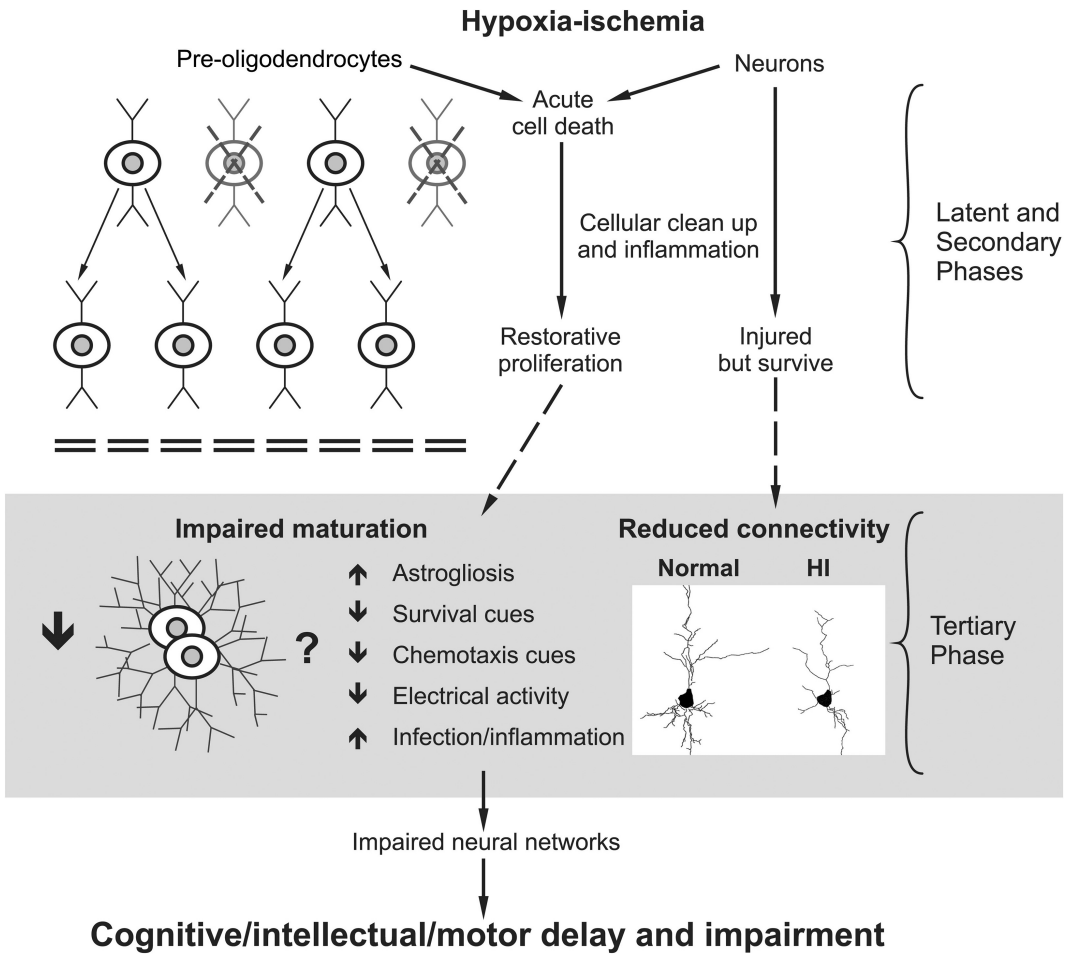


Figure 4.1 Flow diagram outlining the hypothesized relationship between hypoxia and infection/inflammation in the developing brain and long-term reduction in regional brain growth. These mechanisms combine to reduce neuronal arborization (see examples taken 4 weeks after sham control [Con] or hypoxia-ischemia [HI] studies in preterm fetal sheep [59]), leading to persistently impaired connectivity. (Republished by permission from Dean et al. [165].)

largely associated with prolific sprouting of neuronal dendrites, which in turn, mediates the interconnection of neurons [58]. Dean et al. recently found that reversible cerebral ischemia in preterm fetal sheep at 0.65 of gestation, which did not cause acute neuronal loss, was associated with impaired expansion of the dendritic arbor and reduced synaptic density of cortical projection neurons after 4 weeks of recovery (as illustrated in Figure 4.1) [59]. Strikingly, these histologic changes were associated with impairment of cortical growth and the normal maturational decline in cortical fractional anisotropy (FA) on ex vivo MRI scans. Mathematically, these changes in FA after ischemia were consistent with the changes in the growth of dendritic arbor of cortical pyramidal neurons compared with control individuals. These findings are in contrast with the finding in P3 rats that unilateral hypoxia-ischemia leads to markedly reduced FA in the ipsilateral injured cortex [60]. This severe, focal insult causes infarction of the cortex in the middle cerebral artery with disruption of the radial organization, whereas there is no overt cortical injury in the sheep model or typical preterm brain injury in human infants [61].

Supporting the findings in preterm sheep, human survivors of preterm birth show a similar delayed decline in cortical FA consistent with impaired development of cortical gray matter [62,63], whereas FA is reduced in white matter regions [64]. The delayed decline in cortical FA during development before 38

weeks' gestation was proportional to the severity of prematurity and strongly associated both with impaired cortical growth and neurodevelopmental outcomes at 2 years of age [63].

Timing and Etiology of Preterm Brain Injury

Although the precise etiology of acute neural injury in preterm infants is still poorly defined, there is increasing evidence for key events including exposure to hypoxia around the time of birth and preceding (in utero) exposure to infection/inflammation. Postmortem, early imaging, and electroencephalographic (EEG) data suggest that neural injury occurs in the immediate perinatal period in approximately two-thirds of cases, whereas in an appreciable number of cases, injury occurs before the onset of labor, and cases in the chronic postnatal period are the least common [65–67]. EEG abnormalities in the perinatal period are highly predictive of long-term outcome [66,68]. In turn, adverse neonatal and long-term outcomes of premature birth are strongly associated with evidence of exposure to perinatal hypoxia, as shown by metabolic acidosis, active labor, abnormal heart rate traces in labor, and subsequent low Apgar scores [65,69,70]. Although severe perinatal hypoxia only occurs in a minority of premature infants, the incidence is much higher (73/1,000 live births, of which 50% are moderate or severe) than at term (25/1,000 live births, of which 15% are moderate or severe) [71]. While clinical encephalopathy is difficult to assess in very premature infants, larger premature infants, from 31 to 36 weeks' gestation, with moderate to severe metabolic acidosis in cord blood have a high rate of evolving clinical encephalopathy after birth, which in turn, is associated with adverse neurologic outcome [72].

Mechanisms of Hypoxic-Ischemic Injury

Experimentally, prolonged complete umbilical cord occlusion in preterm fetal sheep at 0.6 and 0.7 of gestation is associated with severe neuronal loss in subcortical gray matter regions such as the basal ganglia and hippocampus and diffuse loss of oligodendrocytes in the periventricular white matter, but sparing of the cortex [73–76]. As noted earlier, this pattern is highly consistent with that seen after clinical asphyxia in preterm infants [52]. These data highlight the observation that preterm fetuses and newborns can consistently survive far longer periods of such profound hypoxia than at term before brain injury occurs [77]. Potentially, this remarkable ability to survive may paradoxically allow the preterm fetus to survive longer periods of severe hypoperfusion than is possible at term, as discussed further in Chapter 14.

The localization of WMI to the periventricular region may reflect anatomic vulnerability or relative vulnerability of different populations of oligodendroglia. Older data suggest that there is a transient watershed zone between the short and long penetrating arteries arising from the pia in premature infants [78] that resolves after 32 weeks' gestation. However, more recent data from preterm fetal sheep suggest that the distribution of white matter damage after cerebral ischemia is not explained by differences in local blood flow [79], supporting the hypothesis that the presence of a population of relatively susceptible oligodendrocyte progenitors underlies periventricular WMI.

Postnatal hypotension/hypoperfusion may also contribute to injury. Pathologically low upper body blood flow was found in one-third of infants born before 30 weeks' gestation [80]. In 80% of cases it was lowest at 5–12 hours of age and resolved progressively with time; fewer than 5% of infants had low flows by 48 hours [80,81]. These indirect estimates of cerebral perfusion are supported by evidence of cerebral hypoperfusion on near-infrared spectroscopy [82] and the finding that hypoperfusion is strongly and independently associated with mortality and adverse neurodevelopmental outcome [83].

The mechanisms of this early hypoperfusion are widely debated. It has been suggested that this is potentiated by immaturity of the cerebrovascular autoregulatory response, leading to a pressure-passive circulation, whereby cerebral blood flow is reduced in response to even mild systemic hypotension [84]. Some support for this hypothesis is seen in the finding that many premature infants show a temporal association between changes in mean arterial pressure and intravascular cerebral oxygenation consistent with reduced autoregulation [85]. Further, systemic hypotension after preterm birth has been associated with neurologic deficits in some studies [86–88]. By contrast, many studies in preterm infants have *not* found an association between hypotension during the early neonatal period and PVL or cerebral palsy [89–93]. Curiously, one study found an association only with one definition of hypotension but not others, and

even then only for preterm infants who were ≥27 weeks' gestation and those with less severe illness [93]. This may be because blood pressure is a poor marker of impaired cardiac output and thus of reduced cerebral perfusion [80], and many infants who later develop PVL have an impaired superior vena cava flow despite normal blood pressure [80]. Some have also speculated that, in part, systemic hypoperfusion may be a secondary consequence of preceding exposure to hypoxia [94]. Clearly it is essential to better understand the underlying etiology of hypotension or hypoperfusion before we can understand what to treat. It is striking, for example, that there is still no systematic evidence that treating blood pressure with volume or inotropic agents improves outcome for the majority of babies [95].

Glutamate Excitotoxicity and Preterm White Matter Injury

It is widely hypothesized that exposure of the immature white matter to excitatory amino acids such as glutamate (*excitotoxicity*) during or after exposure to hypoxia-ischemia plays a pivotal role in preterm periventricular WMI [78]. Extracellular glutamate increases dramatically in gray matter during severe hypoxia-ischemia in the term-equivalent and older fetus and newborn [96], and glutamate is highly toxic in vitro [97]. However, even in gray matter there is no clear correlation between the regional increase in glutamate levels during hypoxia-ischemia and ultimate cell death [98], pointing toward differential glutamate receptor distribution and composition as central to in vivo cellular vulnerability [99].

Since white matter lacks synapses, it may seem counterintuitive to implicate glutamate in oligodendrocyte injury. Nevertheless, exposure to high-dose glutaminergic agonists causes severe loss of immature oligodendrocytes both in vivo and in vitro [100,101], and there is in vitro evidence that glutamate can be released from developing oligodendrocytes and axons during hypoxia-ischemia [102,103], for example, through reversal of the glutamate transporter [102,103]. Oligodendrocytes express high levels of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] subtype of glutamate receptor [104], and there is some evidence for transient overexpression of Ca^{2+}-permeable AMPA receptors that could contribute to selective vulnerability of premyelinating oligodendrocytes to hypoxia compared with mature cells [105]. However, against this, in fetal sheep, analysis of receptor subunit expression suggested a high expression of calcium-permeable AMPA receptors in subcortical white matter from near midgestation to term [104]. Finally, there are limited data in the neonatal rat that AMPA receptor blockade after hypoxia-ischemia can reduce loss of oligodendrocytes [106].

Despite these data, it remains unclear whether excitatory amino acids are released by oligodendrocytes or astrocytes at meaningful levels during ischemia in vivo. Although hypoxia-ischemia was associated with a reduction in intracellular glutamate-like reactivity in axons and oligodendrocytes in the white matter of the neonatal rat, extracellular levels of glutamate were not measured [107]. By contrast, a recent study in preterm (0.65 gestation) fetal sheep, an age broadly equivalent to the 26–28 weeks' human infant [79], used microdialysis to demonstrate no significant change in extracellular glutamate levels in the periventricular white matter during or shortly after severe cerebral ischemia (Figure 4.2) [108]. Although a subset of fetuses that were exposed to severe cerebral ischemia showed a delayed increase in extracellular accumulation of most excitatory amino acids, this occurred many days after ischemia, at a time when secondary cytotoxic edema was present [109], strongly suggesting that these changes are mainly an epiphenomenon of failure of release-reuptake mechanisms during evolving cell death and cell lysis (Figure 4.2).

These findings are consistent with data from more mature animals that suggest either no or a minimal increase in extracellular glutamate levels in the white matter tracts during ischemia or asphyxia despite a considerable rise in the gray matter [110–112]. Indeed, in adult cats, whereas extracellular calcium levels rapidly fell after the start of ischemia in gray matter, they actually increased in white matter during the first 20–30 minutes of ischemia and then gradually declined [113], consistent with a lack of acute synaptic activation in white matter during ischemia.

Oxygen Free Radicals

Immature oligodendroglia are also more vulnerable to oxygen free radicals (OFRs) in vitro than mature cells [114]. Such oxidative stress can be mediated by increased extracellular glutamate levels via non-receptor-mediated toxicity in vitro [115], but other pathways may be involved. Consistent with a significant role for OFRs, elevated CSF levels of the lipid

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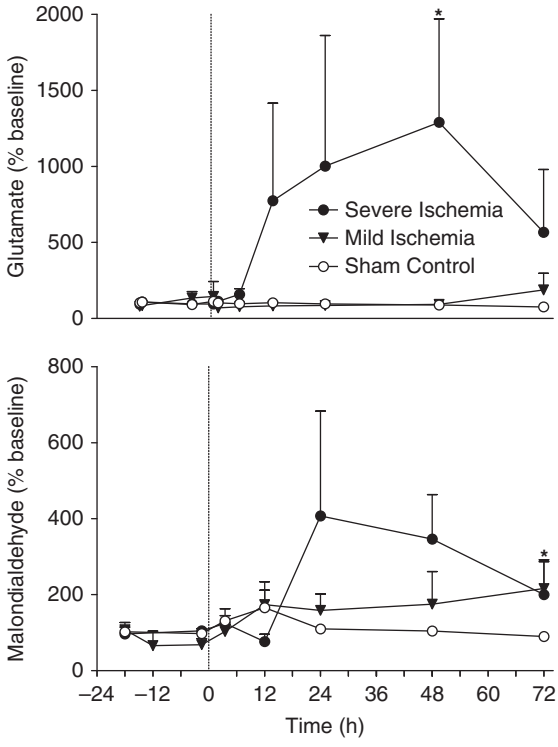


Figure 4.2 Time course of the percent change in extracellular levels of glutamate (top) and the lipid peroxidation product malondialdehyde (bottom) as measured by microdialysis in periventricular white matter in preterm fetal sheep before, during, and following 30 minutes of cerebral ischemia (starting at time 0, shown by the dashed line). Note that malondialdehyde was not measured during ischemia because of sample volume limitations. *$p < 0.05$, severe versus sham-occlusion group by ANCOVA. There was no significant accumulation of either excitatory amino acids such as glutamate or lipid peroxidation products during or shortly after severe cerebral ischemia that was associated with PVL, whereas there was a marked rise well after ischemia [108]. Data are mean ± SEM.

peroxidation products, MDA and 8-isoprostane, in the human premature infant are associated with adverse outcomes [116], and protein nitration and lipid peroxidation of premyelinating oligodendrocytes occur in the diffuse component of PVL [117]. Experimentally, there was a marked increase in cerebral ascorbyl radical production in preterm fetal sheep following umbilical cord occlusion, a model that led to subsequent WMI [118].

By contrast, Fraser et al. found no overall evidence of increased lipid peroxidation in the periventricular white matter after cerebral ischemia in preterm fetal sheep [108]. There was only a trend toward increased 8-isoprostane after ischemia, whereas malondialdehyde increased during the secondary phase of cytotoxic edema, suggesting that lipid peroxidation is also primarily linked with cell death in the developing white matter [108]. Further, the finding that excitatory amino acid levels were not raised during even severe ischemia [115] strongly suggests that non-receptor-mediated glutamate toxicity is unlikely to make a material contribution to PVL. However, it remains possible that there may be aberrantly enhanced activation of Ca^{2+}-permeable AMPA/kainate receptors in response to physiologic extracellular levels of glutamate in the first few hours after cerebral ischemia [119]. Such a mechanism would be consistent with the apparent beneficial effects of AMPA/kainate receptor blockade after hypoxia-ischemia [106] and should be explored further.

Infection/Inflammation and Preterm Brain Injury

In addition to exposure to hypoxia-ischemia, there is increasing evidence of a link between exposure to infection and inflammation and brain damage in preterm infants. Exposure to bacteria and their products such as endotoxin can trigger an inflammatory reaction in the mother or child. This self-defense reaction helps to eliminate or neutralize injurious stimuli and restore tissue integrity [120]. However, excessive neural inflammation may contribute to neural injury [121].

Chorioamnionitis (low-grade infection of the chorionic and amniotic membranes) complicates more than 25% of preterm pregnancies and is strongly associated with preterm labor [122]. In turn, fetal vasculitis (inflammation of blood vessels) in the chorionic plate of the placenta and/or umbilical cord and high levels of proinflammatory cytokines in amniotic and umbilical blood are all highly associated with risk of periventricular WMI in premature babies and with later CP, as reviewed recently [122]. It is striking that the association between fetal vasculitis and CP is much stronger than for chorioamnionitis [121,122]. This suggests that it is the fetal inflammatory response that mediates WMI. These data lead to the hypothesis that inflammatory cytokines released during intrauterine infection both promote preterm delivery and also trigger or exacerbate the development of neural injury in premature infants and later CP [122,123].

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Cytokines and Preterm Brain Injury

Increased levels of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) in cord blood or amniotic fluid have been associated with abnormal cranial ultrasound appearances consistent with WMI and later impaired neurodevelopmental outcome [121]. Preterm infants with cerebral WMI on MRI had higher levels of IL-6, IL-10, and TNF-α in the cerebrospinal (CSF) fluid than infants without WMI [124]. Similarly, elevated cytokine levels in umbilical cord blood predicted cerebral lesions on MRI soon after delivery [125]. In autopsy studies, increased expression of TNF-α, IL-1β, and IL-6 are observed in white matter lesions, mainly in hypertrophic astrocytes and microglial cells around the area of injury [122,126]. There is no treatment for infectious/inflammatory brain injury; indeed, prophylactic maternal antibiotics are associated with *increased* risk of death and disability [127], likely because killing bacteria releases *more* inflammatory bacterial fragments.

Experimental Evidence for a Pathologic Role for Infection and Cytokines

There is increasing direct experimental evidence that these clinical associations are causal. In preterm fetal sheep, exposure to the potent inflammatory bacterial cell wall product lipopolysaccharide (LPS) leads to acute injury of the white matter and cortical subplate neurons, followed by impaired growth of white matter and the cerebral cortex and impaired maturation of electrical activity of the cerebral cortex, closely replicating clinical outcomes [128–130].

However, as discussed earlier, such overt infection is relatively uncommon. Recently, we reported that a stable, low-dose infusion of LPS to preterm fetal sheep over 5 days, which did not perturb fetal blood gases, carotid blood flow, or arterial blood pressure, still markedly impaired the maturation of the cortical EEG [128]. LPS infusion was associated with loss of the normal maturational shift to higher-frequency EEG activity, with reduced alpha and beta power and greater delta power than saline controls from 6 to 10 days (i.e., after the end of the LPS infusion). This impaired cortical maturation developed in the presence of low-grade inflammation, with a transient increase in serum IL-6, induction of microglia, and greater expression of TNF-α-positive cells in the front parietal cortex, consistent with the hypothesis that exposure to proinflammatory cytokines directly contributed to the EEG dysmaturation.

In vitro studies show that proinflammatory cytokines mediate synaptic dysfunction, in part indirectly through adenosine and GABA [131]. These effects appear to be dose dependent, with synaptic inhibition at lower concentrations [132]. Further, TNF-α was reported to inhibit growth and branching of neurons in vitro, which could be reversed by TNF-α receptor blockade [133]. Similarly, exposure to interferon γ, an inflammatory marker that is induced by injury and many inflammatory conditions, is associated with both inhibition of initial dendritic outgrowth in culture and retraction of existing dendrites [134]. Thus, it is highly plausible that chronic low levels of cerebral cytokines associated with infection or with traumatic events such as ventilation can reduce neural excitability and impair connectivity in the cortex. Further long-term studies are essential to confirm this hypothesis.

Synergy with Other Insults: Sensitization and Tolerance

This apparent association between prenatal hypoxia and perinatal infection/inflammation may reflect a combined or even synergistic effect on neuronal development. There are parallels from experimental data in rodents that exposure to mild infection or inflammation can interact to either increase or decrease injury from subsequent insults. For example, intrauterine infection with gram-negative bacteria in the rabbit leads to fetal white matter lesions [122]. In order to investigate the mechanisms of this link, most studies have used the gram-negative endotoxin LPS, a potent inflammatory agent that initiates most components of an inflammatory response [135]. LPS given to the mother intra-amniotically and to the fetus in a variety of species including the fetal rat, mouse, and sheep is associated with white matter damage [121].

The cytokines upregulated following LPS administration include IL-6, IL-8, and TNF-α [135–137]. Their levels typically increase within 2 to 6 hours after LPS administration and then resolve [135], and there is marked attenuation of response with repeated exposure [135]. In fetal sheep, plasma IL-6 and IL-8 concentrations were undetectable 28 days after LPS exposure [136]. In turn, there is evidence that exogenous administration or overexpression of cytokines increases hypoxic or excitotoxic injury in white and gray matter [138], whereas inhibition or

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downregulation of cytokines can reduce ischemic injury [139,140]. Further, in adult mice, neural inflammation precedes the progressive enlargement of brain infarction after hypoxia-ischemia, suggesting that the inflammation is causal rather than a consequence of damage [139].

It is important to appreciate that some cytokines have anti-inflammatory [141] and neuroprotective properties [142]. For example, exogenous transforming growth factor β (TGF-β) and IL-10 can reduce postischemic injury [143,144]. Thus it is likely that the balance between pro- and anti-inflammatory mediators helps to determine whether the inflammatory response causes injury. The potential mechanisms of inflammatory injury include direct toxicity to neurons and white matter cells; immature oligodendrocytes at the stage found in premature infants when they are at greatest risk of PVL [145] seem to be particularly vulnerable [146].

Cytokines can induce apoptosis in many cell types and promote stimulation of capillary endothelial cell proinflammatory responses and leukocyte adhesion and infiltration into the ischemic brain [147]. Further, intracerebral injection of cytokines induces a marked local astrogliosis [148], and cytokines trigger microglial activation with subsequent release of nitric oxide, superoxides, and other inflammatory mediators [149]. Combined neuronal and inducible nitric oxide synthase inhibition in the newborn rat is neuroprotective after hypoxia-ischemia without altering cytokine responses [150], strongly suggesting that much of the toxicity associated with cytokine induction is mediated through release of inducible nitric oxide from microglia.

The Role of Microglia

Microglia form a network of endogenous immunocompetent cells whose primary function is to provide continuous surveillance of the parenchyma and protect the brain during injury and disease [151]. In parallel with the evidence that inflammation has both protective and damaging effects, activated microglia seem to be a "double-edged sword" in the central nervous system [152]. In vitro, for example, microglia promote viability and differentiation of oligodendrocyte progenitor cells under physiologic conditions, whereas they mediate cytotoxic effects after activation by LPS [153]. Activated microglia produce a range of potentially toxic mediators, including cytokines, which in turn, increase the permeability of the blood-brain barrier [154] and may increase entry of macrophages and leukocytes into the brain. High levels of TNF-α, IL-6, and IFN-γ are expressed in macrophages and/or astrocytes in regions of white matter damage in the developing brain [122,155].

Consistent with these data, LPS exposure in fetal sheep was associated with microgliosis rather than astrogliosis in regions of subcortical WMI [137]. There was a significant correlation between the intensity of microglial/macrophage invasion and the severity of WMI, supporting a role for microglial activation in the manifestation of and/or response to injury [137]. A similar link has been reported after excitotoxin damage in mice [156] and in neonatal human neuropathology [157]. It is still unclear whether these cells mainly originate from populations of microglia resident in the brain or may be macrophages invading from the circulation [137].

Conversely, suppression of microglial activation with the tetracycline antibiotic minocycline reduced neural cell loss after LPS infusion in neonatal rats [158]. Similarly, reduced WMI with IL-10 injections in fetal rat pups that had been exposed to *Escherichia coli* infection was associated with suppression of microglial activation, supporting a central role for activated microglia in the genesis of antenatal PVL [159].

Potential Confounding Factors

Potential confounding factors associated with exposure to bacterial products and the inflammatory response in general include pyrexia and secondary tissue hypoxia. For example, maternal pyrexia is associated with adverse neurologic outcome in newborn infants, and hyperthermia greatly exacerbates neurologic injury after hypoxia-ischemia [160]. However, fetal infusions of LPS do not cause pyrexia [161], and thus LPS can cause WMI independently of pyrexia [135,162]. Infection/inflammation may also be associated with secondary hypoxemia and transient hypotension that could compromise cerebral perfusion [135,163]. However, in practice, in preterm fetal sheep, carotid blood flow was increased despite the fall in blood pressure [163]. Further, others found mild cerebral injury despite no change in mean arterial blood pressure following a single intra-amniotic dose of LPS in near-term fetal sheep [164].

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Conclusion

In conclusion, the most striking concept to emerge from recent clinical and experimental studies of the very immature brain has been that perinatal WMI is associated with both acute subcortical gray matter injury and a long-term reduction in gray matter growth and complexity and cognitive impairment. The emerging concept that underpins these observations is that acute early white and gray matter cell loss is associated with exposure to hypoxia and to infection/inflammation, and that this acute injury initiates a phase of chronic programmed cell death that underlies impaired neurodevelopment. The widely hypothesized roles for free-radical-mediated injury and excitotoxicity, on the one hand, and of hypotension/hypoperfusion, on the other, remain surprising and unclear and require further research.

References

1. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics* 2005; **115**: 997–1003.
2. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ (Clinical Research Edition)* 2012; **345**: e7961.
3. Schlapbach LJ, Adams M, Proietti E, et al. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. *BMC Pediatrics* 2012; **12**: 198.
4. Hintz SR, Kendrick DE, Wilson-Costello DE, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. *Pediatrics* 2011; **127**: 62–70.
5. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. *Pediatrics* 2007; **119**: 37–45.
6. Hack M. Young adult outcomes of very-low-birth-weight children. *Semin Fetal Neonatal Med* 2006; **11**: 127–37.
7. Baron IS, Erickson K, Ahronovich MD, et al. Cognitive deficit in preschoolers born late preterm. *Early Hum Dev.* 2011; **87**: 115–9.
8. Committee on Understanding Premature Birth and Assuring Healthy Outcomes, Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. Washington, DC: Institute of Medicine of the National Academies, 2007. Available from http://books.nap.edu/openbook.php?record_id=11622&page=1.
9. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008; **371**: 261–9.
10. Perlman JM. White matter injury in the preterm infant: an important determination of abnormal neurodevelopment outcome. *Early Hum Dev* 1998; **53**: 99–120.
11. Andiman SE, Haynes RL, Trachtenberg FL, et al. The cerebral cortex overlying periventricular leukomalacia: analysis of pyramidal neurons. *Brain Pathol* 2010; **20**: 803–14.
12. Reid SM, Ditchfield MR, Bracken J, Reddihough DS. Relationship between characteristics on magnetic resonance imaging and motor outcomes in children with cerebral palsy and white matter injury. *Res Dev Disabil* 2015; **45–6**: 178–87.
13. Okumura A, Kato T, Kuno K, et al. MRI findings in patients with spastic cerebral palsy. II. Correlation with type of cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 369–72.
14. Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr* 2004; **145**: 593–9.
15. Buser JR, Maire J, Riddle A, et al. Arrested preoligodendrocyte maturation contributes to myelination failure in premature infants. *Ann Neurol* 2012; **71**: 93–109.
16. Gano D, Andersen SK, Partridge JC, et al. Diminished white matter injury over time in a cohort of premature newborns. *J Pediatr* 2015; **166**: 39–43.
17. Haynes RL, Billiards SS, Borenstein NS, et al. Diffuse axonal injury in periventricular leukomalacia as determined by apoptotic marker fractin. *Pediatr Res* 2008; **63**: 656–61.
18. Riddle A, Dean J, Buser JR, et al. Histopathological correlates of magnetic resonance imaging-defined chronic perinatal white matter injury. *Ann Neurol* 2011; **70**: 493–507.
19. Riddle A, Maire J, Gong X, et al. Differential susceptibility to axonopathy in necrotic and non-necrotic perinatal white matter injury. *Stroke* 2012; **43**: 178–84.
20 Back SA, Luo NL, Mallinson RA, et al. Selective vulnerability of preterm white matter to oxidative damage defined by F2-isoprostanes. *Ann Neurol* 2005; **58**: 108–20.
21. Segovia KN, McClure M, Moravec M, et al. Arrested oligodendrocyte lineage maturation in chronic perinatal white matter injury. *Ann Neurol* 2008; **63**: 520–30.

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22. Franklin RJ, Gallo V. The translational biology of remyelination: past, present, and future. *Glia* 2014; **62**: 1905–15.
23. Billiards SS, Haynes RL, Folkerth RD, et al. Myelin abnormalities without oligodendrocyte loss in periventricular leukomalacia. *Brain Pathol* 2008; **18**: 153–63.
24. Verney C, Pogledic I, Biran V, et al. Microglial reaction in axonal crossroads is a hallmark of noncystic periventricular white matter injury in very preterm infants. *J Neuropathol Exp Neurol* 2012; **71**: 251–64.
25. Davidson JO, Drury PP, Green CR, et al. Connexin hemichannel blockade is neuroprotective after asphyxia in preterm fetal sheep. *PLoS One* 2014; **9**: e96558.
26. Ritter J, Schmitz T, Chew LJ, et al. Neonatal hyperoxia exposure disrupts axon-oligodendrocyte integrity in the subcortical white matter. *J Neurosci* 2013; **33**: 8990–9002.
27. Jablonska B, Scafidi J, Aguirre A, et al. Oligodendrocyte regeneration after neonatal hypoxia requires Fox O_1-mediated p27Kip1 expression. *J Neurosci* 2012; **32**: 14775–93.
28. Yuen TJ, Silbereis JC, Griveau A, et al. Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. *Cell* 2014; **158**: 383–96.
29. Tolcos M, Bateman E, O'Dowd R, et al. Intrauterine growth restriction affects the maturation of myelin. *Exp Neurol* 2011; **232**: 53–65.
30. Brehmer F, Bendix I, Prager S, et al. Interaction of inflammation and hyperoxia in a rat model of neonatal white matter damage. *PloS One* 2012; **7**: e49023.
31. Favrais G, van de Looij Y, Fleiss B, et al. Systemic inflammation disrupts the developmental program of white matter. *Ann Neurol* 2011; **70**: 550–65.
32. Nobuta H, Ghiani CA, Paez PM, et al. STAT3-mediated astrogliosis protects myelin development in neonatal brain injury. *Ann Neurol* 2012; **72**: 750–65.
33. Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006; **355**: 685–94.
34. Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. *J Pediatr* 2005; **147**: 609–16.
35. Pierson CR, Folkerth RD, Billiards SS, et al. Gray matter injury associated with periventricular leukomalacia in the premature infant. *Acta Neuropathol* 2007; **114**: 619–31.
36. Lin Y, Okumura A, Hayakawa F, et al. Quantitative evaluation of thalami and basal ganglia in infants with periventricular leukomalacia. *Dev Med Child Neurol* 2001; **43**: 481–5.
37. Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA* 2000; **284**: 1939–47.
38. Counsell SJ, Dyet LE, Larkman DJ, et al. Thalamo-cortical connectivity in children born preterm mapped using probabilistic magnetic resonance tractography. *Neuroimage* 2007; **34**: 896–904.
39. Ball G, Boardman JP, Rueckert D, et al. The effect of preterm birth on thalamic and cortical development. *Cereb Cortex* 2012; **22**: 1016–24.
40. Smyser CD, Snyder AZ, Shimony JS, et al. Effects of white matter injury on resting state fMRI measures in prematurely born infants. *PloS One* 2013; **8**: e68098.
41. Pitcher JB, Riley AM, Doeltgen SH, et al. Physiological evidence consistent with reduced neuroplasticity in human adolescents born preterm. *J Neurosci* 2012; **32**: 16410–6.
42. Pitcher JB, Schneider LA, Burns NR, et al. Reduced corticomotor excitability and motor skills development in children born preterm. *J Physiol* 2012; **590**: 5827–44.
43. Ajayi-Obe M, Saeed N, Cowan FM, et al. Reduced development of cerebral cortex in extremely preterm infants. *Lancet* 2000; **356**: 1162–3.
44. Nosarti C, Al-Asady MH, Frangou S, et al. Adolescents who were born very preterm have decreased brain volumes. *Brain* 2002; **125**: 1616–23.
45. Martinussen M, Fischl B, Larsson HB, et al. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain* 2005; **128**: 2588–96.
46. Isaacs EB, Edmonds CJ, Chong WK, et al. Brain morphometry and IQ measurements in preterm children. *Brain* 2004; **127**: 2595–607.
47. Abernethy LJ, Cooke RW, Foulder-Hughes L. Caudate and hippocampal volumes, intelligence, and motor impairment in 7-year-old children who were born preterm. *Pediatr Res* 2004; **55**: 884–93.
48. Gimenez M, Junque C, Narberhaus A, et al. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. *Neuroimage* 2004; **23**: 869–77.
49. Felderhoff-Mueser U, Rutherford MA, Squier WV, et al. Relationship between MR imaging and histopathologic findings of the brain in extremely sick preterm infants. *AJNR Am J Neuroradiol* 1999; **20**: 1349–57.
50. Takizawa Y, Takashima S, Itoh M. A histopathological study of premature and mature infants with

pontosubicular neuron necrosis: neuronal cell death in perinatal brain damage. *Brain Res* 2006; **1095**: 200–6.

51. Bell JE, Becher JC, Wyatt B, et al. Brain damage and axonal injury in a Scottish cohort of neonatal deaths. *Brain* 2005; **128**: 1070–81.
52. Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. *AJNR Am J Neuroradiol* 1995; **16**: 1837–46.
53. Geddes R, Vannucci RC, Vannucci SJ. Delayed cerebral atrophy following moderate hypoxia-ischemia in the immature rat. *Dev Neurosci* 2001; **23**: 180–5.
54. Goldberg JL, Barres BA. The relationship between neuronal survival and regeneration. *Annu Rev Neurosci* 2000; **23**: 579–612.
55. Jacobson MD, Weil M, Raff MC. Programmed cell death in animal development. *Cell* 1997; **88**: 347–54.
56. Meng SZ, Arai Y, Deguchi K, Takashima S. Early detection of axonal and neuronal lesions in prenatal-onset periventricular leukomalacia. *Brain Dev* 1997; **19**: 480–4.
57. Hirayama A, Okoshi Y, Hachiya Y, et al. Early immunohistochemical detection of axonal damage and glial activation in extremely immature brains with periventricular leukomalacia. *Clin Neuropathol* 2001; **20**: 87–91.
58. de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? *Early Hum Dev* 2006; **82**: 257–66.
59. Dean JM, McClendon E, Hansen K, et al. Prenatal cerebral ischemia disrupts MRI-defined cortical microstructure through disturbances in neuronal arborization. *Sci Transl Med* 2013; **5**: 168ra7.
60. Sizonenko SV, Camm EJ, Garbow JR, et al. Developmental changes and injury induced disruption of the radial organization of the cortex in the immature rat brain revealed by in vivo diffusion tensor MRI. *Cereb Cortex* 2007; **17**: 2609–17.
61. Back SA, Riddle A, Dean J, Hohimer AR. The instrumented fetal sheep as a model of cerebral white matter injury in the premature infant. *Neurotherapeutics* 2012; **9**: 359–70.
62. Vinall J, Grunau RE, Brant R, et al. Slower postnatal growth is associated with delayed cerebral cortical maturation in preterm newborns. *Sci Transl Med* 2013; **5**: 168ra8.
63. Ball G, Srinivasan L, Aljabar P, et al. Development of cortical microstructure in the preterm human brain. *Proc Natl Acad Sci USA* 2013; **110**: 9541–6.
64. Constable RT, Ment LR, Vohr BR, et al. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. *Pediatrics* 2008; **121**: 306–16.
65. de Vries LS, Eken P, Groenendaal F, et al. Antenatal onset of haemorrhagic and/or ischaemic lesions in preterm infants: prevalence and associated obstetric variables. *Arch Dis Child Fetal Neonatal Ed* 1998; **78**: F51–6.
66. Hayakawa F, Okumura A, Kato T, et al. Determination of timing of brain injury in preterm infants with periventricular leukomalacia with serial neonatal electroencephalography. *Pediatrics* 1999; **104**: 1077–81.
67. Becher JC, Bell JE, Keeling JW, et al. The Scottish perinatal neuropathology study: clinicopathological correlation in early neonatal deaths. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F399–407.
68. Kubota T, Okumura A, Hayakawa F, et al. Combination of neonatal electroencephalography and ultrasonography: sensitive means of early diagnosis of periventricular leukomalacia. *Brain Dev* 2002; **24**: 698–702.
69. Weinberger B, Anwar M, Hegyi T, et al. Antecedents and neonatal consequences of low Apgar scores in preterm newborns: a population study. *Arch Pediatr Adolesc Med* 2000; **154**: 294–300.
70. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics* 2003; **112**: 33–9.
71. Low JA. Determining the contribution of asphyxia to brain damage in the neonate. *J Obstet Gynaecol Res* 2004; **30**: 276–86.
72. Salhab WA, Perlman JM. Severe fetal acidemia and subsequent neonatal encephalopathy in the larger premature infant. *Pediatr Neurol* 2005; **32**: 25–9.
73. George S, Gunn AJ, Westgate JA, et al. Fetal heart rate variability and brainstem injury after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R925–33.
74. Dean JM, George SA, Wassink G, et al. Suppression of post hypoxic-ischemic EEG transients with dizocilpine is associated with partial striatal protection in the preterm fetal sheep. *Neuropharmacology* 2006; **50**: 491–503.
75. Dean JM, Gunn AJ, Wassink G, et al. Endogenous alpha[2]-adrenergic receptor-mediated neuroprotection after severe hypoxia in preterm fetal sheep. *Neuroscience* 2006; **142**: 615–28.
76. Bennet L, Roelfsema V, George S, et al. The effect of cerebral hypothermia on white and gray matter injury induced by severe hypoxia in preterm fetal sheep. *J Physiol* 2007; **578**: 491–506.

77. Gunn AJ, Quaedackers JS, Guan J, et al. The premature fetus: not as defenseless as we thought, but still paradoxically vulnerable? *Dev Neurosci* 2001; **23**: 175–9.

78. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 2001; **50**: 553–62.

79. Riddle A, Luo NL, Manese M, et al. Spatial heterogeneity in oligodendrocyte lineage maturation and not cerebral blood flow predicts fetal ovine periventricular white matter injury. *J Neurosci* 2006; **26**: 3045–55.

80. Osborn DA, Evans N, Kluckow M. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central-peripheral temperature difference. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F168–73.

81. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F182–7.

82. Meek JH, Elwell CE, McCormick DC, et al. Abnormal cerebral haemodynamics in perinatally asphyxiated neonates related to outcome. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F110–15.

83. Hunt RW, Evans N, Rieger I, Kluckow M. Low superior vena cava flow and neurodevelopment at 3 years in very preterm infants. *J Pediatr* 2004; **145**: 588–92.

84. Lou HC, Lassen NA, Tweed WA, et al. Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. *Acta Paediatr Scand* 1979; **68**: 57–63.

85. Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007; **61**: 467–73.

86. Martens SE, Rijken M, Stoelhorst GM, et al. Is hypotension a major risk factor for neurological morbidity at term age in very preterm infants? *Early Hum Dev* 2003; **75**: 79–89.

87. Murphy DJ, Hope PL, Johnson A. Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. *BMJ* 1997; **314**: 404–8.

88. Low JA, Froese AB, Galbraith RS, et al. The association between preterm newborn hypotension and hypoxemia and outcome during the first year. *Acta Paediatr* 1993; **82**: 433–7.

89. Trounce JQ, Shaw DE, Levene MI, Rutter N. Clinical risk factors and periventricular leucomalacia. *Arch Dis Child*. 1988; **63**: 17–22.

90. Perlman JM, Risser R, Broyles RS. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. *Pediatrics* 1996; **97**: 822–7.

91. Dammann O, Allred EN, Kuban KC, et al. Systemic hypotension and white-matter damage in preterm infants. *Dev Med Child Neurol* 2002; **44**: 82–90.

92. Cunningham S, Symon AG, Elton RA, et al. Intra-arterial blood pressure reference ranges, death and morbidity in very low birth weight infants during the first seven days of life. *Early Hum Dev* 1999; **56**: 151–65.

93. Limperopoulos C, Bassan H, Kalish LA, et al. Current definitions of hypotension do not predict abnormal cranial ultrasound findings in preterm infants. *Pediatrics* 2007; **120**: 966–77.

94. Bennet L, Booth L, Malpas SC, et al. Acute systemic complications in the preterm fetus after asphyxia: the role of cardiovascular and blood flow responses. *Clin Exp Pharmacol Physiol* 2006; **33**: 291–9.

95. Osborn DA. Diagnosis and treatment of preterm transitional circulatory compromise. *Early Hum Dev* 2005; **81**: 413–22.

96. Tan WK, Williams CE, During MJ, et al. Accumulation of cytotoxins during the development of seizures and edema after hypoxic-ischemic injury in late gestation fetal sheep. *Pediatr Res* 1996; **39**: 791–7.

97. Choi DW. Excitotoxic cell death. *J Neurobiol* 1992; **23**: 1261–76.

98. Mitani A, Andou Y, Kataoka K. Selective vulnerability of hippocampal CA1 neurons cannot be explained in terms of an increase in glutamate concentration during ischemia in the gerbil: brain microdialysis study. *Neuroscience* 1992; **48**: 307–13.

99. McDonald JW, Johnston MV, Young AB. Differential ontogenic development of three receptors comprising the NMDA receptor/channel complex in the rat hippocampus. *Exp Neurol* 1990; **110**: 237–47.

100. Fern R, Moller T. Rapid ischemic cell death in immature oligodendrocytes: a fatal glutamate release feedback loop. *J Neurosci* 2000; **20**: 34–42.

101. Follett PL, Rosenberg PA, Volpe JJ, Jensen FE. NBQX attenuates excitotoxic injury in developing white matter. *J Neurosci* 2000; **20**: 9235–41.

102. Rossi DJ, Oshima T, Attwell D. Glutamate release in severe brain ischaemia is mainly by reversed uptake. *Nature* 2000; **403**: 316–21.

103. Desilva TM, Kinney HC, Borenstein NS, et al. The glutamate transporter EAAT2 is transiently expressed in developing human cerebral white matter. *J Comp Neurol* 2007; **501**: 879–90.

104. Dean JM, Fraser M, Shelling AN, et al. Ontogeny of AMPA and NMDA receptor gene expression in the developing sheep white matter and cerebral cortex. *Brain Res Mol Brain Res* 2005; **139**: 242–50.

105. Itoh T, Beesley J, Itoh A, et al. AMPA glutamate receptor-mediated calcium signaling is transiently enhanced during development of oligodendrocytes. *J Neurochem* 2002; **81**: 390–402.

106. Follett PL, Deng W, Dai W, et al. Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. *J Neurosci* 2004; **24**: 4412–20.

107. Back SA, Riddle A, McClure MM. Maturation-dependent vulnerability of perinatal white matter in premature birth. *Stroke* 2007; **38**: 724–30.

108. Fraser M, Bennet L, van Zijl PL, et al. Extracellular amino acids and peroxidation products in the periventricular white matter during and after cerebral ischemia in preterm fetal sheep. *J Neurochem* 2008; **105**: 2214–23.

109. Fraser M, Bennet L, Gunning M, et al. Cortical electroencephalogram suppression is associated with post-ischemic cortical injury in 0.65 gestation fetal sheep. *Brain Res Dev Brain Res* 2005; **154**: 45–55.

110. Dohmen C, Kumura E, Rosner G, et al. Extracellular correlates of glutamate toxicity in short-term cerebral ischemia and reperfusion: a direct in vivo comparison between white and gray matter. *Brain Res* 2005; **1037**: 43–51.

111. Henderson JL, Reynolds JD, Dexter F, et al. Chronic hypoxemia causes extracellular glutamate concentration to increase in the cerebral cortex of the near-term fetal sheep. *Brain Res Dev Brain Res* 1998; **105**: 287–93.

112. Loeliger M, Watson CS, Reynolds JD, et al. Extracellular glutamate levels and neuropathology in cerebral white matter following repeated umbilical cord occlusion in the near term fetal sheep. *Neuroscience* 2003; **116**: 705–14.

113. Kumura E, Graf R, Dohmen C, et al. Breakdown of calcium homeostasis in relation to tissue depolarization: comparison between gray and white matter ischemia. *J Cereb Blood Flow Metab* 1999; **19**: 788–93.

114. Back SA, Gan X, Li Y, et al. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *J Neurosci* 1998; **18**: 6241–53.

115. Rosin C, Bates TE, Skaper SD. Excitatory amino acid induced oligodendrocyte cell death in vitro: receptor-dependent and -independent mechanisms. *J Neurochem* 2004; **90**: 1173–85.

116. Inder T, Mocatta T, Darlow B, et al. Elevated free radical products in the cerebrospinal fluid of VLBW infants with cerebral white matter injury. *Pediatr Res* 2002; **52**: 213–8.

117. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003; **62**: 441–50.

118. Welin AK, Sandberg M, Lindblom A, et al. White matter injury following prolonged free radical formation in the 0.65 gestation fetal sheep brain. *Pediatr Res* 2005; **58**: 100–5.

119. Deng W, Rosenberg PA, Volpe JJ, Jensen FE. Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. *Proc Natl Acad Sci USA* 2003; **100**: 6801–6.

120. Willoughby RE, Jr., Nelson KB. Chorioamnionitis and brain injury. *Clin Perinatol* 2002; **29**: 603–21.

121. Wang X, Rousset CI, Hagberg H, Mallard C. Lipopolysaccharide-induced inflammation and perinatal brain injury. *Semin Fetal Neonatal Med* 2006; **11**: 343–53.

122. Yoon BH, Park CW, Chaiworapongsa T. Intrauterine infection and the development of cerebral palsy. *BJOG* 2003; **110**: 124–7.

123. Holcroft CJ, Blakemore KJ, Allen M, Graham EM. Association of prematurity and neonatal infection with neurologic morbidity in very low birth weight infants. *Obstet Gynecol* 2003; **101**: 1249–53.

124. Ellison VJ, Mocatta TJ, Winterbourn CC, et al. The relationship of CSF and plasma cytokine levels to cerebral white matter injury in the premature newborn. *Pediatr Res* 2005; **57**: 282–6.

125. Duggan PJ, Maalouf EF, Watts TL, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001; **358**: 1699–700.

126. Kadhim H, Tabarki B, Verellen G, et al. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. *Neurology* 2001; **56**: 1278–84.

127. Flenady V, Hawley G, Stock OM, et al. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database of Systematic Reviews* 2013; **12**: CD000246.

128. Keogh MJ, Bennet L, Drury PP, et al. Subclinical exposure to low-dose endotoxin impairs EEG maturation in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2012; **303**: R270–8.

129. Dean JM, van de Looij Y, Sizonenko SV, et al. Delayed cortical impairment following lipopolysaccharide exposure in preterm fetal sheep. *Ann Neurol* 2011; **70**: 846–56.

130. Mathai S, Booth LC, Davidson JO, et al. Acute on chronic exposure to endotoxin in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2013; **304**: R189–97.

131. Hellstrom IC, Danik M, Luheshi GN, Williams S. Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained

IL-β-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. *Hippocampus* 2005; **15**: 656–64.

132. Luk WP, Zhang Y, White TD, et al. Adenosine: a mediator of interleukin-1beta-induced hippocampal synaptic inhibition. *J Neurosci* 1999; **19**: 4238–44.

133. Summers deLuca L, Gommerman JL. Fine-tuning of dendritic cell biology by the TNF superfamily. *Nat Rev Immunol* 2012; **12**: 339–51.

134. Kim IJ, Beck HN, Lein PJ, Higgins D. Interferon gamma induces retrograde dendritic retraction and inhibits synapse formation. *J Neurosci* 2002; **22**: 4530–9.

135. Duncan JR, Cock ML, Scheerlinck JP, et al. White matter injury after repeated endotoxin exposure in the preterm ovine fetus. *Pediatr Res* 2002; **52**: 941–9.

136. Nitsos I, Rees SM, Duncan J, et al. Chronic exposure to intra-amniotic lipopolysaccharide affects the ovine fetal brain. *J Soc Gynecol Invest* 2006; **13**: 239–47.

137. Duncan JR, Cock ML, Suzuki K, et al. Chronic endotoxin exposure causes brain injury in the ovine fetus in the absence of hypoxemia. *J Soc Gynecol Invest* 2006; **13**: 87–96.

138. Dommergues MA, Patkai J, Renauld JC, et al. Proinflammatory cytokines and interleukin-9 exacerbate excitotoxic lesions of the newborn murine neopallium. *Ann Neurol* 2000; **47**: 54–63.

139. Basu A, Lazovic J, Krady JK, et al. Interleukin-1 and the interleukin-1 type 1 receptor are essential for the progressive neurodegeneration that ensues subsequent to a mild hypoxic/ischemic injury. *J Cereb Blood Flow Metab* 2005; **25**: 17–29.

140. Loddick SA, Wong ML, Bongiorno PB, et al. Endogenous interleukin-1 receptor antagonist is neuroprotective. *Biochem Biophys Res Commun* 1997; **234**: 211–5.

141. Kremlev SG, Palmer C. Interleukin-10 inhibits endotoxin-induced pro-inflammatory cytokines in microglial cell cultures. *J Neuroimmunol* 2005; **162**: 71–80.

142. Loddick SA, Turnbull AV, Rothwell NJ. Cerebral interleukin-6 is neuroprotective during permanent focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 1998; **18**: 176–9.

143. Guan J, Miller OT, Waugh KM, et al. TGF-β1 and neurological function after hypoxia-ischemia in adult rats. *Neuroreport* 2004; **15**: 961–4.

144. Spera PA, Ellison JA, Feuerstein GZ, Barone FC. IL-10 reduces rat brain injury following focal stroke. *Neurosci Lett* 1998; **251**: 189–92.

145. Back SA, Luo NL, Borenstein NS, et al. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci* 2001; **21**: 1302–12.

146. Cai Z, Lin S, Pang Y, Rhodes PG. Brain injury induced by intracerebral injection of interleukin-1β and tumor necrosis factor α in the neonatal rat. *Pediatr Res* 2004; **56**: 377–84.

147. Allan SM, Rothwell NJ. Inflammation in central nervous system injury. *Philos Trans R Soc Lond B* 2003; **358**: 1669–77.

148. Woiciechowsky C, Schoning B, Stoltenburg-Didinger G, et al. Brain-IL-1β triggers astrogliosis through induction of IL-6: inhibition by propranolol and IL-10. *Med Sci Monit* 2004; **10**:BR325–30.

149. Bal-Price A, Brown GC. Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. *J Neurosci* 2001; **21**: 6480–91.

150. van den Tweel ER, Nijboer C, Kavelaars A, et al. Expression of nitric oxide synthase isoforms and nitrotyrosine formation after hypoxia-ischemia in the neonatal rat brain. *J Neuroimmunol* 2005; **167**: 64–71.

151. Raivich G, Bohatschek M, Kloss CU, et al. Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res Rev* 1999; **30**: 77–105.

152. Rock RB, Gekker G, Hu S, et al. Role of microglia in central nervous system infections. *Clin Microbiol Rev* 2004; **17**: 942–64.

153. Pang Y, Cai Z, Rhodes PG. Effects of lipopolysaccharide on oligodendrocyte progenitor cells are mediated by astrocytes and microglia. *J Neurosci Res* 2000; **62**: 510–20.

154. Yan E, Castillo-Melendez M, Nicholls T, Hirst J, Walker D. Cerebrovascular responses in the fetal sheep brain to low-dose endotoxin. *Pediatr Res* 2004; **55**: 855–63.

155. Folkerth RD, Keefe RJ, Haynes RL, et al. Interferon-gamma expression in periventricular leukomalacia in the human brain. *Brain Pathol* 2004; **14**: 265–74.

156. Tahraoui SL, Marret S, Bodenant C, et al. Central role of microglia in neonatal excitotoxic lesions of the murine periventricular white matter. *Brain Pathol* 2001; **11**: 56–71.

157. Kinney HC. Human myelination and perinatal white matter disorders. *J Neurol Sci* 2005; **228**: 190–2.

158. Fan LW, Pang Y, Lin S, et al. Minocycline attenuates lipopolysaccharide-induced white matter injury in the neonatal rat brain. *Neuroscience* 2005; **133**: 159–68.

159. Pang Y, Rodts-Palenik S, Cai Z, et al. Suppression of glial activation is involved in the protection of IL-10 on maternal *E. coli*-induced neonatal white matter injury. *Brain Res Dev Brain Res* 2005; **157**: 141–9.

160. Gunn AJ, Bennet L. Is temperature important in delivery room resuscitation? *Semin Neonatol* 2001; **6**: 241–9.

161. Yoneyama Y, Sawa R, Kubonoya K, et al. Evidence for mechanisms of the acute-phase response to endotoxin in late-gestation fetal goats. *Am J Obstet Gynecol* 1998; **179**: 750–5.

162. Mallard C, Welin AK, Peebles D, et al. White matter injury following systemic endotoxemia or asphyxia in the fetal sheep. *Neurochem Res* 2003; **28**: 215–23.

163. Peebles DM, Miller S, Newman JP, et al. The effect of systemic administration of lipopolysaccharide on cerebral haemodynamics and oxygenation in the 0.65 gestation ovine fetus in utero. *BJOG* 2003; **110**: 735–43.

164. Nitsos I, Moss TJ, Cock ML, et al. Fetal responses to intra-amniotic endotoxin in sheep. *J Soc Gynecol Invest* 2002; **9**: 80–5.

165. Dean JM, Bennet L, Back SA, et al. What brakes the preterm brain? An arresting story. *Pediatr Res* 2014; **75**: 227–33.

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Chapter 5

Prematurity and Complications of Labor and Delivery

Amy E. Judy and Amen Ness

Introduction

Prematurity is a major contributor to perinatal morbidity and mortality in the United States and around the world. *Preterm birth* is defined as delivery occurring prior to 37 completed weeks from the first day of the last menstrual period [1]. The term *low birth weight* is used to describe infants weighing less than 2,500 g at birth and includes neonates who are born after 37 weeks' gestational age. This group of neonates is distinct from the group of premature infants and is the subject of another chapter (Chapter 7). The discussion in this chapter will be confined to the preterm fetus, which is delivered between viability (23–24 weeks) and 37 completed weeks of gestation.

Complications of labor and delivery in both preterm and term gestations have been implicated in adverse neonatal outcomes. Traditionally, cerebral palsy (CP) has been linked to intrapartum events that result in "birth asphyxia" and subsequent neurologic damage. This association has continued to be proposed despite the fact that current evidence suggests that only about 10% of patients with CP, about 1–2/10,000 births, experience serious birth asphyxia [2]. Most studies in this field refer to the term fetus. The preterm neonate has its own unique complications and resulting sequelae.

The Problem of Preterm Birth

In the United States, one of eight infants is born preterm. Preterm birth remains the major contributor to perinatal morbidity and mortality. Rates of preterm birth peaked at 12.8% in 2006 and have subsequently been declining gradually, to 11.4% in 2013 [3]. This decline is thought to be due to a combination of decreasing rates of multiple gestations associated with artificial reproductive technologies, decreases in iatrogenic deliveries between 34–36 weeks, and the use of progesterone in women with a history of prior preterm birth. Two-thirds of preterm births are spontaneous – following cervical insufficiency, preterm labor, or premature rupture of membranes – whereas one-third are due to indicated preterm deliveries for maternal or fetal indications. Preterm births account for the majority of perinatal deaths around the world [4], and in the United States, preterm birth is the leading cause of death among African-American infants [1].

The complications of prematurity progressively increase with decreasing gestational age at delivery. These complications include both morbidities and mortality in the NICU and long-term health and neurocognitive disabilities that may last a lifetime. Major improvements in survival occur with each completed week of gestation from 24 to 33 weeks, after which time minimal increases in survival occur, although morbidity may be decreased. The lower limits of viability are changing, and recent studies have demonstrated survival and improved short-term outcome at gestational ages as early as 23–24 weeks [5]. Delivery prior to 27 weeks is associated with much greater overall survival but is still associated with a high incidence of serious long-term impairment [6]. Very preterm birth (<32 weeks of gestation) represents only 1–2% of all births but is responsible for about 60% of perinatal mortality and 50% of all long-term neurologic morbidity [3,7]. The majority of premature infants (75%) are born between 34 and 37 weeks. This late preterm birth group, while having a much lower risk of the most severe short- and long-term complications, is associated with greater hospital costs and healthcare utilization during the first year of life [8–10]. These late preterm neonates may also be at risk for long-term medical and behavioral disorders, including attention problems, and impaired cognitive and academic performance [11–16].

Despite the significant improvements in the survival of preterm infants over the last 10–20 years, there has been little, if any, improvement in neonatal morbidity; in fact, there is some evidence that rates of

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disability have increased [17]. The neurologic morbidity suffered by these infants imposes a considerable burden on families and the health system.

Traditionally, brain injury in preterm infants has been thought to reflect a fundamental vulnerability to damage of immature oligodendrocytes in periventricular white matter. Periventricular white matter injury (PWMI) is the most common form of neurologic injury in preterm infants, with an increasing incidence associated with decreasing gestational age at birth, and is highly correlated with the development of cerebral palsy (CP) [18,19].

However, animal studies suggest a more complex picture. Experimental studies have consistently shown that premature animals can survive far longer periods of profound hypoxia or ischemia before injury occurs than at term or postnatally [8]. The mechanisms that mediate this remarkable tolerance to hypoxia of the preterm brain are not fully understood. Yet it is precisely this tolerance that, although allowing for survival, may increase the risk for neurologic injury [20].

This chapter reviews the etiologies, management, and complications of preterm birth that affect the risks for neurologic injury related to prematurity.

Causes of Preterm Birth

Preterm birth may occur spontaneously, the result of cervical incompetence, preterm labor, or preterm premature rupture of membranes (PPROM), or it may be iatrogenic, occurring in the setting of maternal or fetal conditions that necessitate preterm delivery. The majority of preterm births are spontaneous, resulting from preterm labor and PPROM, with the remainder occurring due to maternal and/or fetal indications. The cause of premature birth may vary according to socioeconomic status, with the incidence of PPROM being higher in lower socioeconomic groups [21].

Iatrogenic Preterm Delivery. About 20% of preterm deliveries are indicated due to maternal and neonatal complications of pregnancy that necessitate iatrogenic preterm delivery. These include conditions such as hypertensive disorders of pregnancy, maternal cardiac and renal disease, autoimmune conditions, and other surgical and medical conditions. Fetal indications for delivery include nonreassuring fetal status, placental insufficiency and fetal growth restriction, monoamniotic twins, vasa previa, certain fetal anomalies, chorioamnionitis, and bleeding. Other obstetric conditions affecting both the mother and neonate, such as placenta previa and accreta are also indications for preterm delivery.

Spontaneous Preterm Birth. Traditionally, the various clinical presentations, or *phenotypes*, resulting in spontaneous preterm birth were considered distinct and separate entities. A more contemporary understanding is that these phenotypes are various clinical expressions of the preterm parturition process, which includes cervical insufficiency, preterm labor, and PPROM.

Preterm Labor. The pathogenesis of preterm labor with intact membranes has been categorized into four general pathogenic pathways. These are (1) maternal and/or fetal stress with premature activation of the placental-fetal hypothalamic-pituitary-adrenal axis, (2) inflammation resulting from either systemic inflammation or local infection, (3) abruption/decidual hemorrhage, and (4) mechanical stretching from either multiple gestations or polyhydramnios. Intra-amniotic infection/inflammation may be unrecognized because these patients often do not have overt evidence of chorioamnionitis [22,23]. They may have preterm labor that is refractory to tocolysis [24–27]. In addition, there is evidence to suggest that maternal and fetal genotypes may play a role in the genesis of preterm birth.

Preterm Premature Rupture of Membranes. PPROM is defined as rupture of the amniotic membranes prior to 37 weeks of gestation. PPROM accounts for up to 30% of all preterm deliveries and thus is a major concern in perinatal medicine [28]. The interval between PPROM and onset of labor is the *latency period*, and it is inversely related to gestational age at the time of rupture, with 50% of patients with PPROM prior to 26 weeks delivering within 1 week [29]. When PPROM occurs between 28 and 34 weeks, 50% deliver within 24 hours and 80–90% within 1 week [30,31]. Although phenotypically distinct, PPROM has not been shown to be different in its underlying etiology or risk factors from preterm labor or cervical insufficiency.

The specific causes of PPROM are not clearly understood, and there is great overlap with the pathophysiology associated with preterm labor. Weakening of the chorioamniotic membrane has been demonstrated as the pregnancy progresses [32,33]. Polyhydramnios, cervical cerclage procedures, amniocentesis, smoking, and multiple gestations have all been implicated as risk factors for PPROM [34]. Chronic placental abruption and advanced cervical dilation in the setting of cervical

insufficiency also increase the risk of PPROM. However, in the majority of cases, no risk factor is identified. Local infection from vaginal flora ascending through the cervix has been implicated as the etiology in a substantial number of cases [35]. Carriers of group B β-hemolytic *Streptococcus* (GBS) and certain sexually transmitted organisms such as *Chlamydia, Trichomonas, Gonococcus*, and bacterial vaginosis have a higher incidence of PPROM than those who are not carriers [36]. Some bacteria release proteases, which cause membrane weakening and probably early rupture [37]. There are host factors and immune activation mechanisms that probably account for the great variation in incidence of PPROM among populations.

Chorioamnionitis occurs in 15–25% of PPROM cases [38]. Incidence of neonatal sepsis at term is approximately 1/500 deliveries, and this incidence increases dramatically in the setting of PPROM or chorioamnionitis [39,40]. Umbilical cord compression occurs more often in cases of PPROM and rarely may be associated with neonatal hypoxia and even asphyxia [41–43]. Umbilical cord prolapse may complicate pregnancies with PPROM, particularly in cases of nonvertex fetal presentation. Fetal deformation syndrome from PPROM prior to 26 weeks is seen in approximately 3–4% of cases. This syndrome includes compression malformations and lethal pulmonary hypoplasia [44,45]. Historically, early PPROM was thought to be highly associated with lethal pulmonary hypoplasia, but contemporary data suggest that in the setting of substantial latency, even very early PPROM (<20 weeks of gestation) may be associated with neonatal survival in up to 70% of cases, albeit with significant associated morbidity [46].

Extreme prematurity and in utero fetal infection and inflammation have all been linked to the development of periventricular white matter injury (perventricular leukomalacia [PVL]). Infants who develop PVL have an extremely high risk for CP (>80%) and neurodevelopmental delay (50%) [47]. Because the risk for infection – chorioamnionitis – in women with PPROM increases with latency (the time from rupture of membranes to delivery), the risk of prematurity must be constantly weighed against the risk for infection. In women managed with close monitoring and delivery, chorioamnionitis is infrequently associated with fetal infection and may not be related to latency [48].

Cervical Insufficiency. This is a clinical diagnosis made following a history of recurrent rapid painless cervical dilation in the second or early third trimester. Very early preterm parturition is manifested primarily by cervical changes without significant uterine activity but is likely no different in its risk factors and etiology than other types of spontaneous preterm birth [49]. It has been associated with diethylstilbestrol (DES) exposure, cervical trauma from a prior delivery or cervical procedure such as a cone biopsy, and subclinical intrauterine infection/inflammation, though it often occurs without an identified etiology. Traditionally, cervical insufficiency was thought to be an all-or-nothing phenomenon, but the present understanding is that it appears to be the result of an interplay between various factors, including innate or acquired cervical weakness and premature ripening of an otherwise normal cervix. Ultrasonographic measurement of the cervix is used to diagnose cervical shortening, which is associated with an increased risk of cervical insufficiency and preterm birth [50].

Cerclage, a circumferential suture placed around the cervix before 24 weeks, has been used traditionally to treat women with presumed cervical insufficiency. Although the original case series of cerclage in the management of women with an underlying mechanical defect of the cervix and a history of recurrent loss showed success rates of 75–90%, these series used historical cohorts and poorly defined diagnoses and endpoints [15,51]. Four randomized trials of cerclage for sonographically diagnosed short cervix have not shown benefit of this procedure among all comers [52–55], but for women with a history of preterm birth and an ultrasonically identified short cervix, the placement of a cervical cerclage may be beneficial [56]. In women presenting with a dilated cervix in the midtrimester, a single small, randomized trial showed some benefit [55].

Prevention of Preterm Birth

Weekly injections of 17-α-hydroxyprogesterone caproate has been shown to decrease rates of recurrent preterm birth and is recommended for all women with a history of a prior spontaneous preterm birth regardless of phenotype. Treatment is generally initiated at 16 weeks' gestation and continued through delivery [57]. Vaginal progesterone has been shown to decrease rates of preterm birth in women found to have a shortened cervical length (10–20 mm) in the midtrimester and is recommended for nulliparous women and women without a history of preterm birth found to have a shortened cervix [59].

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Risk Factors for Preterm Birth

Maternal Risk Factors. Lower socioeconomic status, ethnicity, and maternal age all have been associated with increased incidence of preterm birth [9]. African-American women have an incidence of preterm birth that is about double that of non-Hispanic white women, and this disparity persists even if socioeconomic status is accounted for [3,10]. The incidence of preterm birth is higher in women under the age of 20 years, and pregnancies after age 35 years are also at increased risk for preterm birth [11]. A short interpregnancy interval (<18 months) has also been shown to increase the risk for a preterm birth [4].

Poor nutritional status and inadequate weight gain during pregnancy are associated with an increased incidence of preterm birth [12]. Body mass index (BMI) less than 19.8 kg/m^2 and large interpregnancy weight loss (decrease in one BMI category or more than 5 kg/m^2) have also been reported as factors for preterm birth [4].

Cocaine abuse [13], alcohol use, and cigarette smoking [14] have all been associated with increased rates of preterm birth. The confounding variables of poor nutrition, inadequate weight gain, and associated medical problems seen commonly in patients suffering substance abuse make it difficult to pinpoint the exact contribution of each risk factor of preterm delivery in such cases, and more recent studies controlling for confounding factors have not consistently demonstrated an association.

Uterine anomalies also increase the risk of preterm delivery. These anomalies are most often congenital, although historically they were also associated with in utero exposure to DES. Preterm birth rates of 15–30% have been reported in these cases. The greatest incidence is noted in patients with demonstrable abnormalities of the genital tract, such as T-shaped uterus or cervical abnormalities [60,61].

Obstetrical Risk Factors. A history of preterm birth is one of the most important risk factors for subsequent preterm delivery. A history of spontaneous preterm birth is associated with a 15–40% recurrence risk depending on the number and gestational age of the prior preterm births [62,63]. The risk increases with the number of preterm births and is higher the earlier in gestation they occurred [15]. Term deliveries attenuate the risk of preterm birth [15]. There is some debate over whether induced abortions increase the rate of preterm delivery [16,64].

Transvaginal cervical length before 24 weeks is correlated with the risk for preterm delivery. The shorter the cervix and the earlier it presents, the greater is the risk for preterm delivery and early preterm delivery. Cervical length is measured routinely from 16 to 24 weeks in women with a prior preterm birth, whereas low-risk women are often screened at the time of their anatomy scan at 18–20 weeks.

Multiple gestations account for 10% of all preterm births in the United States. After a brief plateau, the twin birth rate has again begun to increase in the United States and rose by 2% to 33.7/1,000 births in 2013. Triplet and higher-order multiple gestations continue to decrease and currently compose 1.2/1,000 births [3]. Over 50% of multiple gestations deliver prior to 37 weeks, with higher-order multiple gestations delivering the earliest: 11% of twins deliver very preterm (<32 weeks of gestation) compared with 40% of triplets and 70% of quadruplets [3,65,66]. Approximately 97% of multiple gestations are twins, which deliver preterm about 55% of the time [3]. Currently, assisted reproductive technologies (ART) result in multiple gestations in about 28% of cases [67], and some of the increase in premature delivery over the past several decades has been attributed to increases in multiple gestations due to ART and increasing maternal age [68]. Even among singleton gestations, the incidence of preterm delivery is increased in the setting of ART to 13–15% [69,70].

First-trimester bleeding [71] and third-trimester bleeding from *placental abnormalities* also increase the risk of preterm delivery, either by precipitating spontaneous preterm delivery or because of maternal-fetal compromise necessitating delivery [11,72]. *Fetal anomalies*, especially those leading to polyhydramnios, may cause preterm labor due to excessive uterine distension.

Diagnosis of Preterm Labor

The diagnosis of preterm labor is important in order to initiate appropriate tocolytic therapy to attempt to delay delivery for two purposes:

1. To initiate interventions that may improve the outcome of premature neonates, including the administration of antenatal corticosteroid and magnesium sulfate, and
2. To allow for maternal transport to a facility with an appropriate level of care for the premature neonate.

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The criteria for the diagnosis of preterm labor seem deceptively simple, i.e., gestational age of 20–37 weeks with regular uterine contractions and documented change. Unfortunately, the diagnosis of cervical change based on a manual examination is subjective, and even identification of uterine contractions can be challenging, particularly in the significantly obese patient. The majority of women diagnosed with preterm labor do not deliver preterm. Two predictive tests, fetal fibronectin and ultrasonic measurement of cervical length, can be used to help triage women in suspected preterm labor. Fetal fibronectin may help to rule out preterm labor by virtue of its high negative predictive value [73]. The absence of fetal fibronectin in the cervicovaginal secretions of a woman with suspected preterm labor indicates that she is highly unlikely to deliver within the next two weeks (negative predictive value 98%). Similarly, a normal cervical length has a high negative predictive value [74].

Initial assessment of the patient in suspected preterm labor should include ultrasonic confirmation of the gestational age and presentation of the fetus, evaluation for ruptured membranes, and demonstration of fetal well-being with continuous electronic fetal monitoring (EFM). Contraindications to tocolysis include certain maternal medical conditions such as poorly controlled heart disease or severe preeclampsia, significant bleeding, evidence of fetal compromise, and fetal anomalies incompatible with life. The possibility of intra-amniotic infection should be considered because chorioamnionitis and/or maternal sepsis preclude tocolysis. Various tocolytic agents exist, and maternal comorbidities must be considered in the decision to proceed with tocolysis and the choice of tocolytic administered.

With PPROM in the absence of clinical chorioamnionitis, antibiotic prophylaxis helps to prolong latency and should be administered for a period of 7 days [75,76].

Preparation for Delivery of the Preterm Fetus

Maternal Transport

The most important factor to consider in cases in which preterm delivery may occur is the availability of resources to provide optimal care to both the neonate and the mother. Delivery in perinatal centers specializing in the care of preterm neonates is associated with better prognosis compared with preterm neonates who are transported after birth [77–79]. Prior to arranging for maternal transport, the gestational age and birth weight need to be determined. The use of real-time sonography will reliably estimate fetal weight and gestational age, with a small margin of error, in the preterm fetus [80–81]. The gestational age at which maternal transfer is indicated varies according to the level of neonatal care available. Most obstetric/pediatric facilities have the resources to care for neonates at 36 weeks of gestation or later and at birth weights of >2,500 g. If the gestation is previable, then transport may not confer an advantage in terms of neonatal survival. In practical terms, many community hospitals are uncomfortable with the possibility that a "previable gestation" may actually be larger or more mature than anticipated and that delivery will have occurred without adequate facilities. The philosophy of "when in doubt, ship them out" is often the most prudent approach. Most maternal transports will be made for gestational ages of 23–36 weeks. However, diagnosis of fetal anomalies or serious maternal illness may necessitate transfer at any gestational age.

Close communication between referring physicians, accepting maternal-fetal physicians, neonatologists, and other appropriate pediatric staff is essential. The patient and her family need to receive a realistic and consistent evaluation of the situation, including the risks, benefits, alternatives, and ultimately prognosis. Survival rates and follow-up data need to be known for the individual institution, and counseling should be initiated by both the obstetric and neonatology staffs as soon as is feasible. The type of transportation used is region specific, but as a general rule, transports from less than 100 miles (160 km) can be accomplished by ground ambulance, whereas air transport is often used for greater distances. Mountains, road conditions, weather, and patient acuity will all influence the choice of method of transport. Once the decision to transport is made, it is advantageous to have a transport team available. At many institutions, physician and nurse teams are specially trained to transport either the pregnant mother or the neonate. These are two distinctly different types of health professionals: maternal-fetal transport is done by personnel trained in obstetrics, whereas neonatal transport is done by persons trained in care of the sick neonate.

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There must be an efficient mechanism of initiating a request for transport. One phone call to the referring center or regional dispatch center should set in motion a chain of events leading to appropriate transportation. Medical staff at the referring hospital will need to contact the accepting institution's staff without difficulty in order to provide appropriate information concerning the patient. The obstetricians accepting a maternal-fetal transport will need to contact their neonatology group to inform them of the impending transport and confirm availability of a neonatal bed. If there is a problem with this, alternative strategies need to be devised.

The referring institution needs to provide as much information as possible so that adequate resources can be mobilized to deal with specific problems. Examples include the availability of pediatric surgical specialties or blood for transfusion. There are cases in which a maternal-fetal transport team may arrive after an unexpected delivery or find that transport would be inadvisable and delivery preparations should be undertaken. In this type of situation, close communication between the maternal-fetal and neonatal teams is vital.

Discussion needs to be instituted concerning the use of medications or other interventions prior to initiation of transport. When there is a maternal-fetal transport, discussion generally includes administration of antenatal corticosteroids and magnesium sulfate for fetal neuroprotection and, depending on the case, the use of tocolytic agents and/or antibiotics for PPROM, as well as interventions for maternal conditions including antihypertensive and antiseizure medications in cases of hypertensive disorders of pregnancy.

Antenatal Interventions for the Premature Neonate

The use of pharmacologic agents given to the pregnant patient in order to improve neonatal outcome is an extremely important consideration. These include antenatal corticosteroids to reduce the risk of respiratory distress syndrome (RDS) and magnesium sulfate for fetal neuroprotection.

Antenatal Corticosteroids. The original consensus conference of the National Institutes of Health [82] recommends that all women between 24 and 34 weeks of pregnancy at risk for preterm delivery be considered candidates for antenatal corticosteroid therapy. Currently, steroids may be considered as early as 23 weeks of gestation if the patient desires a trial of neonatal resuscitation [82a]. Optimal therapeutic benefits begin 24 hours after initiation of therapy and last 7 days. Because there is evidence suggesting that mortality, RDS, and intraventricular hemorrhage are reduced even when treatment lasts for less than 24 hours, steroids should be given unless delivery is imminent. The most commonly used regimen is betamethasone 12 mg intramuscularly 24 hours apart. Dexamethasone 5 mg intramuscularly every 12 hours for four doses is an acceptable alternative.

Magnesium Sulfate. A Maternal-Fetal Medicine Units Network study demonstrated a potential benefit of magnesium sulfate before delivery of the premature infant. This multicenter randomized, controlled trial involved administration of magnesium sulfate to women with advanced preterm labor, PPROM, or indicated delivery from 24–31 weeks 6 days of gestation. A reduction by 50% of moderate to severe CP among surviving infants at age 2 years was observed in those neonates exposed to magnesium sulfate compared with neonates receiving placebo [83]. Subsequent meta-analyses have been conducted that have similarly demonstrated a reduction in the incidence of CP of any severity by 30% and a reduction in the incidence of moderate to severe CP by 40–45%, without any associated increase in perinatal or infant death [84]. Studies vary in dosing regimens, with most including a 4- to 6-g bolus of magnesium sulfate followed by an infusion of 1–2 g/h. Ideally, the magnesium sulfate bolus should be initiated 12 hours prior to anticipated delivery.

Management of Labor and Delivery

Once delivery is imminent, optimal management of the delivery process is important. The influence of events of labor and delivery on perinatal "brain damage" has been the focus of both obstetricians and pediatricians since the early nineteenth century. Little [85] and Freud [86] stated that the major cause of CP and mental retardation (MR) was intrapartum "brain damage." Prolonged labors and traumatic deliveries supported this impression, and it has only recently been proved that only about 10% of cases of CP and MR can be attributed to events of labor and delivery [87–89]. It is this 10% of patients in which monitoring and some type of intervention may have a meaningful impact on perinatal outcome.

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Pain relief is an essential element in the management of patients in preterm labor. It should be accepted that all analgesic medications used in obstetrics cross the placenta. Some medications may indeed lead to temporary respiratory depression of the neonate, but other causes for the problem must be sought. There is evidence that CNS depressants may in fact protect the CNS of the fetus from the effects of hypoxia [90]. Continuous epidural anesthesia is a safe and effective method of pain relief. General anesthesia for emergency operative delivery poses no threat to the fetus provided that maternal oxygenation is maintained and hypotension avoided.

Fetal Monitoring

Intrapartum hypoxia and acidosis in the preterm fetus may be a significant factor in subsequent complications of prematurity [91]. Continuous EFM appears to predict fetal hypoxia in the preterm fetus with some degree of accuracy [92,93] but is only one parameter of fetal condition, and it must be evaluated along with the total clinical picture. In a study of 40 preterm pregnancies with biochemically confirmed fetal acidosis (base deficit >12 mmol/L), EFM was predictive in 71% (60% of those with mild acidosis and 83% of those with moderate or severe acidosis) [94]. Unfortunately, some pregnancies with moderate to severe asphyxia are difficult to prevent either because the fetal asphyxial exposure began before fetal surveillance was initiated or because of the sudden onset of a profound fetal insult. Nevertheless, EFM may help to allow for intervention prior to the development of moderate or severe asphyxia.

Even the preterm fetus is well adapted to tolerating the intermittent episodes of decreased oxygen delivery that occur with contractions in labor. While preterm pregnancies have three times the frequency of moderate and severe asphyxia compared to term pregnancies [94–96], midtrimester fetal sheep are neurologically more tolerant of cord occlusion than mature fetal sheep, suggesting that the immature fetus will tolerate a longer exposure to asphyxia than the term fetus, but this survival eventually results in sudden profound cardiovascular decompensation [96]. The premature fetus is more susceptible to the effects of hypoxemia, and the onset of metabolic acidosis may occur more rapidly, which may lead to fetal or neonatal death or poor long-term outcome [97,98].

While a normal EFM tracing implies normal oxygenation and acid-base status, "nonreassuring" patterns have a wider range of predictability. In many cases, nonreassuring patterns are a result of early gestational age, fetal rest cycles, and medications; these patterns may be difficult to distinguish from those resulting from hypoxia and early acidosis. The fetal heart rate (FHR) should be evaluated systematically, a mechanism for changes in FHR proposed, and the clinical situation assessed. Judgment concerning further management of labor should be made with all relevant information. If there are conflicting data and evidence of acidosis is not overwhelming, further evaluation of the fetus and strategies to improve uterine blood flow, fetal oxygenation, and acid-base status must be undertaken (see Chapter 15). Standard measures to improve fetal status include maintenance of normal maternal cardiac output, maximizing maternal and fetal oxygenation, and control of uterine activity. In the setting of variable decelerations, amnioinfusion has been demonstrated to reduce the incidence of cord compression as well as the incidence of cesarean delivery in patients with PPROM [99].

If there is an impression of significant acidosis, delivery by the most expedient method may be indicated. Individual circumstances in each case must be considered, and the overriding principle must be optimal outcome for both the mother and the fetus. The implications of prematurity associated with delivery at any gestational age must be weighed against the probability of acidosis based on fetal monitoring. At extremely premature gestations, substantial evidence of fetal acidosis is generally required before proceeding with delivery, whereas in the late preterm period, a lesser degree of concern may justify delivery.

It should be noted that umbilical cord blood gases, particularly arterial, are more accurate in assessing fetal condition in the preterm neonate than are Apgar scores, which are quite unreliable at early gestational ages [100].

Route of Delivery

Indications for cesarean delivery are similar to those for the term fetus. Previous enthusiasm for liberal use of cesarean delivery for preterm deliveries has been tempered by retrospective studies showing no difference in neonatal mortality between cesarean and vaginal delivery [101–103], and a recent Cochrane review also found no difference in neonatal outcomes between planned vaginal and cesarean deliveries, with increased maternal morbidity associated with cesarean delivery [104].

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Vertex Presentation. The currently accepted approach is to allow labor with continuous fetal monitoring. Delivery en caul (membranes intact) may decrease the risk of trauma and fluctuations of cerebral blood flow in response to cord compression [105] but may be difficult to achieve practically in any but the most precipitous deliveries.

Breech Presentation. Breech delivery has largely fallen out of practice since Hannah et al. found significantly decreased rates of perinatal morbidity and mortality associated with planned cesarean delivery for term singleton neonates compared with vaginal breech delivery [106]. In the preterm neonate there are increased concerns that the lower extremities, abdomen, and thorax may deliver through an incompletely dilated cervix and leave the relatively larger fetal head trapped behind the cervix. A recent systematic review of breech preterm neonates similarly found a decrease in neonatal mortality of 37% associated with cesarean delivery [107], further supporting a practice of cesarean delivery for these neonates.

But some would argue that at periviable gestational ages the increased maternal morbidity associated with the likely classical uterine incision may not justify the incremental improvements in neonatal morbidity gained through cesarean delivery. En caul vaginal breech delivery may result in reduced risks of head entrapment and cord prolapse and similar rates of perinatal morbidity and mortality when compared with cesarean delivery [108]. A retrospective study comparing cesarean to vaginal delivery for breech fetuses 23–24 6/7 weeks of gestation found increased survival among neonates >500 g but no difference in 6-month survival [109]. In the appropriately counseled patient, attempted vaginal delivery of the periviable breech singleton may remain a consideration.

Operative Vaginal Delivery

Normal spontaneous vaginal delivery is considered a physiologic process, and complications with spontaneous delivery are relatively uncommon. Acute events in the late second stage of labor may cause fetal and neonatal complications that necessitate expeditious and/or assisted delivery. When operative vaginal delivery of the preterm fetus is indicated, the gestational age of the fetus should be considered when choosing between vacuum- and forceps-assisted vaginal deliveries. Most authorities consider vacuum extraction inappropriate before 34 weeks of gestation because of concerns for intraventricular hemorrhage [110].

Of historical interest is the practice of prophylactic forceps-assisted vaginal delivery of the premature fetus, which has been found to be potentially hazardous [11,111,112]. This practice has been largely abandoned.

Cesarean Delivery

When abdominal delivery of the preterm fetus is indicated, atraumatic delivery must be accomplished. A low transverse uterine incision is preferable, but a lack of development of the lower uterine segment with preterm neonates may necessitate a *classical incision* (a vertical uterine incision extending into the muscular upper uterine segment). Classical incisions are associated with increased risks of maternal postoperative morbidity [113] and of uterine rupture with labor in subsequent pregnancies of 4–9% [114]. An additional consideration is the increasing risk of abnormal placentation associated with repeat cesarean delivery (Chapter 9).

The splint technique, in which the surgeon's arm is placed in the uterus to the fundus, and the entire fetus is then delivered with the head held in the surgeon's hand and the trunk flat against the forearm with the buttocks stabilized in the antecubital fossa, is often helpful in delivery of a malpresentation [115] and can also be of use in multiple gestations. Nitroglycerine and other uterotonics can be useful when delivery is inhibited by significant uterine tone.

Multiple Gestations

Multiple gestations of a higher order (greater than two) are generally delivered by cesarean section. In twin gestations, the mode of delivery may largely be determined by presentation of both twins, with similar considerations as in term gestations. The gestational age and estimated fetal weight of the neonates must be considered in the case of breech extraction. Data are conflicting regarding planned vaginal delivery of preterm neonates of any presentation. Some authors have reported high rates of grade 3–4 intraventricular hemorrhage among very low-birth-weight (<1,500 g) twins delivered vaginally regardless of presentation [116]. In contrast, Sentilhes et al. retrospectively compared neonatal outcomes for approximately 300 neonates between 26 0/7 to 31 6/7 weeks' gestation assigned to planned vaginal versus planned cesarean delivery and found similar rates of severe neonatal

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morbidity and mortality between groups [117], as did Barret et al. in their study of neonates down to 32 weeks' gestation [118]. Real-time sonography should be used to help determine the position and route of delivery. Availability of both obstetric and neonatal expertise is important in decisions on the location of delivery, and there should be no hesitation in abandoning difficult vaginal delivery and performing cesarean section if indicated.

Miscellaneous Obstetric Interventions for the Preterm Fetus

Several systematic reviews and meta-analyses have demonstrated the potential benefits of delayed cord clamping in the preterm neonate [119,120]. Delayed cord clamping of 30–180 seconds in preterm neonates has been associated with decreased transfusions for anemia, decreased incidence of intraventricular hemorrhage, and decreased rates of necrotizing enterocolitis. The need for immediate neonatal resuscitation in preterm neonates must be balanced against the delay inherent in cord clamping, and the decision to defer clamping should be made in consultation with attendant neonatologists.

The Preterm Brain

The preterm brain is highly susceptible to injury outside the uterus. During the third trimester, the fetal brain volume, including both cortical gray matter and white matter, increases four- to fivefold [121]. Even at 32 weeks, the fetal brain has only achieved about 60% of its term weight. In very preterm infants, fetal cerebral blood flow is often passive and autoregulation not well developed. It is not surprising, then, that diffuse white matter injury can be seen in more than half of infants weighing less than 1,500 g. As a result, and despite improved survival, the very preterm infant remains at high risk for adverse neuropsychological sequelae, including CP, cognitive disabilities, and seizure disorders. Even with optimal neonatal care, including the use of antenatal steroids, postnatal surfactant, magnesium, and caffeine, a large number of children born preterm have neurodevelopmental and behavioral impairments that persist into adulthood.

Conclusion

The premature fetus and neonate are at increased risk for brain injury compared with term infants. This is due both to prenatal factors that may have brought about the preterm delivery and to neonatal complications. Despite improvements in obstetric and neonatal care that have decreased the incidence of intrapartum and neonatal deaths, there has been no corresponding decrease in the incidence of CP. This finding has served to highlight the issue of how much CP is related to antepartum as opposed to intrapartum events. If we are to reduce brain injury in preterm infants, we must focus our research efforts on early detection of antenatal precursors to brain injury while continuing to improve our intrapartum and neonatal care.

References

1. World Health Organization. Prevention of perinatal morbidity. In *Public Health Papers 42*. Geneva: WHO, 1969.
2. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: multivariate analysis of risk. *N Engl J Med* 1986; **315**: 81–6.
3. Martin JA, Hamilton BE, Osterman MJK, et al. *Births: Final Data for 2013. National Vital Statistic Reports*, vol. **64**, no. 1. Hyattsvill, MD: National Center for Health Statistics, 2015.
4. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. *Am J Obstet Gynecol* 2007; **110**: 404–15.
5. Cooper RK, Goldenberg RL, Creasy RK, et al. A multicenter study of preterm birth weight and gestational age specific mortality. *Am J Obstet Gynecol* 1993; **168**: 78–84.
6. Ferrara TB, Hoekstra RE, Couser RS, et al. Survival and follow-up of infants born at 23–26 weeks' gestational age: effects of surfactant therapy. *J Pediatr* 1994; **124**: 119–24.
7. Hack M, Fanaroff AA. Outcomes of children of extremely low birth weight and gestational age in the 1990s. *Early Hum Dev* 1999; **53**: 193–218.
8. Gunn AJ, Quaedackers JS, Guan J, et al. The premature fetus: not as defenseless as we thought, but still paradoxically vulnerable? *Dev Neurosci* 2001; **23**: 175–9.
9. Fedrick J, Anderson ABM. Factors associated with spontaneous preterm birth. *Br J Obstet Gynaecol* 1976; **83**: 342–50.
10. US Department of Health and Human Services. *Report of the Secretary's Task Force on Black and Minority Health* (Publication 0-487-637 [QL3]), vol. **6**: *Infant Mortality and Low Birth Weight*. Hyattsville, MD: National Center for Health Statistics, 1985.

11. Bakketeig LS, Hoffman HJ. Epidemiology of preterm birth: results from longitudinal study of births in Norway. In Elder MG, Dendricks CH, eds., *Preterm Labour*. London: Butterworths, 1981: 17–46.
12. Abrams B, Newman V, Key T, et al. Maternal weight gain and preterm delivery. *Obstet Gynecol* 1989; **74**: 577–83.
13. MacGregor SW, Keith LG, Chasnoff IJ, et al. Cocaine use during pregnancy: adverse perinatal outcome. *Am J Obstet Gynecol* 1987; **57**: 686–90.
14. Shiono PH, Klebanoff MA, Rhoads GG. Smoking and drinking during pregnancy. *JAMA* 1986; **255**: 82–4.
15. Keirse M, Rush R, Anderson A, et al. Risk of pre-term delivery in patients with previous preterm delivery and/or abortion. *Br J Obstet Gynaecol* 1978; **85**: 81–5.
16. Linn S, Schoenbaum S, Monson R, et al. The relationship between induced abortion and outcome of subsequent pregnancies. *Am J Obstet Gynecol* 1983; **146**: 136–40.
17. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics* 2005; **115**: 997–1003.
18. Back SA, Rivkees SA. Emerging concepts in periventricular white matter injury. *Semin Perinatol* 2004; **28**: 405–14.
19. Leviton A, Paneth N. White matter damage in preterm newborns: an epidemiologic perspective. *Early Hum Dev* 1990; **24**: 1–22.
20. Barrett RD, Bennet L, Davidson J, et al. Destruction and reconstruction: hypoxia and the developing brain. *Birth Defects Res C Embryo Today* 2007; **81**: 163–76.
21. Meis PJ, MacErnest J, Moore ML. Causes of low birth weight births in public and private patients. *Am J Obstet Gynecol* 1987; **156**: 1165–8.
22. Bobbitt JR, Ledger WJ. Unrecognized amnionitis and prematurity: a preliminary report. *J Reprod Med* 1977; **19**: 8–12.
23. Bobbitt JR, Ledger WJ. Amniotic fluid analysis: its role in maternal and neonatal infection. *Obstet Gynecol* 1978; **51**: 56–62.
24. Leigh J, Garite TJM. Amnionitis and the management of premature labor. *Obstet Gynecol* 1986; **67**: 500–6.
25. Gravett MG, Hummel D, Eschenbach DA, et al. Preterm labor associated with subclinical amniotic infection and with bacterial vaginosis. *Obstet Gynecol* 1986; **67**: 229–37.
26. Hameed C, Teiane N, Verma UL, et al. Silent chorioamnionitis as a cause of preterm labor refractory to tocolytic therapy. *Am J Obstet Gynecol* 1984; **149**: 726–30.
27. Duff P, Kopelman JN. Subclinical intraamniotic infection in asymptomatic patients with refractory preterm labor. *Obstet Gynecol* 1987; **69**: 756–69.
28. Kaltreider DF, Kohl S. Epidemiology of preterm delivery. *Clin Obstet Gynecol* 1980; **23**: 17–31.
29. Taylor J, Garite TJ. Premature rupture of membranes before fetal viability. *Obstet Gynecol* 1984; **64**: 615–20.
30. Mead PB. Management of the patient with premature rupture of the membranes. *Clin Perinatol* 1980; **7**: 243–55.
31. Kennedy KA, Clark SL. Premature rupture of the membranes: management controversies. *Clin Perinatol* 1992; **19**: 385–97.
32. Artal JP, Sokol RJ, Newman M, et al. The mechanical properties of prematurely and non-prematurely ruptured membranes. *Am J Obstet Gynecol* 1976; **125**: 655–9.
33. Lavery JP, Miller CE, Knight RD. The effect of labor on the rheologic response of chorioamniotic membranes. *Obstet Gynecol* 1982; **60**: 87–91.
34. Naeye RL. Factors that predispose to premature rupture of the fetal membranes. *Obstet Gynecol* 1982; **60**: 93–8.
35. Lonky NN, Hayashi RH. A proposed mechanism for premature rupture of membranes. *Obstet Gynecol Surv* 1988; **43**: 22–8.
36. Minkoff H, Grunebaum AN, Schwarz RH, et al. Risk factors for prematurity and premature rupture of membranes: a prospective study of vaginal flora in pregnancy. *Am J Obstet Gynecol* 1984; **150**: 965–72.
37. Iams JD, McGregor JA. Cervicovaginal microflora and pregnancy outcome: results of a double blind, placebo-controlled trial of erythromycin treatment. *Am J Obstet Gynecol* 1990; **163**: 1580–91.
38. Garite TJ, Freeman RK, Linzy EM, et al. Prospective randomized study of corticosteroids in the management of premature rupture of membranes and the premature gestation. *Am J Obstet Gynecol* 1981; **141**: 508–15.
39. Gibbs RS, Blanco JD, St Clair PJ, et al. Quantitative bacteriology of amniotic fluid from patients with clinical intraamniotic infection at term. *J Infect Dis* 1982; **145**: 1–8.
40. Yoder PR, Gibbs RS, Blanco JD, et al. A prospective controlled study of maternal and perinatal outcome after intra-amniotic infection at term. *Am J Obstet Gynecol* 1983; **145**: 695–701.
41. Garite TJ, Freeman RK. Chorioamnionitis in the preterm gestation. *Obstet Gynecol* 1982; **54**: 539–45.
42. Gabbe SG, Ettinger BB, Freeman RK, et al. Umbilical cord compression associated with amniotomy:

laboratory observations. *Am J Obstet Gynecol* 1976; **126**: 353–6.

43. Wilson JC, Levy DC, Wilds PL. Premature rupture of membranes prior to term: consquences of non-intervention. *Obstet Gynecol* 1982; **60**: 601–6.
44. Morretti M, Sibai BM. Maternal and perinatal outcome of expectant management of premature rupture of membranes in the mid-trimester. *Am J Obstet Gynecol* 1988; **159**: 390–6.
45. Major CA, Kitzmiller JL. Perinatal survival with expectant management of mid-trimester rupture of membranes. *Am J Obstet Gynecol* 1990; **163**: 838–44.
46. Lindner W, Pohlandt F, Grab D, et al. Acute respiratory failure and short-term outcome after premature rupture of the membranes and oligohydramnios before 20 weeks of gestation. *J Pediatr* 2002; **140**(2): 177–182.
47. Resch B, Resch E, Maurer-Fellbaum U, et al. The whole spectrum of cystic periventricular leukomalacia of the preterm infant: results from a large consecutive case series. *Childs Nerv Syst* 2015; **31**(9):1527–32.
48. Ekin A, Gezer C, Taner CY, et al. Risk factors and perinatal outcomes associated with latency in preterm premature rupture of membranes between 24 and 34 weeks of gestation. *Arch Gynecol Obstet* 2014; **290**: 449–55.
49. Iams JD. Prevention of preterm parturition. *N Engl J Med* 2014; **370**: 254–61.
50. Zemlyn S. The length of the uterine cervix and its significance. *J Clin Ultrasound* 1981; **9**: 267–9.
51. Rush RLO. Incidence of preterm delivery in patients with previous preterm delivery and/or abortion. *S Afr Med J* 1979; **56**: 1085–7.
52. Rust OA, Atlas RO, Jones KJ, et al. A randomized trial of cerclage versus no cerclage among patients with ultrasonographically detected second-trimester preterm dilatation of the internal os. *Am J Obstet Gynecol* 2000; **183**: 830–5.
53. Berghella V, Odibo AO, Tolosa JE. Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial. *Am J Obstet Gynecol* 2004; **191**: 1311–17.
54. To MS, Alfirevic Z, Heath VCF, et al. Cervical cerclage for prevention of preterm delivery in women with short cervix: randomized controlled trial. *Lancet* 2004; **363**: 1849–53.
55. Althusius SM, Dekker GA, Hummel P, et al. Final results of the cervical incompetence prevention randomized cerclage trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2001; **185**: 1106–12.
56. Owen J, Hankins G, Iams JD, et al. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. *Am J Obstet Gynecol* 2009; **201**(375): e1–8.
57. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17α-hydroxyprogesterone caproate. *N Eng J Med* 2003; **384**: 2379–85.
58. Althuisius SM, Dekker GA, Hummel P, et al. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2003; **189**: 907–10.
59. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011; **38**: 18–31.
60. Herbst AL, Hubby MM, Blough RR, et al. A comparison of pregnancy experiment in DES-exposed and DES-unexposed daughters. *J Reprod Med* 1980; **24**: 62–9.
61. Kaufman RH, Noller K, Adam E, et al. Upper genital tract abnormalities and pregnancy outcome in diethylstilbestrol-exposed progeny. *Am J Obstet Gynecol* 1985; **148**: 973–84.
62. Iams JD, Goldenberg RL, Mercer BM, et al. The preterm prediction study: recurrence risk of spontaneous preterm birth. *Am J Obstet Gynecol* 1998; **178**: 1035–40.
63. Papiernik E, Kaminski M. Multifactorial study of the risk of prematurity at 32 weeks of gestation. *J Perinat Med* 1974; **2**: 30–6.
64. Chung C, Smith R, Steinhoff P, et al. Induced abortion and spontaneous fetal loss in subsequent pregnancies. *Am J Public Health* 1982; **72**: 548–54.
65. US Department of Health and Human Services, Public Health Service. *Vital Statistics of the United States, 1982,* vol. 1: *Natality*. Hyattsville, MD: Department of Health, 1986.
66. Neilson JP, Verkuyl DAA, Crowther CA, et al. Preterm labor in twin pregnancies: prediction by cervical assessment. *Obstet Gynecol* 1988; **72**: 719–23.
67. Society for Assisted Reproductive Technology. Clinic Summary Report: All SART Member Clinics. Available at www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0.
68. Elliot JP. High order multiple gestations. *Semin Perinatol* 2005; **5**: 305–11.
69. Dunietz GL, Holzman C, McKane P, et al. Assisted reproductive technology and the risk of preterm birth among primiparas. *Fertil Steril*, 2015; **103**(4): 974–9.

70. Australian Institute of Health and Welfare National Perinatal Statistics Unit. *Assisted Conception in Australia and New Zealand*. Sydney: AIHW, 1992.

71. Williams MA, Millendorf R, Liererman E, et al. Adverse infant outcomes associated with first trimester vaginal bleeding. *Obstet Gynecol* 1991; **78**: 14–8.

72. Roberts G. Unclassified antepartum haemorrhage incidence and perinatal mortality in a community. *J Obstet Gynaecol Br Commonwlth* 1970; **77**: 492–5.

73. Peaceman AM, Andrews WW, Thorp JM, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. *Am J Obstet Gynecol* 1997; **177**: 13–18.

74. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous preterm delivery. *N Engl J Med* 1996; **334**: 567–72.

75. Mercer BM, Arheart KL. Antimicrobial therapy in expectant management of preterm premature rupture of the membranes. *Lancet* 1995; **346**: 1271–9.

76. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes: a randomized controlled trial. *JAMA* 1997; **278**: 989–95.

77. Usher R. Changing mortality rates with perinatal intensive care and regionalization. *Semin Perinatol* 1977; **1**: 309–19

78. Gortmaker S, Sobol A, Clark C, et al. The survival of very low-birth weight infants by level of hospital of birth: a population study of perinatal systems in four states. *Am J Obstet Gynecol* 1985; **152**: 517–24.

79. Kitchen W, Ford G, Orgill A, et al. Outcome in infants with birth weight 500–999 grams: a regional study of 1979 and 1980 births. *J Pediatr* 1984; **104**: 921–7.

80. Hadlock FP, Harrist RB, Carpenter RJ, et al. Sonographic estimation of fetal weight: the value of fetal length in addition to head and abdominal measurements. *Radiology* 1984; **152**: 497–501.

81. Seeds JW, Cefalo RL, Bowes WA. Femur lengths in the estimation of fetal weight less than 1500 grams. *Am J Obstet Gynecol* 1984; **149**: 233–5.

82. National Institutes of Health. *Consensus Statement: Effect of Antenatal Steroids for Fetal Maturation on Perinatal Outcomes*. Bethesda, MD: NIH, 1994: 1–24.

82a. American College of Obstetricians and Gynecologists. Antenatal corticosteroid therapy for fetal maturation. Committee Opinion No. 677. *Obstet Gynecol* 2016; **128**: e187–94.

83. Rouse D, Hirtz DG, Thom E, et al. A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.

84. Constantine MM, Weiner SJ. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Obstet Gynecol* 2009; **114**: 354–64.

85. Little WJ. On the influence of abnormal parturition, difficult labors, premature birth, and asphyxia neonatorum on the mental and physical condition of the child, especially in relation to deformities. *Trans Obstet Soc Lond* 1862; **2**: 293–344.

86. Freud S. *Die infantile Cerebrallähmung*. Vienna: Hölder, 1897.

87. Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr* 1988; **112**: 515–19.

88. Committee on Obstetrics, Maternal and Fetal Medicine. Fetal and neonatal neurologic injury. *ACOG Technical Bulletin 163*. ACOG, Washington, DC, 1992.

89. Naeye RL, Peters EC, Bartholomew M, et al. Origins of cerebral palsy. *Am J Dis Child* 1989; **143**: 1154–6.

90. Myers RE, Myers SE. Use of sedative, analgesic and anesthetic drugs during labor and delivery: bane or boon. *Am J Obstet Gynecol* 1979; **133**: 83–108.

91. Low JA, Gallbraith RS, Muir DW, et al. Factors associated with motor and cognitive deficits in children after intrapartum fetal hypoxia. *Am J Obstet Gynecol* 1984; **148**: 533–9.

92. Bowes WA, Gabbe S, Bowes C. Fetal heart rate monitoring in premature infants weighing 1500 grams or less. *Am J Obstet Gynecol* 1980; **137**: 791–6.

93. Westgren LMR, Malcus P, Sveningsen NW. Intrauterine asphyxia and longterm outcome in preterm fetuses. *Obstet Gynecol* 1986; **67**: 512–16.

94. Low JA, Killen, H, Derrick J. The prediction of asphyxia in preterm pregnancies. *Am J Obstet Gynecol* 2001; **186**: 279–82.

95. Low JA, Killen H, Derrick J. Antepartum fetal asphyxia in the preterm pregnancy. *Am J Obstet Gynecol* 2002; **188**: 461–5.

96. Low JA. Determining the contribution of asphyxia to brain damage in the neonate. *J Obstet Gynaecol Res* 2004; **30**: 276–86.

97. Low JA, Boston RW, Pancham FR. Fetal asphyxia during the intrapartum period in intrauterine growth retarded infants. *Am J Obstet Gynecol* 1972; **113**: 351–7.

98. Westgran LMR, Malcus P, Svenningsen NW. Intrauterine asphyxia and long-term outcome in preterm fetuses. *Obstet Gynecol* 1986; **67**: 512–16.

99. Nageotte MP, Freeman RK, Garite TJ, et al. Prophylactic intrapartum amnioinfusion in patients with preterm premature rupture of membranes. *Am J Obstet Gynecol* 1985; **153**: 557–62.

100. Goldenberg RL, Huddlestone JF, Nelson KG. Apgar scores and umbilical arterial pH in preterm newborn infants. *Am J Obstet Gynecol* 1984; **149**: 651–4.

101. Olshan AF, Shy KK, Luthy DA. Cesarean birth and neonatal mortality in very low birth weight infants. *Obstet Gynecol* 1984; **64**: 267–70.

102. Yu VYH, Bajak B, Cutting D, et al. Effect of mode of delivery on outcome of very low birth weight infants. *Br J Obstet Gynaecol* 1984; **91**: 633–9.

103. Kithen W, Ford GW, Doyle LW, et al. Cesarean section or vaginal delivery at 24 to 28 weeks' gestation: comparison of survival and neonatal and two year morbidity. *Obstet Gynecol* 1985; **66**: 149–57.

104. Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons. *Cochrane Database Syst Rev* 2013; **9**: CD000078.

105. Goldenberg RL, Davis RO. En caul delivery of the very premature infant. *Am J Obstet Gynecol* 1983; **145**: 645–6.

106. Hannah ME, Hannah WJ, Hewson SA, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. *Lancet* 2000; **356**: 1375–83.

107. Bergenhenegouwen LA, Meertens LJ, Schaaf J, et al. Vaginal delivery versus caesarean section in preterm breech delivery: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2014; **172**: 1–6.

108. Richmond JR, Morin L, Benjamin A. Extremely preterm vaginal breech delivery en caul. *Obstet Gynecol* 2002; **99**: 1025–30.

109. Tucker Edmonds B, McKenzie F, Macheras M, et al. Morbidity and mortality associated with mode of delivery for breech periviable deliveries. *Am J Obstet Gynecol* 2015; **213**(1): e1–12.

110. Tejani N, Verma U, Hameed C, et al. Method and route of delivery in the low birth weight vertex presentation correlated with early periventricular/ intraventricular hemorrhage. *Obstet Gynecol* 1987; **69**: 1–4.

111. Schwarz DB, Miodovnik MK, Lavin JP Jr. Neonatal outcome among low birth weight infants delivered spontaneously or by low forceps. *Obstet Gynecol* 1983; **62**: 283–6.

112. Kriewall TJ. Structural, mechanical, and material properties of fetal cranial bone. *Am J Obstet Gynecol* 1982; **143**: 707–14.

113. Lee HC, Gould JB. Survival advantage associated with cesarean delivery in very low birth weight vertex neonates. *Obstet Gynecol* 2006; **107**: 97–105.

114. Lee HC, Gould JB. Survival rates and mode of delivery for vertex preterm neonates according to small- or appropriate-for-gestational-age status. *Pediatrics* 2007; **1118**: e1836–44.

115. Druzin ML. Atraumatic delivery in cases of malpresentation of the very low birth weight fetus at cesarean section: the splint technique. *Am J Obstet Gynecol* 1986; **154**: 941–2.

116. Barzilay E, Mazaki-Tovi S, Amikam U, et al. Mode of delivery of twin gestation with very low birth weight: is vaginal delivery safe? *Am J Obstet Gynecol* 2015; **213**:219.e1–8.

117. Sentilhes L, Oppenheimer A, Bouhours A-C, et al. Neonatal outcome of very preterm twins: policy of planned vaginal or cesarean delivery. *Am J Obstet Gynecol* 2015; **213**(73): e1–7.

118. Barret JFR, Hannah ME, Hutton EK et al. A randomized trial of planned cesarean or vaginal delivery for twin pregnancy. *N Engl J Med* 2013; **369**: 1295–1305.

119. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012; **8**: CD003248.

120. Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonatology* 2008; **93**(2): 138–144.

121. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants. *Anesth Anag* 2015; **120**: 1337–51.

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Chapter 6

Risks and Complications of Multiple Gestation

Yair Blumenfeld and Samantha Do

Introduction

In the United States in 2013, the twin birth rate rose 2% to 33.7/1,000 births (3.4% of all births) [1]. The twinning rate rose 76% from 1980 through 2009 but was generally stable from 2009 through 2012. Multiple births have a tremendous impact on prematurity. In 2013, 11.4% of live births were born prematurely, and of multiple gestations, 56% were born preterm, 55% were low birth weight (<2,500 g), and 9.7% were very low birth weight (<1,500 g) [1]. Infants from multiple gestations thus carry a tremendous economic burden; in 2005, the annual cost of prematurity in the United States was well over $26 billion [2]. In addition to prematurity, twins, regardless of type, are at higher risk for neurologic injury. Multiple studies have correlated cerebral palsy (CP) with multiple gestations [3–7]. For example, a case-control study based on the Swedish Medical Birth Registry between 1984 and 1998 showed a 1.4 odds ratio (95% confidence interval [CI] 1.1–1.6) of CP in twin gestations relative to their singleton counterparts [8]. Finally, twins pose interesting and challenging diagnostic and management dilemmas. From conception to delivery, and even beyond, twin gestations behave remarkably differently from their singleton counterparts and have a myriad of unique physiologic changes and pathologic conditions that one must consider when caring for these special pregnancies.

Embryology

Approximately two-thirds of twins are dizygotic, with an incidence of 7–11/1,000 births [9]. The incidence of dizygotic twinning is influenced by race, heredity, maternal age, parity, and especially fertility drugs [9]. Dizygotic twins result from fertilization of two oocytes by different spermatozoa, and thus each zygote has a different genetic makeup. Each twin implants separately in the uterus and has a separate chorionic sac and amniotic cavity. Monozygotic twins, however, occur at a relatively constant rate, approximately 1/250 births, and result from splitting of the zygote at various stages of development. When splitting occurs at the two-cell stage (within 3 days of fertilization), each resulting embryo will have its own placenta, amniotic sac, and chorionic cavity [10]. If splitting occurs later, at the early blastocyst stage (between 4 and 8 days after fertilization), the resulting embryos will have a common placenta and chorionic sac but separate amniotic cavities [10]. Rarely, the separation occurs at the bilaminar germ disk stage (between 8 and 12 days after fertilization), resulting in two embryos that share a single placenta, as well as a common chorionic and amniotic sac [10]. Even more rare are conjoined twins, resulting from a split during development of the primitive node and streak (after day 13 after fertilization).

Zygosity can be determined prenatally by ultrasound only if the fetuses are monoamnionic or monochorionic. Dichorionic, diamnionic twins may be either dizygotic or monozygotic. Obstetrically, clarifying the chorionicity of twin gestations as early as possible is of vital importance because antenatal, intrapartum, and postnatal risks vary by chorionic type. Specifically, monochorionic twins are at increased risk of midtrimester twin-twin transfusion syndrome and stillbirth, particularly at late preterm and early term gestational ages. Therefore, monochorionic twins are routinely followed with more frequent antenatal surveillance, and the recommendation for delivery is by 36–37 weeks' gestation compared with delivery at between 38 and 39 weeks' gestation for dichorionic twins [11].

Diagnosis

Until real-time ultrasound became available in the 1970s, twin gestations were largely diagnosed at the time of delivery. The treating obstetrician may have been suspicious clinically of the possibility of multiple

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gestations by a larger than expected abdominal size or by multiple moving fetal parts. Advances in ultrasound imaging and, more recently, the shift toward increased first-trimester imaging have had a tremendous impact on the antenatal diagnosis and care of multiple gestations.

Probably no parameter on ultrasound evaluation is more important than determining the chorionicity of multiple gestations. Imaging parameters such as determining the sex of the fetuses, placental location and origin, thickness (less than or greater than 2 mm), and number of layers of the membranes are often used to achieve this goal [12]. Sometimes, in pregnancies in which there is a single placental mass, it may be difficult to distinguish one large placenta from two placentas that are "fused." In these situations, the presence of a triangular projection of placental tissue extending beyond the chorionic surface, termed the *twin-peak sign*, indicates two fused placentas [9]. A prospective study comparing ultrasound criteria with placental pathology found that the combination of placental location, dividing membrane thickness, presence or absence of the twin-peak sign, and fetal gender had 91% specificity and sensitivity for determining the chorionicity, amnionicity, and zygosity of 110 twins at midgestation [13]. A more recent study analyzing 545 twin sets found the sensitivity and specificity of sonographic diagnosis of monochorionicity to be 81.1% and 96%, respectively, with examinations performed before 14 weeks' gestation less likely to misclassify chorionicity than those with sonographic examinations at between 15 and 20 weeks' gestation [14].

Prematurity

The mean gestational age of delivery for twin pregnancies is 35.3 weeks, more than 4 weeks earlier than for singletons [11]. Multiple gestations are also six times more likely to be born preterm (<37 weeks) and eight times more likely to be born very preterm (<32 weeks) [11]. In a large cohort study of more than 33,800 neonates, twins represented only 2.6% of newborns but 12.2% of all preterm births, 15.4% of neonatal deaths, and 9.5% of all fetal deaths [15]. Spontaneous labor accounted for 54% of all preterm twin pregnancies, premature rupture of membranes accounted for 22%, and indicated deliveries accounted for 23% (including maternal hypertension, fetal distress, and fetal growth abnormalities) [15].

The pathophysiologic mechanisms leading to preterm labor and delivery in twins may be quite different from those in singletons. Stretching alone can induce increased myometrial contractility, prostaglandin release, expression of gap junction protein or connexin 43, and increased oxytocin receptors in pregnant and nonpregnant myometrium [16,17]. Compared with spontaneous twins, in vitro fertilization (IVF) twins are at an increased risk for preterm delivery and have been reported to deliver at earlier gestational ages [18].

Prediction

Currently, the most validated predictive markers of preterm labor are cervical length and fetal fibronectin measurements. A short cervix, often defined as less than 2.5 cm in the second trimester (normal cervix is ~3.5–4 cm), is associated with a 25% risk of preterm labor in singletons but up to 70% in twins [19]. Similarly, the presence of fetal fibronectin (FFN), a protein released by the decidual membrane, has a positive predictive value of 83.1% in singletons and up to 100% in twins [19,20]. Studies comparing the utility of combining both have shown that the presence of short cervix and positive FFN at 24 weeks carries a 25% risk of delivery within 2–4 weeks for singleton gestations but up to 50% in twins [19]. Today, both are used in assessing the risk of preterm labor in twin gestations [21–24].

Prevention

Cervical cerclage for patients with a short cervix or a history of cervical incompetence remains controversial in singleton pregnancies, and it is even more controversial for twin gestations [25]. In the 1980s, two prospective studies evaluating the role of prophylactic cerclage in multiple gestations did not show a definitive benefit from the procedure [26–28]. In a 2005 meta-analysis of women with twins and a short cervix, those who received cerclage actually had a higher risk of preterm delivery [25]. Furthermore, two retrospective studies of ultrasound-indicated cerclage due to a short cervix also demonstrated no benefit to cerclage [29,30]. In a more recent study of 140 women with twins and a short cervix (<25 mm), 57 of whom received a cerclage, cerclage placement was not associated with a significant effect on perinatal outcomes compared with control individuals [31]. However, in the planned subgroup analysis of asymptomatic twin pregnancies with cervical length less than 15 mm before 24 weeks, cerclage was associated with significant prolongation of pregnancy by almost

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4 weeks, significantly decreased spontaneous preterm birth at less than 34 weeks by 49%, and admission to neonatal intensive care by 58% compared with control individuals [31].

Intramuscular progesterone (17α-hydroxyprogesterone caproate) supplementation has been validated as a means of preventing the recurrence of preterm labor in singleton gestations [32]. When the same study group evaluated the role of progesterone for multiple gestations, equal benefit was not found [33]. Similarly, vaginal progesterone supplementation was found to be effective in preventing preterm birth in singleton gestations with a short cervix, although a similar effect was not found in multiple gestations, with some studies even indicating increased preterm birth risk in twins [34–36]. Therefore, there is still debate regarding the role of progesterone in twin pregnancies, including the optimal dose and route of administration, and there is currently no consensus nor sufficient data to support the routine use of progesterone supplementation for preterm labor prevention in twins.

Intravaginal pessary has been suggested recently as a method of preterm birth prevention in singletons with a short cervix, and a large prospective, randomized trial is planned to evaluate the effect of pessary in twins with a short cervix [37].

Treatment

There are limited data regarding the benefit of acute tocolysis for preterm labor in twin pregnancies. Most of the data available come from the few retrospective and prospective trials that mostly included singletons but also some twin sets. Hales et al. reported magnesium sulfate to be as efficacious in twins as it is in singletons [38]. O'Leary in 1986 described prophylactic oral terbutaline to increase the mean gestational age of delivery in 28 twin pairs [39]. In the largest randomized, prospective trial comparing magnesium sulfate with nifedipine, which included 37 twin pregnancies of 192 participants, no difference was observed in delay of delivery, gestational age of delivery, or major neonatal outcomes between the two study drugs [40]. Overall, there is limited information regarding the benefit of tocolytics in twin pregnancies, especially their efficacy and effects on birth weight and neonatal mortality. That said, tocolytic therapy may provide short-term prolongation of pregnancy, which enables the administration of antenatal corticosteroids as well as transport to a tertiary-care facility if indicated [11].

Monochorionic Twins

Monochorionic twins, twins resulting from division of the fertilized egg at various stages, have a relatively stable prevalence of ~1/250 births. All monochorionic twins are monozygotic, but not all monozygotic twins are monochorionic. Though originally thought to arise independently of assisted reproductive technology (ART), recent studies from a single academic IVF center describe lower rates of monozygotic twins after 2002 and higher rates of monozygotic twins with blastocyst transfer compared with day 3 embryo transfers, thus suggesting an effect on the rates of monochorionic twins by assisted reproduction [41,42].

Besides twin-to-twin transfusion syndrome, monochorionic twins are at a higher risk for single-twin demise, twin growth abnormalities, preterm labor and delivery, and adverse neonatal outcomes, including neurologic deficits [43]. A retrospective study of day 3 cranial ultrasounds performed on 101 multiple-gestation neonates delivered prior to 36 weeks, including 89 twins and 12 triplets, revealed a 13.8% incidence of antenatal necrosis of the cerebral white matter [44]. The incidence was much higher in monochorionic than in dichorionic twins (30% versus 3.3%, $p < 0.001$) [44]. In addition to prenatal neurologic injury, recent studies have shown monochorionic twins to be at increased risk for congenital cardiac defects [45,46].

The death of one twin in a monochorionic pair is associated with significant risk of hypoxic–ischemic injury in the survivor [43,47,48]. This neurologic injury likely happens instantaneously following the demise of the cotwin and is thought to be caused either by acute vascular flow changes or by embolization of fetal material through vascular anastomoses. Antenatal MRI has been performed on surviving cotwins, and various lesion types and locations have been reported [49].

The management, counseling, and neonatal risk stratification for monochorionic twins depend largely on whether the twins are monoamnionic or diamnionic. Monochorionic, monoamnionic twins are at extremely high risk for cord entanglement, single-twin demise, and preterm delivery. These twins are often admitted to the hospital at 24–28 weeks' gestation and delivered at 32–34 weeks' gestation [50]. Monochorionic, diamnionic twins are often managed on an outpatient basis as long as adequate fetal growth and neonatal well-being are reassuring. There is a debate regarding the optimal timing of delivery in

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monochorionic, diamnionic twins due to the risk of single-cotwin demise with progressive gestation. Large cohort studies addressing perinatal mortality rates and gestational age in twins have shown the lowest perinatal mortality at 37–38 weeks (compared with 39–40 weeks for singletons) [51,52]. A large retrospective Dutch cohort study showed higher rates of fetal mortality in monochorionic than dichorionic twins after 32 weeks' gestation and suggested that the optimal time to deliver monochorionic twins is at or before 37 weeks' gestation [53]. The American College of Obstetricians and Gynecologists currently recommends delivery by 38 weeks' gestation for monochorionic, diamniotic twins [11].

Twin-to-Twin Transfusion Syndrome

Twin-to-twin transfusion syndrome (TTTS) is a pathologic condition in which placental arterial and venous anastomoses lead to unequal sharing of fetal blood supply and discordant growth in monozygotic twins [54]. Studies conducted on placentas of TTTS twins suggest that it is the deep arteriovenous connections that lead to this phenomenon [55]. Classically, the condition will result in a *donor twin*, characterized by intrauterine growth restriction, anemia, and oligohydramnios, and a *recipient twin*, in which the blood volume overload will ultimately lead to hydropic changes, polycythemia, polyhydramnios, and heart failure. TTTS is seen in approximately 5–15% of monochorionic twins [54,56].

Clinical Presentation and Diagnosis

In 1999, a staging system for TTTS (the Quintero staging system) was introduced that incorporated discordant amniotic fluid volumes between gestational sacs, absent bladder in the donor twin, arterial Doppler abnormalities, presence of fetal hydrops, and neonatal demise [57]. The staging system, designated from class 1 to 5 in severity, not only has prognostic implications for neonatal morbidity and mortality but also has been used since to triage patients for prenatal invasive surgical treatment modalities [57]. In cases of severe oligohydramnios, the donor twin may have a "stuck twin" appearance due to its proximity to the uterine wall and limited ability to move freely within its amniotic cavity. Additional modifying staging systems have been introduced, with particular emphasis on cardiac findings [58].

Management

Early studies of TTTS reported perinatal mortality rates as high as 90–100% when the disease was diagnosed midtrimester [59]. Today, the management and outcome of these twins will vary by center depending on the gestational age and severity of disease at the time of diagnosis. The natural course of TTTS is relatively unpredictable. In a limited study of 18 TTTS twins followed for 90 "week-to-week changes," a progression of disease was seen in 14.5%, down-staging was present in 12.2%, and no change was seen in 72.2% [60].

Over the years, multiple treatment modalities have been attempted aimed at resolving the unequal sharing of blood supply. Amnioreduction via serial amniocenteses, amniotic septostomy, and selective fetocide via cord occlusion of one of the cotwins have all been described. Serial amniocenteses remain the most widely available and practiced therapy for TTTS. A large review of neonatal outcomes from 223 sets of twins undergoing amnioreduction for TTTS showed a 78% live-birth rate, 60% alive at 4 weeks of life, and 48% of sets with both neonates alive at 4 weeks of life. Neurologic scans in survivors revealed abnormalities in 24% of recipients and 25% of donors [61].

Endoscopic laser photocoagulation was introduced in the late 1980s and early 1990s as a treatment for early and severe TTTS. A recent European multicenter prospective, randomized study comparing serial amnioreduction with endoscopic laser surgery was stopped early due to the observation of increased neonatal survival and decreased incidence of periventricular leukomalacia and other fetal neurologic complications in the laser photocoagulation group [62]. A similar multicenter prospective clinical trial conducted in the United States did not show a difference in the overall fetal and neonatal survival between amnioreduction and laser surgery [63]. More recent large retrospective cohort studies suggest an overall gestational age of delivery of 31–32 weeks' gestation following laser coagulation, with at least one twin survivor in up to 80–85% of cases [64,65].

Neonatal Outcomes

Progressive TTTS is often associated with severe neonatal morbidity and mortality, including severe adverse neurologic outcomes. Overall, neonatal outcomes will depend largely on the gestational age at diagnosis, severity of disease, treatment modality, and presence of cotwin demise [43]. In a large cohort

study of monochorionic twins, those with TTTS had higher rates of RDS, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), renal failure, persistent pulmonary hypertension of the newborn (PPHN), and fetal demise and lower 1-year survival [56]. Intracranial Doppler flow abnormalities have also been reported in monochorionic twins with TTTS, and these have been correlated with worse outcomes [66]. In a retrospective study of 29 TTTS cases, 18 treated with serial amnioreduction and 11 with conservative management, perinatal mortality was 50%, with a mean gestational age of delivery of 28 weeks. Abnormal cranial ultrasounds were seen in 41% of neonates, and the incidence of CP was 21% (50% in cases of a single-twin survivor and 14.3% in cases of double survivors) [67]. A prospective long-term study of 167 surviving neonates of second-trimester TTTS treated with laser photocoagulation from a single center reported 86% intact neurodevelopmental outcomes in survivors, 7% mild neurologic abnormalities, and 6% major neurodevelopmental abnormalities [68]. Another report of 82 TTTS pregnancies treated with fetoscopic laser surgery reported a 70% perinatal survival and 17% (19/115) neurodevelopmental impairment at 2 years of life, including CP (eight cases), mental developmental delay (nine cases), psychomotor developmental delay (12 cases), and deafness (one case) [69]. Neurodevelopmental impairment in TTTS treated with laser surgery is associated with advanced gestational age at laser surgery, low gestational age at birth, low birth weight, and high Quintero stage [70].

Abnormal Growth

Aside from twin-to-twin transfusion syndrome, abnormal growth is present in up to 15–25% of twin gestations, with monochorionic twins having an increased risk of growth restriction compared with dichorionic twins [11,71]. Abnormal growth may be either *discordant growth*, classified as 15–25% weight difference between the cotwins, or *small for gestational age (SGA)/intrauterine growth restriction (IUGR)*, classified as estimated weight less than 10% for either one or both twins. Abnormal growth in twin gestations may be a result of abnormal placentation as well as increased fetal metabolic demand. In a study of 1,318 twin pairs (926 with twins of appropriate weight for gestational age and 392 with twins small for gestational age), discordant growth was an independent risk factor for cesarean delivery and adverse neonatal outcomes [72]. Other studies have also shown similar increased risk of neonatal morbidity and mortality with discordant growth [73,74]. A prospective cohort study of 42 expectantly managed monochorionic twins with selective intrauterine growth restriction compared with 29 dichorionic and 32 monochorionic appropriately grown twin controls showed higher rates of parenchymal brain damage in the monochorionic growth-restricted group (12% versus 1.7% and 0%, respectively) [75].

Because of the adverse neonatal risks with abnormal growth, twins are routinely monitored with serial growth ultrasounds in the second and third trimesters. Management of growth abnormalities will depend on the gestational age and severity at the time of diagnosis. Bed rest and hospitalization, though often recommended, have not been proven to correct or prevent progressive fetal growth abnormalities [76].

Peripartum Management

Although delivery by cesarean section is a well-accepted practice for multiple gestations of triplets and greater, the mode of delivery for twin gestations remains controversial. Though often delivered via cesarean section, most physicians will determine the optimal route of delivery based on fetal presentation and clinical experience. Most obstetricians are comfortable delivering twin gestations vaginally if the twins are of concordant weight and in the vertex-vertex presentation. Fewer obstetricians feel comfortable performing a vertex-breech delivery, and even fewer would perform an internal podalic version and breech extraction for a vertex-transverse presentation.

Vertex-vertex twins are present in 38% of twins at the time of delivery, vertex-breech in 42%, and non-vertex-presenting twins in 20% [77]. Data regarding the safety of vertex delivery, followed by a breech extraction, is mixed for vertex-breech presentation. The American College of Obstetricians and Gynecologists (ACOG) states: "[T]he route of delivery for twins should be determined by the position of the fetuses, the ease of fetal heart rate monitoring, and maternal and fetal status. Data are insufficient to determine the best route of delivery for higher order multiple gestations (triplets and higher)" [11]. A large retrospective study of 15,185 second nonvertex twins reported increased neonatal morbidity and mortality with vaginal delivery versus elective cesarean section, even when excluding twins who were delivered via a combined vaginal–cesarean section [78]. Morbidity

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included infant injury, low Apgar scores, ventilation use, and seizures. A recent prospective, randomized trial of planned cesarean versus planned vaginal delivery with 2,784 women, 1,049 of whom had vertex/nonvertex twins, found that a planned cesarean delivery did not significantly decrease or increase the risk of fetal or neonatal death or serious neonatal morbidity compared with a planned vaginal delivery [79]. A smaller retrospective cohort study from a single practice with experienced obstetricians found that 100% of 130 patients with vertex/nonvertex twins who had a planned vaginal delivery achieved a successful vaginal delivery of twin B if twin A was delivered vaginally using active management of delivery of the second twin using breech extraction [80].

There is also some controversy regarding the vertex-breech delivery of fetuses weighing less than 1,500 g. Most experts refrain from doing so despite multiple retrospective studies showing no benefit to cesarean section in this situation [81,82]. Also, most clinicians will not attempt a vertex-breech delivery if the estimated weight of the second twin is 20% more than that of the presenting fetus.

There are some data regarding vaginal birth after cesarean (VBAC) delivery in twin gestations. Most studies, including a large cohort study of over 1,600 twin pregnancies, report uterine rupture rates similar to those in singleton VBAC deliveries [83–85].

Conclusion

The rates of multiple gestations appear to be stable. With these rates, the high incidence of complications in multiple gestations, namely, prematurity and growth abnormalities, will continue to occupy future obstetricians and neonatologists. It is our hope that advances in our understanding of pathophysiologic mechanisms leading to these adverse outcomes will result in improved preventive, diagnostic, prophylactic, and therapeutic modalities, thereby reducing the risks and complications associated with these special pregnancies.

References

1. Martin JA, Hamilton BE, Osterman MJ, et al. Births: final data for 2013. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2015; **64**(1): 1–65.
2. March of Dimes. Peri Stats, 2008. Available at www.marchofdimes.com/peristats.
3. Alberman ED. Cerebral palsy in twins. *Guy's Hosp Rep* 1964; **113**: 285–95.
4. Goodman R. Cerebral palsy in twins. *Dev Med Child Neurol* 1993; **35**(4): 370.
5. Livinec F, Ancel PY, Marret S, et al. Prenatal risk factors for cerebral palsy in very preterm singletons and twins. *Obstet Gynecol* 2005; **105**(6): 1341–7.
6. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *BMJ* 1993; **307**(6914): 1239–43.
7. Pharoah PO. Twins and cerebral palsy. *Acta Paediatr* 2001; **90**(436): 6–10.
8. Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. *Obstet Gynecol* 2006; **108**(6): 1499–1505.
9. Cunningham FG. *Williams obstetrics*, 24th edn. New York: McGraw-Hill Medical, 2014.
10. Sadler TW. *Langman's Medical Embryology*, 13th edn. Philadelphia: Wolters Kluwer, 2015.
11. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies (ACOG Practice Bulletin No. 144). *Obstet Gynecol* 2014; **123**(5): 1118–32.
12. Monteagudo A, Timor-Tritsch IE, Sharma S. Early and simple determination of chorionic and amniotic type in multifetal gestations in the first fourteen weeks by high-frequency transvaginal ultrasonography. *Am J Obstet Gynecol* 1994; **170**(3): 824–9.
13. Scardo JA, Ellings JM, Newman RB. Prospective determination of chorionicity, amnionicity, and zygosity in twin gestations. *Am J Obstet Gynecol* 1995; **173**(5): 1376–80.
14. Blumenfeld YJ, Momirova V, Rouse DJ, et al. Accuracy of sonographic chorionicity classification in twin gestations. *J Ultrasound Med* 2014; **33**(12): 2187–92.
15. Gardner MO, Goldenberg RL, Cliver SP, et al. The origin and outcome of preterm twin pregnancies. *Obstet Gynecol* 1995; **85**(4): 553–7.
16. Newman RB, Iams JD, Das A, et al. A prospective masked observational study of uterine contraction frequency in twins. *Am J Obstet Gynecol* 2006; **195**(6): 1564–70.
17. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. *BJOG* 2006; **113**(Suppl. 3): 17–42.
18. Nassar AH, Usta IM, Rechdan JB, et al. Pregnancy outcome in spontaneous twins versus twins who were conceived through in vitro fertilization. *Am J Obstet Gynecol* 2003; **189**(2): 513–18.
19. Goldenberg RL, Iams JD, Das A, et al. The Preterm Prediction Study: sequential cervical length and

fetal fibronectin testing for the prediction of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 2000; **182**(3): 636–43.

20. Lockwood CJ, Senyei AE, Dische MR, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med* 1991; **325**(10): 669–74.
21. Gibson JL, Macara LM, Owen P, et al. Prediction of preterm delivery in twin pregnancy: a prospective, observational study of cervical length and fetal fibronectin testing. *Ultrasound Obstet Gynecol* 2004; **23**(6): 561–6.
22. Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 1996; **175**(4 Pt 1): 1047–53.
23. Ruiz RJ, Fullerton J, Brown CE. The utility of fFN for the prediction of preterm birth in twin gestations. *JOGNN* 2004; **33**(4): 446–54.
24. Fox NS, Saltzman DH, Klauser CK, et al. Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length. *Am J Obstet Gynecol* 2009; **201**(3): e313–15.
25. Berghella V, Odibo AO, To MS, et al. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005; **106**(1): 181–9.
26. Dor J, Shalev J, Mashiach S, et al. Elective cervical suture of twin pregnancies diagnosed ultrasonically in the first trimester following induced ovulation. *Gynecol Obstet Invest* 1982; **13**(1): 55–60.
27. MRC/RCOG Working Party on Cervical Cerclage. Interim report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomized trial of cervical cerclage. *BJOG* 1988; **95**(5): 437–45.
28. Eskandar M, Shafiq H, Almushait MA, et al. Cervical cerclage for prevention of preterm birth in women with twin pregnancy. *Int J Gynaecol Obstet* 2007; **99**(2): 110–12.
29. Roman AS, Rebarber A, Pereira L, et al. The efficacy of sonographically indicated cerclage in multiple gestations. *J Ultrasound Med* 2005; **24**(6): 763–8; quiz 770.
30. Newman RB, Krombach RS, Myers MC, McGee DL. Effect of cerclage on obstetrical outcome in twin gestations with a shortened cervical length. *Am J Obstet Gynecol* 2002; **186**(4): 634–40.
31. Roman A, Rochelson B, Fox NS, et al. Efficacy of ultrasound-indicated cerclage in twin pregnancies. *Am J Obstet Gynecol* 2015; **212**(6): e781–6.
32. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17α-hydroxyprogesterone caproate. *N Engl J Med* 2003; **348**(24): 2379–85.
33. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17α-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; **357**(5): 454–61.
34. Fonseca EB, Celik E, Parra M, et al. Fetal Medicine Foundation second trimester screening G: progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; **357**(5): 462–9.
35. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011; **38**(1): 18–31.
36. Brubaker SG, Pessel C, Zork N, et al. Vaginal progesterone in women with twin gestations complicated by short cervix: a retrospective cohort study. *BJOG* 2015; **122**(5): 712–18.
37. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet*. 2012; **379**(9828): 1800–6.
38. Hales KA, Matthews JP, Rayburn WF, Atkinson BD. Intravenous magnesium sulfate for premature labor: comparison between twin and singleton gestations. *Am J Perinatol* 1995; **12**(1): 7–10.
39. O'Leary JA. Prophylactic tocolysis of twins. *Am J Obstet Gynecol* 1986; **154**(4): 904–5.
40. Lyell DJ, Pullen K, Campbell L, et al. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial. *Obstet Gynecol* 2007; **110**(1): 61–7.
41. Milki AA, Jun SH, Hinckley MD, et al. Incidence of monozygotic twinning with blastocyst transfer compared to cleavage-stage transfer. *Fertil Steril* 2003; **79**(3): 503–6.
42. Moayeri SE, Behr B, Lathi RB, et al. Risk of monozygotic twinning with blastocyst transfer decreases over time: an 8-year experience. *Fertil Steril* 2007; **87**(5): 1028–32.
43. Adegbite AL, Castille S, Ward S, Bajoria R. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. *Am J Obstet Gynecol* 2004; **190**(1): 156–63.
44. Bejar R, Vigliocco G, Gramajo H, et al. Antenatal origin of neurologic damage in newborn infants. II.

Multiple gestations. *Am J Obstet Gynecol* 1990; **162**(5): 1230–6.

45. Bahtiyar MO, Dulay AT, Weeks BP, et al. Prevalence of congenital heart defects in monochorionic/diamniotic twin gestations: a systematic literature review. *J Ultrasound Med* 2007; **26**(11): 1491–8.
46. Pettit KE, Merchant M, Machin GA, et al. Congenital heart defects in a large, unselected cohort of monochorionic twins. *J Perinatol* 2013; **33**(6): 457–61.
47. Okumura A, Hayakawa F, Kato T, et al. Brain malformation of the surviving twin of intrauterine co-twin demise. *J Child Neurol* 2007; **22**(1): 85–8.
48. Morokuma S, Tsukimori K, Anami A, et al. Brain injury of the survivor diagnosed at 18 weeks of gestation after intrauterine demise of the co-twin: a case report. *Fetal Diagn Ther* 2008; **23**(2): 146–8.
49. Righini A, Salmona S, Bianchini E, et al. Prenatal magnetic resonance imaging evaluation of ischemic brain lesions in the survivors of monochorionic twin pregnancies: report of 3 cases. *J Comput Assist Tomogr* 2004; **28**(1): 87–92.
50. Ezra Y, Shveiky D, Ophir E, et al. Intensive management and early delivery reduce antenatal mortality in monoamniotic twin pregnancies. *Acta Obstet Gynecol Scand* 2005; **84**(5): 432–5.
51. Minakami H, Sato I. Reestimating date of delivery in multifetal pregnancies. *JAMA* 1996; **275**(18): 1432–4.
52. Kahn B, Lumey LH, Zybert PA, et al. Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice. *Obstet Gynecol* 2003; **102**(4): 685–92.
53. Hack KE, Derks JB, Elias SG, et al. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. *BJOG* 2008; **115**(1): 58–67.
54. Society for Maternal-Fetal Medicine, Simpson LL. Twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2013; **208**(1): 3–18.
55. Bajoria R, Wigglesworth J, Fisk NM. Angioarchitecture of monochorionic placentas in relation to the twin-twin transfusion syndrome. *Am J Obstet Gynecol* 1995; **172**(3): 856–63.
56. Lutfi S, Allen VM, Fahey J, et al. Twin-twin transfusion syndrome: a population-based study. *Obstet Gynecol* 2004; **104**(6): 1289–97.
57. Quintero RA, Morales WJ, Allen MH, et al. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999; **19**(8 Pt 1): 550–5.
58. Rychik J, Tian Z, Bebbington M, et al. The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease. *Am J Obstet Gynecol* 2007; **197**(4): e391–8.
59. Chescheir NC, Seeds JW. Polyhydramnios and oligohydramnios in twin gestations. *Obstet Gynecol* 1988; **71**(6 Pt 1): 882–4.
60. Luks FI, Carr SR, Plevyak M, et al. Limited prognostic value of a staging system for twin-to-twin transfusion syndrome. *Fetal Diagn Ther* 2004; **19**(3): 301–4.
61. Mari G, Roberts A, Detti L, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. *Am J Obstet Gynecol* 2001; **185**(3): 708–15.
62. Senat MV, Deprest J, Boulvain M, et al. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004; **351**(2): 136–44.
63. Crombleholme TM, Shera D, Lee H, et al. A prospective, randomized, multicenter trial of amnioreduction vs selective fetoscopic laser photocoagulation for the treatment of severe twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2007; **197**(4): e391–9.
64. Ruano R, Rodo C, Peiro JL, et al. Fetoscopic laser ablation of placental anastomoses in twin-twin transfusion syndrome using 'Solomon technique'. *Ultrasound Obstet Gynecol* 2013; **42**(4): 434–9.
65. Papanna R, Block-Abraham D, Mann LK, et al. Risk factors associated with preterm delivery after fetoscopic laser ablation for twin-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2014; **43**(1): 48–53.
66. Degani S, Leibovitz Z, Shapiro I, et al. Instability of Doppler cerebral blood flow in monochorionic twins. *J Ultrasound Med* 2006; **25**(4): 449–54.
67. Lopriore E, Nagel HT, Vandenbussche FP, Walther FJ. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome. *Am J Obstet Gynecol* 2003; **189**(5): 1314–19.
68. Graef C, Ellenrieder B, Hecher K, et al. Long-term neurodevelopmental outcome of 167 children after intrauterine laser treatment for severe twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2006; **194**(2): 303–8.
69. Lopriore E, Middeldorp JM, Sueters M, et al. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. *Am J Obstet Gynecol* 2007; **196**(3): e231–4.
70. Lopriore E, Ortibus E, Acosta-Rojas R, et al. Risk factors for neurodevelopment impairment in twin-twin transfusion syndrome treated with fetoscopic laser surgery. *Obstet Gynecol* 2009; **113**(2 Pt 1): 361–6.

71. Masheer S, Maheen H, Munim S. Perinatal outcome of twin pregnancies according to chorionicity: an observational study from tertiary care hospital. *J Matern Fetal Neonatal Med.* 2015; **28**(1): 23–5.
72. Amaru RC, Bush MC, Berkowitz RL, et al. Is discordant growth in twins an independent risk factor for adverse neonatal outcome? *Obstet Gynecol* 2004; **103**(1): 71–6.
73. Branum AM, Schoendorf KC. The effect of birth weight discordance on twin neonatal mortality. *Obstet Gynecol* 2003; **101**(3): 570–4.
74. Demissie K, Ananth CV, Martin J, et al. Fetal and neonatal mortality among twin gestations in the United States: the role of intrapair birth weight discordance. *Obstet Gynecol* 2002; **100**(3): 474–80.
75. Gratacos E, Carreras E, Becker J, et al. Prevalence of neurological damage in monochorionic twins with selective intrauterine growth restriction and intermittent absent or reversed end-diastolic umbilical artery flow. *Ultrasound Obstet Gynecol* 2004; **24**(2): 159–63.
76. Gulmezoglu AM, Hofmeyr GJ. Bed rest in hospital for suspected impaired fetal growth. *Cochrane Database Syst Rev* 2000(2): CD000034.
77. Chasen ST, Spiro SJ, Kalish RB, Chervenak FA. Changes in fetal presentation in twin pregnancies. *J Matern Fetal Neonatal Med* 2005; **17**(1): 45–48.
78. Yang Q, Wen SW, Chen Y, et al. Neonatal death and morbidity in vertex-nonvertex second twins according to mode of delivery and birth weight. *Am J Obstet Gynecol* 2005; **192**(3): 840–7.
79. Barrett JF, Hannah ME, Hutton EK, et al. A randomized trial of planned cesarean or vaginal delivery for twin pregnancy. *N Engl J Med* 2013; **369**(14): 1295–1305.
80. Fox NS, Silverstein M, Bender S, et al. Active second-stage management in twin pregnancies undergoing planned vaginal delivery in a U.S. population. *Obstet gynecol.* 2010; **115**(2 Pt 1): 229–233.
81. Davison L, Easterling TR, Jackson JC, Benedetti TJ. Breech extraction of low-birth-weight second twins: can cesarean section be justified? *Am j obstet gynecol* 1992; **166**(2): 497–502.
82. Morales WJ, O'Brien WF, Knuppel RA, Gaylord S, Hayes P. The effect of mode of delivery on the risk of intraventricular hemorrhage in nondiscordant twin gestations under 1500 g. *Obstet Gynecol* 1989; **73**(1): 107–10.
83. Ford AA, Bateman BT, Simpson LL. Vaginal birth after cesarean delivery in twin gestations: a large, nationwide sample of deliveries. *Am J Obstet Gynecol* 2006; **195**(4): 1138–42.
84. Miller DA, Mullin P, Hou D, Paul RH. Vaginal birth after cesarean section in twin gestation. *Am J Obstet Gynecol* 1996; **175**(1): 194–8.
85. Sansregret A, Bujold E, Gauthier RJ. Twin delivery after a previous caesarean: a twelve-year experience. *J Obstet Gynaecol Canada* 2003; **25**(4): 294–8.

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Chapter 7

Intrauterine Growth Restriction

William W. Hay Jr., Alistair G. S. Philip, and David K. Stevenson

Introduction

Intrauterine growth restriction of the fetus (IUGR) causes significant problems during fetal life, immediately after birth, and later in life, including structural and functional neurodevelopmental disorders [1]. Animal models confirm that growth restriction at critical early stages of development permanently reduces brain neuronal number, axonal length, dendritic arborization, and synapse formation, which lead to reduced cognitive capacity and behavioral dysfunction later in life [2]. Understanding the basic problems that contribute to IUGR and the abnormal neurodevelopmental characteristics of such infants, therefore, is important to complement other discussions in this text about fetal and neonatal brain injury.

Terminology and Definitions

IUGR refers to a slower than normal rate of fetal growth. The term *restriction* is preferred to *retardation* to avoid linking slow growth and small size at birth with mental retardation. Several terms have been used, often interchangeably, for IUGR, but most of them refer to the size of the fetus or newborn at a given gestational age in comparison with normally grown infants (e.g., small for gestational age, light for dates, and hypotrophy). These terms are not comparable, however, because some smaller than normal fetuses or newborns did not experience growth restriction, whereas others within the normal weight-for-age range did. Table 7.1 illustrates a standard classification schema of fetal growth.

Interpretation of Fetal Growth Using Growth Curves

Ideally, growth in an individual fetus would be assessed by serial anthropometric measurements during gestation with comparison with normally growing fetuses of the same gestational age and with definitely known dates of conception. Approximations of such ideal fetal growth curves have been developed from serial ultrasound measurements of fetuses that subsequently were born at term in healthy condition and with normal anthropometric measurements, providing continuous rather than cross-sectional indices of fetal growth. These curves correlate better with the expected rate of normal fetal growth than cross-sectional population-based growth curves of infants born at different gestational ages because the intrauterine growth of those infants was likely affected by the same pathologic factors that led to their preterm birth. Serial ultrasound measurements of fetal growth also can assess how environmental factors, such as acute, severe maternal illness with associated undernutrition, could affect fetal growth and how improved nutrition could restore fetal growth toward normal.

While fetal ultrasound measurements have been used to develop fetal growth parameters and population growth curves, their assessments of length and head circumference are not as accurate as those actually measured in newborn infants, and their estimates of weight are rough extrapolations from so-called normal infants born at the same gestational age. As a result, most estimates of fetal growth are based on growth curves derived from cross-sectional anthropometric measurements of newborn infants at every possible gestational age, although there probably is no ideal fetal growth curve derived from postnatal cross-sectional measurements. Many growth curves have been developed from a variety of locations, populations, mothers of various socioeconomic statuses, and altitudes. Birth weights in recent years may be slightly greater than noted in these earlier growth curves when more extreme limitations on weight gain during pregnancy were

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imposed by most obstetricians in North America. Given recent trends toward larger infants from the now worldwide epidemic of maternal obesity, current cross-sectional growth curves predict greater weight for gestational age (for both males and females), particularly later in gestation, even though they are parallel to the many other growth curves from mixed populations around the world (Figure 7.1), at least up through 36–38 weeks of gestation [1].

Table 7.1 Classification of Fetal Growth

Small for gestational age (SGA)	Birth weight < 10th percentile for gestational age
Appropriate for gestational age (AGA)	Birth weight between 10th and 90th percentile for gestational age
Large for gestational age (LGA)	Birth weight > 90th percentile for gestational age
Intrauterine growth restriction (IUGR)	Slower than normal rate of fetal growth
Normal birth weight	>2,500 g at term gestation
Low birth weight (LBW)	<2,500 g
Very low birth weight (VLBW)	<1,500 g
Extremely low birth weight (ELBW)	<1,000 g

While the majority of SGA infants will have some degree of IUGR, some are predestined to fall below the 10th percentile on a genetic, racial, or familial basis. Such SGA infants are constitutionally small and did not experience growth restriction. In contrast, some infants who have a birth weight that is appropriate for gestational age (AGA, between the 10th and 90th percentiles) may be small because of the effects of IUGR. Thus an infant can be "relatively" SGA when its weight is at the 25th percentile, but its length and head circumference are at the 75th percentile. In this case, the weight/length ratio (or the Ponderal index = [weight (g)]/[length (cm)]^3) is less than normal, indicating that growth rates of internal organs, adipose tissue, and skeletal muscle, which are the principal determinants of weight, were less than normal. Importantly, birth weight at any gestational age does not always represent previous fetal growth rate.

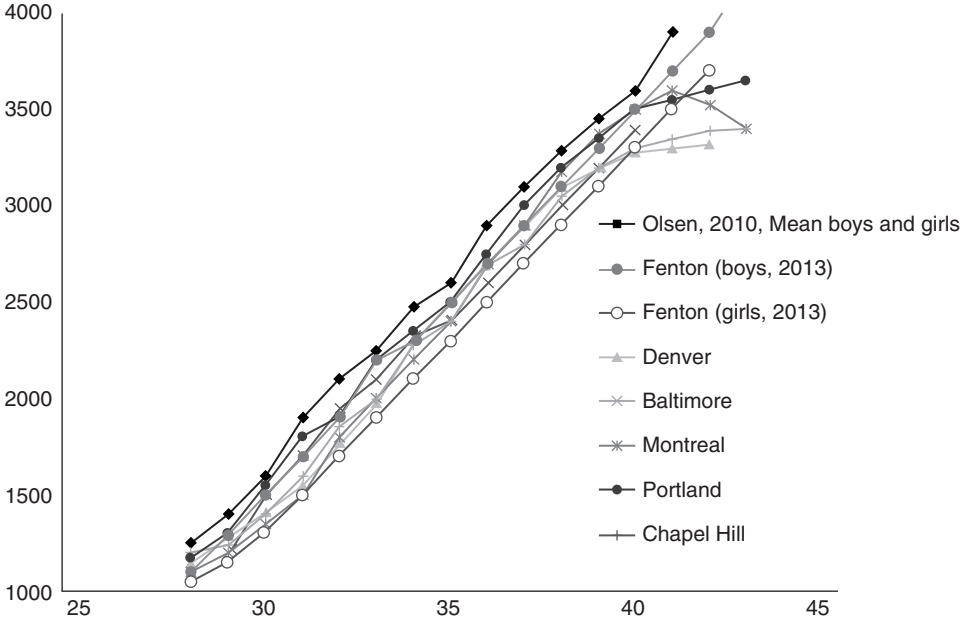


Figure 7.1 Birth weights by gestational age from six sources. (Adapted from Naeye R, Dixon J. Distortions in fetal growth standards. *Pediatr Res* 1978; 12:987–91, with permission; Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2003; 13:59; Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010; 125:e214-24.)

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Symmetric and Asymmetric Growth Restriction

The simplest classification is to consider infants with IUGR as either symmetrically (proportionally) or asymmetrically (disproportionally) grown. Most symmetrically grown infants will have a normal Ponderal index, whereas the asymmetrically grown infants will have a decreased Ponderal index. The principal distinction of asymmetrically grown infants is their apparently greater head/weight ratio but more normal head/length ratio, implying greater reduction in growth of soft tissues (fat and muscle) and internal organs compared with brain growth, leading to the concept of *brain sparing*. This is misleading because the brain also is growth restricted in such infants, although not as much as the soft tissues and other organs. Thus the head circumference in such infants may appear to be relatively large, but it is frequently below the 10th percentile for gestational age.

Although redistribution of blood flow from hypoxemia in IUGR fetuses may favor brain growth [3], as might preservation of normal neuronal glucose transporter concentrations despite fetal hypoglycemia [4], such "adaptations" may be incomplete and result in deficient growth of the brain, particularly when the hypoxia is chronic, as occurs in most human cases of placental insufficiency [5,6]. Supporting evidence comes from studies using MRI that showed decreases in brain volume in IUGR/SGA infants, although this was less affected than body weight [7]. Furthermore, longer-term outcome studies consistently show worse neurodevelopmental outcomes in IUGR infants who have smaller than normal brains [8].

In many instances of IUGR, decrease in size may represent an appropriate adaptive response to reduced availability of nutrients. This adaptation to adverse nutrient transfer also can result in long-term sequelae (see later), particularly when IUGR is extreme. Mild IUGR, which usually develops late in gestation when cell division is slowing but cell growth (hypertrophy) continues, may allow for "catch-up growth," whereas severe IUGR, which starts much earlier in gestation and thus limits cell division, is more likely to result in permanent growth restriction. However, such clear-cut distinctions are not always possible. While symmetric and asymmetric growth patterns begin in the second trimester, symmetrically grown infants with relatively marked IUGR are more likely to have had a predetermined genetic limitation in growth capacity (e.g., a chromosomal problem such as trisomy 18) or chronic growth failure from an early in utero insult (e.g., congenital viral infection), whereas the asymmetrically grown infants are more likely to have suffered from oxygen and nutrient deficiencies that develop later in gestation (e.g., decreased uteroplacental blood flow and placental transport function with maternal preeclampsia).

For many years it was believed that a chronic insult resulted in a decrease in cell number, but a subacute or acute insult produced a decrease in cell size. While growth restriction early in gestation may be more likely to produce permanent stunting due to fewer cells, this is not an absolute outcome or completely confined to early gestation and still can occur in later gestation if growth restriction is sufficiently severe. This helps to explain the difficulty in predicting previous fetal growth rate or subsequent neonatal and infancy growth rates based only on birth weight.

Of particularly note, neonatal outcome is similar in IUGR infants of the same clinical severity, whether or not they could be defined as AGA or SGA according to neonatal growth curve standards. Neonatal curves are misleading, therefore, in detecting low-birth-weight infants according to clinical outcomes and should be used only when obstetric data are unavailable. Improved techniques of diagnosing and evaluating the status of the infant with IUGR have resulted in improved management of the fetus and newborn and are providing a more rational if in some cases still experimental basis for making clinical decisions about what is optimal for the fetus regarding timing of delivery. At times it is difficult to decide what the best management may be, and in many cases earlier delivery may be the best option for fetal survival. Decisions about when to deliver the IUGR fetus should involve a combined obstetric-pediatric approach.

Factors Affecting Fetal Growth

The maternal phenotype exerts a major influence on fetal size at birth, primarily by regulating the growth, size, and functional capacity of the placenta, which is the primary determinant of fetal growth. The principle involved is known as *maternal constraint*, which represents the capacity of the uterus, particularly the endometrial surface area, to support growth of the placenta and thus the fetus. Nutritional deficiencies in the mother also reduce fetal growth, but even severe maternal fasting to the point of chronic starvation

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Table 7.2 Maternal Conditions Associated with Intrauterine Growth Restriction (IUGR)

Both very young and advanced maternal age
Maternal prepregnancy short stature and thinness
Poor maternal weight gain during the latter third of pregnancy
Maternal illness during pregnancy
Failure to obtain normal medical care during pregnancy
Lower socioeconomic status
African-American race (in the United States)
Multiple gestation
Uterine and placental anomalies
Polyhydramnios
Preeclampsia
Hypertension, both chronic and pregnancy induced
Chronic, severe diabetes
Intrauterine infections
Cigarette smoking, cocaine use, and other substance abuse

Table 7.3 Placental Growth Disorders that Lead to or Are Associated with IUGR

Abnormal umbilical vascular insertions (circumvallate, velamentous)
Abruption (chronic, partial)
Avascular villi
Decidual arteritis
Fibrinosis, atheromatous changes
Cytotrophoblast hyperplasia, basement membrane thickening
Infectious villitis
Ischemic villous necrosis and umbilical vascular thromboses; multiple infarcts
Multiple gestations (limited endometrial surface area, vascular anastomoses)
Partial molar pregnancy
Placenta previa
Single umbilical artery
Spiral artery vasculitis, failed or limited erosion into intervillous space
Syncytial knots
Tumors, including chorioangioma and hemangiomas

seldom reduces fetal weight at term by more than 10%. Table 7.2 identifies a large variety of maternal factors that affect the rate of fetal growth.

Placental Growth Factors. The primary regulator of fetal growth is the placenta, including its size and its functional capacity to transport nutrients to the fetus [9]. Nearly all cases of IUGR involve a smaller than normal placenta, and many of these placentas also have reduced transport capacity independent of placental size (e.g., reduced glucose and amino acid transporter proteins and thus glucose and amino acid transport) [10]. Placental growth disorders that can restrict fetal growth are listed in Table 7.3. In most of these cases, the placenta is simply smaller than normal, although some include specific deficits in trophoblast growth and vascular supply to the trophoblast villi. The most common example is preeclampsia, in which the placenta has decreased growth of terminal villi and reduced placental blood flow (ischemic placental disease), which limit oxygen, glucose, and amino acid transport to the fetus.

The placenta also produces hormones that maintain the fetoplacental unit, including chorionic gonadotropins, placental growth hormone, and placental somatotropins. Placental growth hormone and placental lactogen are important in maintaining increased concentrations of glucose and amino acids in the mother, which are then available for transplacental passage to the fetus [10]. The placenta also produces leptin, although the contributions of the fetus and placenta have not yet been clearly delineated. Leptin is positively associated with fetal fat mass [11]. It appears that concentrations of leptin (and other adipocytokines) are significantly lower in IUGR than in AGA fetuses after 34 weeks' gestation, which may contribute to obesity later in life [12].

Adiponectin in the maternal circulation has been found to decrease placental amino acid transporter expression and amino acid transport to fetus, resulting in reduced fetal growth [13].

Fetal Growth Factors. The major growth factor elaborated by the fetus is insulin. Overproduction of fetal insulin leads to macrosomia, whereas underproduction, as found in congenital agenesis of the pancreas or transient or persistent neonatal diabetes mellitus, is associated with growth restriction. All growth-restricted fetuses in animal models, naturally growth-restricted animals, and humans have low insulin concentrations. The principal disorder involves reduced pancreatic

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β-cell replication from cell cycle arrest, although reduced angiogenesis is seen commonly in such pancreases [14,15]. As a result, the number of β cells is reduced, which limits overall capacity to produce insulin. Fetal hypoxia from placental insufficiency also increases norepinephrine production, which suppresses both insulin production and insulin action (glucose and amino acid utilization), as well as cortisol, which enhances protein breakdown and contributes to fetal hepatic glucose production via upregulation of gluconeogenesis [16].

Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) also are important growth factors in the fetus, and circulating levels of IGF-1 in fetal and cord blood correlate well with fetal size [17]. IGF-1 is produced in the fetal liver and is positively regulated by fetal glucose supply and concentration. Additionally, IGF-1 plays an important role in fetal brain development, supporting proliferation of oligodendrocytes and neurons, as well as neuronal elongation, dendritic arborization, and axonal differentiation [18]. Furthermore, because fetal IGF-1 is decreased by reduced nutrient supply, particularly of glucose, it is likely that reduced neuronal growth and development in IUGR fetuses are the result of nutrient deprivation acting through reduced IGF-1 production and action. Such conditions might underlie the poorer neurodevelopmental outcomes of severely IUGR infants who have relative microcephaly.

Maternal IGF-1 and IGF-2 and insulin do not cross the placenta and have little direct effect on the fetus. They do, however, interact with the placenta and are instrumental in maintaining an intact fetoplacental unit [17]. Mutations of the *IGF1, IGF1r, and IGF2* genes in humans cause both intrauterine fetal and postnatal infant growth restriction [19]. Similarly, the IGF-binding proteins and proteases that affect binding protein function modulate the delivery of IGF to the placenta. IGF-1 also appears to regulate trophoblast concentration of Glut 1 glucose transporters in the human placenta, supporting increased glucose transport by the placenta to the fetus [20].

Although fetal growth hormone (GH) has little effect on the intrauterine growth of the fetus, fetuses with GH deficiency tend to be shorter at birth. Some infants with IUGR have hypersecretion of GH, but there may be a reduction or delayed development of receptor sites for GH or in the amount of GH-binding protein. Thyroid hormones have a modest effect on fetal growth, and fetal thyroid deficiency or reduced free thyroxine (T_4) produces both developmental abnormalities and reduced fetal growth in part by decreasing oxygen consumption and glucose oxidation and also by decreasing circulating and tissue concentrations of IGF-1 [21].

Cortisol secretion increases in IUGR fetuses in response to hypoxic-ischemic conditions. It is a catabolic hormone that can reduce protein accretion as well as promote gluconeogenesis, both of which lead to fetal growth failure and can restrict placental growth and nutrient transport to the fetus and thus result in overall reduced fetal growth rates [21].

Vasoactive intestinal peptide (VIP) is another fetal growth factor that positively regulates neuronal proliferation and fetal growth. Inhibition of VIP in fetal mice produces smaller fetuses with fewer neurons and microcephaly [22].

The absence or abundance of the various sex hormones does not appear to significantly affect fetal growth. However, the male fetus is usually 100–150 g heavier than the female.

Incidence of IUGR

Up to 10% of all live-born infants and at least 30% of low-birth-weight (LBW) infants suffer from IUGR. Perinatal mortality rate in these infants can be as high as 4–10 times that of appropriately grown infants. The true incidence of IUGR on a worldwide basis, however, is difficult to ascertain. While a close approximation can be made in developed countries, the incidence of IUGR is not known in many developing nations because many women in these countries give birth at home, and often the weight, gestational age, and follow-up evaluations of the infants are not known. Estimates are that as many as 90% of all LBW infants are born in developing countries, where the incidence of LBW infants could be as great as 45%. When the incidence of low birth weight exceeds 10%, it most commonly is due to the increase in the number of infants with IUGR.

Intrauterine Growth Restriction and Preterm Birth

Many preterm infants already are growth restricted at birth, with estimates ranging from 10% to 30% or 40%. The pathophysiologic processes causing severe IUGR probably lead to preterm labor and preterm delivery. Several mechanisms may be involved. Poor placental perfusion, growth, and function. In preeclampsia, for example, poor endometrial vascular support for growth

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of the placenta leads to placental growth failure, limiting placental supply of growth-promoting hormones to the fetus (e.g., human placental lactogen [hPL], steroid hormones, and insulin-like growth factor 1 [IGF-1] [21]) and effective maternal-fetal nutrient exchange.

IUGR associated with fetal infections, anemia, cardiac failure, and neuromuscular disorders are also associated with preterm birth. Fetal infections from ascending intrauterine infections can damage the fetal brain and the neuroendocrine axis that support fetal growth via insulin-like growth factors (IGFs) and insulin and also can damage the fetal heart, leading to diminished cardiac output, poor placental perfusion, and inadequate nutrient substrate uptake. Such conditions also contribute to preterm birth. Placental growth failure leading to placental insufficiency and fetal hypoglycemia, hypoxemia, and acidosis increase production of prostaglandins and the activation of labor-promoting cytokines, leading to preterm delivery [23]. Placental insufficiency in women at the age limits of childbearing produce IUGR infants who often are born preterm. IUGR and preterm birth also are more common in young, still-growing adolescent girls who appear to be less capable of mobilizing fat reserves in late pregnancy, apparently reserving them instead for their own continued development [24]. Maternal smoking and substance abuse reduce placental blood flow and inhibit uteroplacental vascular development, both leading to IUGR and preterm birth.

Late preterm birth is commonly iatrogenic, performed when suspected fetal acidosis and heart rate abnormalities are seen, more often in severely affected IUGR pregnancies.

Etiology of IUGR

IUGR is a result of one of three general mechanisms: (1) chromosomal/genetic abnormalities, (2) fetal infection/toxicity, or (3) compromised nutrient substrate and oxygen delivery to the fetus. The last group accounts for the majority of infants with IUGR and usually is the result of *placental insufficiency*, which is a global term for many mechanisms that restrict nutrient substrate and oxygen transfer to the fetus by the placenta. The etiology of IUGR, however, clearly is multifactorial.

Fetal Factors

Infectious Agents. Infectious agents causing or associated with IUGR are listed in Table 7.4. There is evidence to establish a causal relationship with IUGR only for rubella, cytomegalovirus, and toxoplasmosis [25]. These agents directly inhibit cell division or cause increased apoptosis, which may lead to cellular death and a decreased number of fetal cells. However, intrauterine infections with other organisms, including syphilis, varicella-zoster, human immunodeficiency virus (HIV), *Trypanosoma*, and malaria, have also been associated with IUGR. It has been difficult in most of these cases to differentiate between infection-specific causes and those related to poor maternal health and nutrition. Placental infection without affecting the fetus directly has been demonstrated for tuberculosis, syphilis, malaria, and coccidiomycosis. Congenital infection is implicated in less than 10% of patients with IUGR, and the incidence may be as low as 3%.

Table 7.4 Infectious Agents Causing or Associated with IUGR

Viral	Cytomegalovirus
	Rubella
	Varicella-zoster
	Human immunodeficiency virus
Bacterial	Syphilis
Protozoal	*Toxoplasma gondii*
	Plasmodium malariae
	Trypanosoma cruzi

Genetic Causes. Maternal genes are more important for fetal growth and development than fetal genes, and paternal genes play a strong role by promoting the growth and function of the placenta to provide nutrients to the fetus. The role of race also cannot be ignored, with consistent increases in the number of LBW infants born to African-American women in the United States, which is not all explained by increased rates of preterm delivery. Environmental factors (see later) may be more important than genetic factors in this regard, however, and undernutrition, malnutrition, poor prenatal care, and other factors may be important etiologic considerations.

Chromosomal Causes. Chromosomal abnormalities include infants with trisomy 21, 13, and 18. In addition, infants with triploidy, various deletion syndromes, and super X syndromes (XXY, XXXY, XXXX) tend to be of low birth weight. Another association with IUGR is maternal uniparental disomy 7 (where both chromosomes come from the same parent – in this case the mother). Only 2–5% of infants with IUGR have chromosomal abnormalities, but the incidence may be much greater if both IUGR and mental retardation are present.

Syndromes. Infants with varying types of congenital heart disease, those with single umbilical arteries, and monozygotic twins also frequently suffer from IUGR. Donors of twin-to-twin transfusions tend to be growth restricted, whereas the recipient twin is often normally grown. These factors account for a very small fraction of infants with IUGR.

Metabolic Disorders. Certain metabolic and endocrine disorders are associated with low birth weight and growth restriction. These include infants with transient neonatal diabetes mellitus, neonatal thyrotoxicosis, Menkes syndrome, hypophosphatasia, and I-cell disease, as well as iron-overload disease.

Malformations. As many as 5–15% of fetuses with growth restriction have congenital malformations and/or dysmorphic syndromes such as thanatophoric dwarfing, leprechaunism, or Potter, Cornelia de Lange, Smith-Lemli-Opitz, Seckel, Silver, and Williams syndromes. IUGR infants also have increased associations with VATER or VACTERL (vertebral, anal, cardiovascular, tracheoesophageal, renal, radial, and limb) conditions [26].

Placental Factors

IUGR from placental insufficiency (PI) affects 5–10% of all pregnancies, is a primary cause of stillbirth, and leads to 10-fold higher rates of neonatal morbidity and mortality. Ischemic placental disease (which includes IUGR) accounts for well over half of all indicated preterm deliveries, thus adding to the incidence of preterm birth [27]. Abnormalities of placental function leading to IUGR are listed in Table 7.5. The placenta has a great reserve capacity and may lose up to 30% of its function without affecting fetal growth. Placental abnormalities such as hemangiomas, circumvallate placentas, and infarctions account for less than 1% of infants with IUGR. It also has been stated that no single lesion of the placenta accounts for IUGR but rather it is an accumulation (or total burden) of placental injury and secondary placental growth failure that produces growth restriction. The most common maternal condition that reduces placental growth, preeclampsia, involves decreased growth of terminal villi in the placenta, which will primarily reduce oxygen and glucose transport to the fetus. Reduced glucose supply alone decreases fetal growth rate and oxygen consumption rate (metabolic rate) proportionally, showing the tight linkage of energy supply and growth during periods of rapid growth such as occurs in the fetus.

Table 7.5 Placental Factors Associated with IUGR

Decreased placental mass
Absorption
Infarction
Partial separation
Multiple gestation
Intrinsic placental disorders
Poor implantation
Placental malformation
Vascular disease
Villitis
Decreased placental blood flow
Maternal vascular disease
Hypertension
Hyperviscosity

The incidence of IUGR increases in multiple gestation due to the inability of the placentas to grow large enough to meet the growth needs of the fetuses. 15–25% of twins suffer from IUGR, and the incidence increases with triplets and quadruplets. Monochorionic twinning contributes disproportionately to IUGR.

Maternal Factors

See Table 7.6.

Maternal Size. Larger mothers have larger uteruses with greater endometrial surface area and uterine circulation that allow for greater placental growth. Smaller mothers produce smaller placentas for the same reason. Small mothers whose size is familial produce smaller fetuses, but these infants are not considered growth restricted. Still, they might grow bigger if there were some way in which to increase the size of the uterus in such small mothers.

Maternal Nutrition. The state of maternal nutrition is a major factor in determining fetal growth and size at birth, and recent studies have defined molecular mechanisms for this interaction [28]. Significant maternal malnutrition will make conception less likely. If the malnourished woman does conceive, the adequacy of maternal nutrition tends to affect the fetus primarily during the last trimester of pregnancy. The actual impact of severe maternal

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Table 7.6 Maternal Factors Associated with IUGR

Maternal malnutrition
Disordered eating prior to pregnancy
Decreased maternal prepregnancy weight and height
Decreased weight gain during pregnancy
Labor-intensive occupation
Decreased plasma volume
Prior poor obstetrical history
Previous stillbirth
Previous infant with IUGR
Low socioeconomic status
Maternal illness
Maternal drug use and abuse

malnutrition may be greater, however, because data from populations with severe malnutrition were obtained only from the offspring that survived a full gestation and birth. Interestingly, female fetuses exposed to starvation in the first trimester of pregnancy subsequently give birth to growth-restricted infants themselves [29].

Dietary supplementation of malnourished pregnant women, especially if the supplementation is provided for an extended period during gestation, can increase the birth weight of their infants significantly, but this occurs primarily when women were in negative energy balance before the supplements and had a high energy workload. When women are in positive energy balance, dietary supplementation has little effect on birth weight.

There also are conflicting data regarding the effect of supplemental nutrition in various populations, and not all have shown beneficial effects. In fact, most studies have shown worse IUGR and increased fetal and neonatal morbidity and even mortality, particularly with protein supplementation. Research has not yet determined why in such cases supplementation has produced such adverse effects. This conundrum has been a major limitation to further attempts at prenatal prevention or amelioration of IUGR and all of its many adverse outcomes. Even in cases of IUGR, but also in otherwise normal pregnancies, maternal obesity and a diet enriched in calories (both simple sugars and lipids) produce fatter infants [30,31]. This is particularly true in type 2 diabetic pregnancies [32].

Specific deficiencies of micronutrients also can contribute to reduced fetal growth, even if the mother's diet appears to be adequate in calorie and protein intake. Deficiency of zinc in pregnant women has been associated with increased rates of prematurity, perinatal death, and fetal growth restriction [33]. Zinc supplementation in such women has improved perinatal outcome, though there is little evidence that it has increased fetal growth. Thiamine deficiency in pregnancy also has been associated with growth restriction of the fetus, as found in mothers with inadequate total nutritional intake, hyperemesis, alcohol abuse, and various infections, including HIV infection [34].

Although severe maternal malnutrition is uncommon in developed countries, it still exists in population areas where appropriate nutrition, nutritional supplementation, or nutritional consultation is lacking. It also is seen in pregnant women with severe gastrointestinal disease, such as Crohn's disease or ulcerative colitis, women with hyperemesis, or women who use excessive energy in labor-intensive occupations. Among women delivering IUGR/SGA infants at term, there is a much higher incidence of disordered eating in the 3 months prior to pregnancy compared with controls or those delivering prematurely [35].

Maternal Illness. Maternal illness, especially preeclampsia, not only has an adverse effect on the growth of the fetus, but it also predisposes the infant to preterm birth, especially if the mother's or infant's condition necessitates early delivery. The presence of IUGR adversely affects survival in these preterm infants. Multiparous women with preeclampsia have a greater risk of having an infant with IUGR than does a nulliparous mother with this disease. Neonates born growth restricted after pregnancies complicated by preeclampsia have a lower IQ at the age of 3 years compared with growth-restricted babies without preeclampsia [36]. During gestation, the mother's plasma volume and cardiac output increase to accommodate the increased uterine blood flow rate. Not surprisingly, therefore, hypertensive women with growth-restricted fetuses have decreased plasma volumes compared with hypertensive women whose fetuses are normally grown.

Chronic illnesses in the mother, including those listed in Table 7.7, are associated with the birth of growth-restricted infants. The more common of these

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Table 7.7 Maternal Illness Associated with IUGR

Acute illness
Preeclampsia
Eclampsia
HELLP syndrome[a]
Chronic illness
Chronic hypertension
Chronic renal disease
Collagen-vascular disease
Cyanotic heart disease
Chronic pulmonary disease
Diabetes mellitus (classes B–F)
Thyrotoxicosis
Chronic anemia
Maternal phenylketonuria

[a]HELLP = hemolysis, elevated liver enzymes, and low platelet count.

Table 7.8 Drugs Taken by Mothers that Are Associated with IUGR

Tobacco
Alcohol
Marijuana
Heroin
Methadone
Cocaine
LSD
Coumadin
Hydantoin
Trimethadone

are women with chronic hypertension and chronic anemias such as sickle-cell disease, sickle-C disease, and thalassemia. Women who have antiphospholipid antibodies, even if they are not diagnosed as having systemic lupus erythematosus (SLE), have an increased risk of giving birth to infants with IUGR [37].

Women with a history of poor outcome in pregnancy have an increased risk of having a subsequent birth of a growth-restricted infant. A woman who has had a growth-restricted infant doubles her risk of having a second infant with IUGR. After two such outcomes, the risk of having a fetus with IUGR is quadrupled. Women who have growth-restricted infants should have a thorough search for an underlying maternal disorder if the reason for the IUGR is otherwise not apparent. Mothers of infants with IUGR were often growth restricted at birth themselves.

Environmental Factors

Medications and Drugs. Medications and drugs taken by mothers not only lead to various congenital malformations but also can be associated with fetal growth restriction[1]. The infants of women with the highest concentrations of serum cotinine, the major metabolite of nicotine, are over 440 g lighter at birth than the infants of women who did not smoke [38,39], but other factors in mothers who smoke, such as decreased maternal nutrition, decreased uterine blood flow, increased production of carbon monoxide (CO), and impaired fetal oxygenation, also can cause IUGR. Together, these factors may underlie the highly significant association between maternal smoking during pregnancy and a small fetal (or neonatal) head circumference (and thus brain size) for gestational age [40].

Other drugs taken by the mother that have been implicated in causing growth restriction are shown in Table 7.8. Alcohol not only causes fetal growth impairment but also may lead to permanent damage to the fetus and newborn. The quantity of alcohol ingested, maternal size, and the ability of the mother to metabolize alcohol all determine how much alcohol is transported to the fetus [41].

The incidence of illicit drug use by pregnant women in the United States can only be surmised, and accurate follow-up data are not available for infants delivered from such women. The consensus is that 15–40% of infants of drug-abusing mothers are growth restricted, and in some infants of cocaine-abusing mothers, the decrease in head circumference (and thus brain size) is more pronounced than is the decrease in length and weight [42]. Similar data indicate that the same outcome occurs in pregnant women who regularly smoke marijuana [43], although such women usually ingest other illicit drugs and drink alcohol and smoke during pregnancy; thus the specific effect of marijuana on fetal growth is uncertain.

Caffeine, especially if taken in quantities greater than 300 mg/day, has been associated with decreased fetal growth. Lesser intakes of caffeine do not seem to have an adverse effect on fetal growth, but high

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caffeine intake may be related to smoking, which may be more important than caffeine in producing the associated fetal growth restriction [44]. Specific syndromes such as fetal hydantoin, fetal warfarin, and fetal trimethadione syndromes are associated with an increased incidence of growth restriction [1]

Maternal Hypoxia. Maternal hypoxia that produces fetal hypoxia also significantly reduces fetal growth [45]. Infants born to mothers who live at 10,000 ft (3,000 m) or more above sea level weigh approximately 250 g less at birth than infants born to mothers who live at sea level. High-altitude hypoxia also could reduce active transport of amino acids to the fetus by the placenta [46], and its excessive glucose consumption could reduce glucose and thus energy supply to the fetus that would limit anabolism [47]. Long-term adaptation to higher altitude has been shown to lead to improved birth weight relative to recent immigrants to high-altitude regions, who more commonly produce smaller infants [48]. A principal multigenerational adaptation that has improved fetal growth involves relatively increased uteroplacental blood flow [49]. Indigenous high-altitude ancestry also protects against hypoxia-associated fetal growth restriction in a dose-dependent fashion, consistent with the involvement of genetic factors [50]. Some of the genes involved appear to be influenced by parent-of-origin effects, given that maternal transmission restricts and paternal transmission enhances fetal growth.

Maternal Stress. Maternal stress from excessive workload also may restrict fetal growth. In a recent study from Thailand, the risk of delivering an SGA infant was increased for women working more than 50 hours per week, for those whose work involved protracted squatting, and for those having high psychological job demands [51].

Toxins. Mercury toxicity in pregnant women and their fetuses was highlighted during the 1950s to 1970s when three separate epidemics of mercury poisoning occurred in Minamoto and Niigata, Japan, and Iraq. While all mercury compounds can cause harm to the fetus, methyl mercury has the greatest toxicity [52]. Mercury compounds cross the placenta readily and have teratogenic and adverse growth effects on the fetus.

Mothers exposed to radiation, other pollutants, and contaminated food or water over a prolonged period of time appear to be at risk for delivery of infants with IUGR. The incidence of these factors and the severity of their possible effects are not known at present.

Detection of the Fetus with IUGR

Ultrasound is the preferred method of evaluating fetal growth and, in many instances, fetal well-being. Initial studies are usually performed at 8–10 weeks' gestation to document fetal viability, the presence of multiple gestation, and gross fetal malformation and to confirm the gestational age of the fetus. The biparietal diameter (BPD), the abdominal circumference (AC), and the femur length (FL) are the usual biometric measurements taken during ultrasonographic examination. Measurements of the BPD between 12 and 18 weeks' gestation are accurate in detecting gestational age within 5–6 days. However, measurements of individual parameters are not very good predictors of IUGR. To predict the appropriateness of intrauterine growth more accurately, the ultrasound examination should be performed serially in the second and third trimesters, but at least early in the third trimester. The estimated fetal weight (EFW) at such times relies on multiple measurements, including the abdominal circumference and ratios of head circumference (HC)/AC and FL/AC [53]. The optimal time to perform the examination is not clear, but it is estimated that over 50% of infants with IUGR will be detected by 32 weeks' gestation. Thus several ultrasounds, coupled with other fetal surveillance techniques, may have to be performed to monitor the growth of the fetus and to determine the optimal time of delivery of these infants [54]. In pregnancies with multiple gestations, more frequent serial ultrasonographic examinations should be carried out during the last trimester. Fetal 3D cranial ultrasound has the additional advantage of quantifying the size of the smaller brain volume in IUGR fetuses, with normal or accelerated cortical maturation as previously depicted with postnatal MRI examination [55]. Decreased amounts of amniotic fluid have been found to correlate well with IUGR in cases of preeclampsia, but not as a rule in most other cases of IUGR.

Assessment of fetal well-being with the biophysical profile (BPP), while not used to detect IUGR, has been found to be more useful in predicting an abnormal fetal outcome in IUGR cases than either the contraction stress test (CST) or the nonstress test (NST) alone.

Doppler flow-velocity waveform evaluations of the fetal circulation also are used to assess fetal well-being and appropriate growth. During conditions of placental insufficiency, blood flow in the umbilical artery decreases during diastole, progressing from

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increased pulsatility of blood flow as vascular resistance increases to absent blood flow and then reversed blood flow. Doppler velocimetry abnormalities have been shown to develop in a sequential fashion as placental insufficiency progressively worsens and may predict the risk of fetal acidosis and perinatal mortality, as well as help to predict optimal timing of delivery [3,54]. The fetal umbilical artery, aorta, and cerebral arteries have been studied, and varying indices have been evaluated, including the resistance index (RI), the pulsatility index (PI), and the systolic/diastolic (S/D) ratio of these vessels, to help assess the state of well-being of the fetus. The most accurate predictor of poor neonatal outcome is an abnormal umbilical cord Doppler waveform, which has been associated with abnormal blood flow in the fetal middle cerebral artery in IUGR fetuses. However, Doppler assessment of the middle cerebral artery may reveal blood flow redistribution even when the umbilical artery Doppler is normal, especially when the HC/AC ratio is elevated [56]. The cerebroplacental ratio (CPR) quantifies the redistribution of cardiac output by dividing the Doppler indices of the middle cerebral artery (MCA) with the umbilical artery (UA) CPR measurements. Irrespective of the CPR calculation used, brain sparing of blood flow relative to the placenta is significantly associated with an adverse perinatal outcome in IUGR [57].

Fetal Doppler parameters, including umbilical artery, middle cerebral artery, aortic isthmus, ductus venous, and myocardial performance index, also have been evaluated in fetuses with IUGR and compared with abnormal umbilical artery Doppler values to determine the value of gestational age and the fetal Doppler parameters to predict the risk of cranial ultrasound abnormalities, including interventricular hemorrhage, periventricular leukomalacia, and basal ganglia lesions. In one study, IUGR fetuses had a significantly higher incidence of cranial ultrasound abnormalities (40.0% versus 12.2%, $p < 0.001$) than controls [58]. Within the group with IUGR, all predictive variables were individually associated with the risk of cranial ultrasound abnormalities, but fetal Doppler rather than gestational age at birth was identified as the best predictor. Thus evaluation of fetal Doppler parameters rather than gestational age at birth discriminates IUGR preterm fetuses at risk of an abnormal neonatal brain scan.

Preclinical MRI studies, primarily in animal models, are now showing considerable promise in detecting brain malformations and even inflammation associated with axonal cytoarchitecture disruption and increased neurodegeneration. Proton magnetic resonance spectroscopy (^{1}H MRS), another noninvasive method, is being used in similar studies to identify metabolic abnormalities that predict fetal brain abnormalities [59].

Cordocentesis (percutaneous umbilical vein blood sampling), despite its increased risk/benefit ratio, can be used to document hypoxemia, lactic acidemia, and increased numbers of nucleated red blood cells (NRBCs) in the fetal circulation and to identify infants who are in need of immediate delivery [60]. Lactate in particular can help to identify IUGR infants with the smallest placentas who have the least capacity to tolerate ischemic stress from uterine contractions [61].

Associated Problems and Complications

See Table 7.9.

Fetal and Neonatal Hypoxia and Ischemia (Asphyxia). The infant with IUGR is much more likely to experience difficulties during labor and delivery because the IUGR in most of these cases was the result of uteroplacental insufficiency, making it more

Table 7.9 Clinical Problems Commonly Encountered with IUGR

Fetal and neonatal hypoxia-ischemia
Fetal heart rate abnormalities
Require resuscitation in delivery room
Persistent pulmonary hypertension
Glucose disorders
Hypoglycemia
Hyperglycemia
Hypocalcemia
Hypothermia
Hematologic problems
Neutropenia
Thrombocytopenia
Increased nucleated red blood cells
High hematocrit/hyperviscosity
Susceptibility to infection
Necrotizing enterocolitis
Pulmonary hemorrhage
Large anterior fontanel

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likely that the partially compromised fetus becomes a severely compromised fetus during labor with further reductions in uterine and placental blood flows. Experiments in pregnant sheep with IUGR placenta and fetus suggest that the association of severe IUGR with hypoxia is related to an imbalance in the development of placental structure and oxidative metabolism, which leads to a progressive decrease in oxygen transfer to the fetus and a reduction in net umbilical O_2 uptake (fetal oxygen consumption rate) [62].

The consequences of hypoxia in the IUGR fetus as term gestation and labor approach are critical because the degree and duration of hypoxia are predictive of neurologic outcome [63]. The Doppler cerebral/umbilical ratio (cerebral resistance index/umbilical resistance index) assesses the adaptive response of the fetus to the hypoxic stress. As variability (vasoconstriction and vasodilation) is lost over time with progressive IUGR, the vulnerability of the fetus to hypoxemia and ischemia during labor and delivery increases. Even normal Doppler indices, however, do not always predict normal outcome because the causes of IUGR that limit growth and neurodevelopmental outcomes still can be independent of the infant's response to labor and delivery [64]. In fetuses whose placentas are already compromised, as the frequency and strength of contractions increase during labor, blood flow to the fetus is further reduced, preventing the fetus from recovering between contractions. Lack of blood flow leads to decreased oxygen delivery and development of combined respiratory and metabolic acidosis, resulting in fetal hypoxia-ischemia, frequently manifested by late decelerations on fetal heart rate monitoring. In addition, there may be variable decelerations (or cord compression patterns) because decreased blood flow to the fetus may have produced a decrease in the quantity of amniotic fluid surrounding the fetus. This increases the probability that uterine contractions will be transmitted to the umbilical cord (especially the umbilical vein), further compromising blood flow to the fetus. Fetuses with IUGR also often have a very thin umbilical cord that lacks the protection of Wharton's jelly from compression.

At the time of delivery, the hypoxic-ischemic, acidotic fetus becomes a hypoxic-ischemic, acidotic neonate, and prompt attention is required in the delivery room and early neonatal period to prevent further compromise. If the fetus has been subjected to chronic intrauterine hypoxia, there is the potential for increased pulmonary vascular resistance, including reduced vascular compliance and elasticity [65]. In most milder cases, inhaled nitric oxide and oxygen can reduce the contractile portion of the pulmonary vascular resistance, but when the fetal hypoxia is chronic and more severe, structural overgrowth of vascular myocytes and perivascular adventitial cells (fibroblasts) of arterioles and capillaries occurs, leading to irreversible narrowing of the vessel lumen and persistently increased and nitric oxide–nonresponsive pulmonary vascular resistance. Particularly when combined with neonatal hypoxia, the potential for developing persistent pulmonary hypertension and systemic hypoxemia is markedly increased.

Hypoglycemia. Preterm and SGA infants are prone to develop hypoglycemia, with the highest risk occurring in infants born preterm and SGA with IUGR [66]. It has generally been believed that the predisposition to develop hypoglycemia results from reduced placental-to-fetal glucose supply and depletion of fetal hepatic glycogen stores. Such beliefs probably focused on preterm infants with limited or no enteral nutrition and increased postnatal glycogenolysis. However, infants with IUGR and hypoglycemia are able to respond to the administration of glucagon and increase their concentrations of glucose in serum [67]. More recent studies in IUGR animal models show relatively normal amounts of both hepatic and muscle glycogen [68], and human AGA and SGA infants have similar rates of glycogenolysis, suggesting that they both have similar hepatic contents of glycogen [69]. These stores appear to be maintained by an increase in glucose and insulin sensitivity that maintains cell glucose uptake despite low glucose and insulin concentrations. This is a common biological response to reduced glucose supply and is supported by evidence of maintained or even upregulated cell membrane glucose transporters Glut 1 (ubiquitous glucose transporter), Glut 4 (insulin-dependent glucose transporter), and Glut 3 (neuronal glucose transporter) [68]. To the extent that these fetal adaptations to reduced glucose supply persist after birth, they would tend to increase glucose utilization and, in turn, lead to persistent hypoglycemia if the glucose supply from hepatic production and/or intravenous or enteral feedings is insufficient [70].

Risk for hypoglycemia in IUGR infants also is increased due to their relatively larger brain, especially with asymmetric IUGR. Because the brain relies almost exclusively on glucose for its high rate of

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energy metabolism, it is necessary to calculate glucose requirements (oral or intravenous) based on what the weight would have been if the infant's brain size were symmetric with body size (e.g., choose a weight consistent with the size of the head rather than the actual weight).

Recent studies in the IUGR fetal lamb model also have shown that insulin secretion can be increased after birth. During fetal life, IUGR infants are relatively hypoxic, often profoundly so in later gestation, leading to increased norepinephrine secretion, which then suppresses insulin secretion [16]. After birth, increased oxygenation and improved circulation reduce norepinephrine secretion and concentrations, releasing their inhibition of insulin secretion. This appears to be accompanied by an exaggerated insulin secretion response to glucose and amino acid stimulation, producing a hyperinsulin-like condition [71]. Not uncommonly, this excessive insulin secretion can persist in some IUGR SGA infants [72], perhaps augmented by increased glucose utilization capacity due to their larger brain-to-body weight (and liver weight) ratio and the aforementioned increase in peripheral glucose and insulin sensitivity. Infants with IUGR also have been shown to have limited capacity to use 3-carbon precursors to make glucose via the gluconeogenic pathways, an older observation that might reflect increased insulin sensitivity, although, as discussed below, hepatic insulin resistance to the usual suppression of gluconeogenesis is more common in the fetal condition and could continue after birth and contribute to persistent hepatic glucose production.

Episodes of hypoglycemia in IUGR infants are particularly concerning for potential brain injury because the exaggerated insulin secretion and effects on glucose utilization suppress lipolysis and thus ketone formation, limiting their supply as alternative substrates for brain energy metabolism. Furthermore, the majority of IUGR infants have reduced subcutaneous fat stores [73], limiting the potential supply of fatty acids for ketone production. For this reason, intravenous dextrose administration should be used earlier and for longer periods in such infants after birth until full enteral feeding has been established and the infant can maintain normal-range plasma glucose concentrations as the IV dextrose infusion rate is gradually reduced.

Hyperglycemia. In contrast to the increased risk of hypoglycemia, hyperglycemia also is relatively common in very small SGA IUGR infants, and somewhat paradoxically, treatment of hypoglycemia with "normal" amounts of glucose may lead to hyperglycemia in some of these infants. Fetal hepatic glucose production, via glycogenolysis initially and then by gluconeogenesis, is well documented in IUGR animal models [74]. This appears to be a common metabolic response to the relative hypoglycemia in utero and helps to maintain sufficient fetal plasma glucose concentrations for the brain and heart despite reduced glucose supply from the placenta. After birth, such fetal-initiated glucose production cannot be suppressed by insulin or glucose [75]. If glucose supply is excessive and more than compensates for the tendencies to hypoglycemia, persistent hepatic glucose production might exaggerate total glucose supply and lead to hyperglycemia. This may help to explain how hyperglycemia occurs when glucose delivery from aggressive intravenous infusions (above 7–8 mg/min/kg) is provided.

Hypocalcemia. Many infants, particularly those with IUGR, who are prone to develop hypoglycemia are also prone to develop hypocalcemia [76]. Hypocalcemia may be due to transient hypoparathyroidism or possibly to an overproduction of calcitonin, which is increased in stressed neonates. With modern-day neonatal intensive care, it is unusual to encounter the more severe clinical manifestations of hypocalcemia, such as seizure activity.

Hypothermia. The increased surface-area-to-body-weight ratio of the IUGR infant promotes heat loss more rapidly than in the appropriately grown infant, and characteristically, such infants increase metabolic rate, which helps to sustain body temperature [77]. The ability to produce heat also may be compromised in IUGR infants, who have decreased insulation from adipose tissue (white fat) and depleted stores of brown fat that are used for nonshivering thermogenesis. Furthermore, the tendency to develop hypoglycemia and the lack of fat and thus ketone production mean that oxidative metabolism of glucose and the supply of alternative energy substrates to produce heat are deficient. The end result of cooling is metabolic acidosis because peripheral vasoconstriction decreases the delivery of oxygen to the tissues and increases anaerobic metabolism with the accumulation of lactic acid.

Hematologic Problems. Infants with IUGR are more likely to be born with a high hematocrit, an erythropoietic response to hypoxia from placental insufficiency, a natural process that tends to preserve

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blood oxygen content in the IUGR fetus despite low PO_2 values. At the same time, particularly in severely IUGR fetuses and infants born to hypertensive mothers, thrombocytopenia and neutropenia have been observed. It is believed that the pluripotent stem cell is stimulated to produce the erythroid series at the expense of neutrophils and platelets. In such cases, an inhibitor of neutrophil production is produced by the placenta, noted particularly in IUGR infants born to mothers with HELLP syndrome (more recently called preeclampsia with severe features) secondary to advanced preeclampsia.

Overproduction of erythropoietin has been noted in both term and preterm SGA infants, and studies in the fetus using cordocentesis have documented hypoxic-ischemic conditions and lactic acidemia. The number of erythroblasts (NRBCs) is markedly increased in some of these fetuses. Cordocentesis also has demonstrated that levels of erythropoietin are increased in IUGR fetuses displaying erythroblastosis, and it may be possible to distinguish IUGR from the small but healthy fetus on this basis. Thus, in the neonate with a marked increase in the number of NRBCs and a normal to high hematocrit, the most likely explanation is chronic intrauterine hypoxemia (although infection may also stimulate NRBC production). It is not clear what the duration of the hypoxemic insult needs to be to produce a significant elevation of NRBCs, although the duration of insult can be estimated based on the numbers of NRBCs, which are more elevated with persistent fetal heart rate abnormalities [78].

High hematocrits, especially a venous hematocrit over 65%, may lead to hyperviscosity syndrome, which includes several clinical manifestations involving the CNS, including lethargy alternating with jitteriness or even seizures. In extreme cases, fetal or neonatal cerebral hemorrhage and/or stroke can occur, leading to permanent adverse neurodevelopmental outcomes. While partial exchange transfusion with saline has been used to lower the hematocrit to prevent the sequelae of the hyperviscosity syndrome, this intervention does not prevent such sequelae, and exchange with protein-containing solutions actually can produce worse outcomes, probably due to clumping of red blood cells with the added protein.

At the opposite end of the spectrum, some infants with IUGR are anemic. This occurs most notably in the twin-to-twin transfusion syndrome, where the donor twin is inadequately perfused and has compromised intrauterine growth in association with anemia. The combination of anemia and reduced circulation may decrease oxygen supply to the brain and cause brain injury in such cases.

Susceptibility to Infection. IUGR fetuses and newborns are more likely to develop hypoxic-ischemic conditions, which may predispose to bacterial infection. Total T cells, helper and inducer T-lymphocytes, and B cells all are deficient in number in infants who are SGA from IUGR [79]. Such an immunologic handicap seems to predispose to severe infection, including meningitis. This problem may be more severe in SGA IUGR infants who were stressed with recent nutritional deficiency, as indicated by a low Ponderal index. Hypothermia (see earlier) also has been associated with a predisposition to develop bacterial infection because SGA IUGR infants may not respond to infectious agents as well as normally grown infants.

Intestinal Perforation and Necrotizing Enterocolitis (NEC). Because IUGR infants often have an increased incidence of hypoxia-ischemia, acidosis, and hyperviscosity, their intestinal blood flow might be compromised. The increased susceptibility to infection adds an additional risk. Thus it is not surprising that an increased incidence of early intestinal perforation and later NEC has been seen in IUGR infants, which may be predictable based on absent end-diastolic frequencies in fetal Doppler studies. Delayed enteral feeding or slow advance of smaller than usual enteral feedings is common in such infants [80], although this practice is highly controversial because some centers now are finding improved feeding tolerance and no increase in NEC rates when enteral feedings in such infants are started early, if still cautiously, with mother's milk [81,82].

Neurodevelopmental and Neurobehavioral Outcomes

Accelerated Neurologic Development.

Acceleration of neurologic maturation has been confirmed in high-risk pregnancies, some of which (but not all) resulted in infants with growth restriction. This acceleration of maturation may relate to the severity of placental insufficiency, with the benefits being lost in the most severe cases. Maternal

hypertension was implicated in approximately half the cases. Some practitioners have interpreted accelerated brain maturation in asymmetric IUGR infants based on apparently accelerated neurobehavioral development at birth, but it is more likely that such behavioral characteristics are the result of peripheral neuromuscular activation and not brain neuronal development.

Although many infants with apparent acceleration of neurologic maturation in stressed pregnancies are born SGA from IUGR, this is not always the case, suggesting that the effects on the nervous system may precede the effects on overall growth. The exact mechanism for accelerated neurologic maturation remains to be elucidated. Additional support comes from neurophysiologic studies in which brainstem auditory evoked responses were more rapid in SGA infants than in AGA infants [83]. In contrast, development of visual evoked potentials in IUGR/SGA infants may be delayed [84]. Furthermore, although accelerated neurologic maturation would seem to provide an unanticipated benefit; when infants with IUGR are followed for longer periods of time, they do not sustain this advantage. Indeed, by school age, they may be at a disadvantage [85].

Altered Behavior. Despite accelerated neurologic development in some IUGR/SGA infants, this is not always the case. With increasing severity of insult, it is likely that the behavior of the infant will be compromised by more injurious conditions, such as hypoxia. Increasing severity of fetal hypoxia and ischemia will have a marked effect on the biophysical profile, one aspect of which is fetal movement. In uncomplicated IUGR cases, there is no clear effect on the quality of general movements [86]. However, it is commonly observed that infants with IUGR behave differently soon after delivery. In particular, they may feed poorly and have lower activity scores, with a trend toward less visual fixation and visual pursuit. Many studies have documented less muscle tone, decreased activity, less responsiveness, and more difficulty in modulating state. A high-pitched cry is more common. Most behavioral studies have been performed in term IUGR infants. Little is known about differences in preterm IUGR infants.

Parental Interaction. Many infants with IUGR appear scrawny (especially those with low Ponderal index) and may be considered less attractive to parents than the expectation of what their baby "should" look like. In addition, as noted earlier, the infant's behavior may be distorted and provide less interaction between infant and parents. The cry may be particularly aversive to adults, although not necessarily to the point of increased risk of child abuse or neglect [87]. Quite limited data are available on subsequent parent-infant interaction. Although there may be some differences early in the first year, these differences in interaction seem to resolve by 6 months [88].

Developmental Outcomes

Historical Perspective. Many early studies of IUGR infants were plagued by methodologic problems, including not distinguishing among those born at different gestational ages or those with limited familial or genetic growth potential, lack of evidence of severity of fetal growth restriction measured by Doppler velocimetry or by serial measurements of fetal growth trajectory, or considering infants who had chromosomal abnormalities or evidence of congenital infection. Even recent studies have been limited by uncontrolled confounding factors such as perinatal morbidity, including degree of prematurity, singleton versus multiple gestation, birth order, inborn or outborn status (requiring transport), presence of abnormal umbilical artery waveforms, and a variety of neonatal complications, such as asphyxia, hypoglycemia, polycythemia, and cold stress, all of which can affect ultimate outcome. Socioeconomic status and environment also affect growth and development of IUGR/SGA infants, with strong associations between socioeconomic factors and the cognitive development and school performance of growth-restricted children [89].

In IUGR twins with markedly discordant birth weights, the smaller twin maintains a disadvantage in intellect that persists into adulthood[90], even though head circumference, IQ deficits, and catch-up growth are less affected than other measures. In contrast to the twin studies, singleton IUGR infants show considerable variability in catch-up growth, leading to the conclusion that appropriate classification at birth is needed, together with categorization by etiology of IUGR. Some of the older studies may have been complicated by problems such as hypoglycemia

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and undernutrition. Nevertheless, despite the tendency to remain smaller than average in physical dimensions, the intellectual deficits of infants with IUGR described in the past were not always striking, and major neurologic deficits were considered to be uncommon.

Current Status of Adverse Developmental Outcomes from IUGR. IUGR is associated with higher rates of fetal, perinatal, and neonatal morbidity and mortality [91]. Evidence also suggests that children who had IUGR are at risk for poorer neurodevelopmental outcomes from 6 months to 3 years of age. The heterogeneity of primary outcomes, assessment measures, adjustment for confounding variables, and definitions of IUGR, however, limits synthesis and interpretation. Sample sizes in most studies were small, and some examined preterm IUGR children without including term IUGR or AGA comparison groups, limiting the value of such studies [92]. Despite such variability among assessments, the consequences of IUGR are many and marked, including short-term metabolic, hematologic, and thermal disturbances that lead to metabolic syndrome in children and adults. Additionally, IUGR severely affects short- and long-term fetal brain development, brain function (including motor, cognitive, and executive functions), and neurobehavior and neuropsychology [93]. After correcting for genetic and congenital infections, intellectual and neurologic functional outcomes depend significantly on the frequency and severity of adverse perinatal events, particularly hypoxic-ischemic encephalopathy around birth and hypoxia and perhaps hypoglycemia in the early neonatal period. IUGR children born preterm or with evidence of fetal circulatory redistribution are more severely affected [94]. When such adverse events are minimal or absent, developmental outcomes are better but still exist [95], with the greatest deficits occurring in infants with the most severely growth-restricted brains. Similarly, SGA children studied recently in Norway were found to have lower IQ scores at 5 and 9 years and smaller brain volumes at 15 years compared with those in the control group, but these findings were seen only in those with fetal growth restriction [96].

Development of Term Infants with IUGR. Older studies showed that outcomes among infants with IUGR born at term were variable and not that severe, with severity largely confined to infants with marked reductions in head circumference and/or major adverse perinatal disorders such as asphyxia. Continued studies, however, have consistently shown that neurologic disorders and other morbidities are observed more commonly among full-term SGA infants as a group, whether or not IUGR was documented. When IUGR is documented, it is a significant contributor to an increased risk of CP and neonatal death [97]. Such risks are diminished, however, in full-term mild to moderately SGA infants who had limited evidence of severe IUGR and normal brain growth, no hypoxic-ischemic injury, and good environmental support, reducing the adverse impact on behavior or mental ability even into adolescence or adulthood [98].

Despite reassurance of lesser degrees than often assumed of grossly abnormal neurologic outcome in term SGA infants, there is still concern for mild brain dysfunction among these children. Many studies have documented minor neurodevelopmental abnormalities, including hyperactivity, short attention span, learning problems, poor fine-motor coordination, hyperreflexia, and an increased number of diffuse EEG abnormalities [99]. Many term SGA infants develop speech problems, including delayed onset of speech, immature vocabulary with persistent infantile articulation, poor executive functions, and poor receptive and expressive abilities for age, which are correlated with slower relative head growth [100]. Even in adolescence, such infants tend to have lower test scores, especially in mathematics, and an increased incidence of various learning disabilities.

Development of Preterm Infants with IUGR. The outcomes of preterm IUGR/SGA infants are less certain because many older studies did not clearly distinguish between IUGR problems and those due to preterm birth or distinguish early preterm birth from late preterm birth [101]. Most preterm IUGR/SGA infants, for example, have a developmental disability, with 20% having major neurologic sequelae. Neurodevelopmental disability is most strongly related to perinatal asphyxia. When more aggressive obstetric intervention is undertaken, the outlook appears to improve. Cesarean section at 28–33 weeks' gestation for suspected growth restriction and abnormal unstressed cardiotocograms markedly improves outcomes.

As obstetric evaluation and intervention changed, more infants with IUGR were delivered at earlier stages of gestation. Attempting to prolong gestation beyond about 36 weeks may not benefit the fetus, but

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earlier delivery increases the risks common to extreme prematurity. More recently, IUGR fetuses are being delivered at even earlier gestations. It seems likely that some of these fetuses would have died in utero, and others might have suffered severe neurologic injury. While the need for special education is higher and becomes apparent at an earlier age in these preterm SGA infants when they reach school age, several recent studies have provided reasonably encouraging data about long-term outcome (see section on follow-up of VLBW infants born SGA).

Overall, however, IUGR is associated with more cognitive disability in infants who were born preterm[102], and infants suffering the dual insults of preterm birth and growth restriction are at higher risk of neurodevelopmental deficit than with either condition alone [103,104]. Furthermore, diffuse cerebral damage caused by intrauterine hypoxia and ischemia (decreased uterine and placental blood flow, and reduced blood flow to the fetal brain as cardiac failure develops) probably accounts for the differences in expression of brain damage seen in preterm AGA and IUGR/SGA children.

Mortality and Morbidity. Morbidity and mortality rates in IUGR infants (see section on associated problems and complications) are directly related to the severity of the IUGR [105] and to the fact that morbidity and mortality increase progressively as birth weight falls below the 10th percentile at each gestational age, emphasizing the impact of more severe IUGR on predisposing to or causing adverse outcomes.

Physical Growth. Most IUGR/SGA infants show some catch-up growth, particularly those with late gestational growth restriction in response to nutritional deprivation. For the majority of more severely and chronically IUGR infants, however, catch-up growth is limited, leading to significantly lower weights, heights, and head circumferences during infancy to early childhood and older compared with normally grown infants [106]. Such catch-up growth occurs primarily from birth to 6 months of age, although some infants continue accelerated growth for the first year. A few of these infants will achieve a normal growth percentile and thereafter have a growth rate that is similar to appropriately grown children. In general, IUGR/SGA infants remain shorter and relatively underweight for age as they grow older, even through adolescence and early adulthood.

Most organs in the IUGR fetus are growth restricted, including the liver, skeletal muscle, heart, and lung, but most importantly, the brain is growth restricted, even in asymmetrically growth restricted infants. In general, head circumference parallels growth in length during catch-up and sustained growth periods, whereas postnatal growth of lean mass and muscularity remains restricted [107]. Head size at the time of birth and the degree of head size catch-up growth thereafter are prognostic of future neurodevelopment because head size directly correlates with brain size, volume, weight, and cellularity. More recent studies have shown that the animal models very likely do predict what happens in human IUGR [108]. There is a significant reduction in the size of the somatosensory cortex, hippocampus, and corpus callosum. The motor cortex may be spared of identifiable deficits. Apoptotic proteins are upregulated, whereas those important to neuronal survival, growth, and differentiation are downregulated. Neuronal apoptosis and astrogliosis occur diffusely throughout the brain regions. White matter injury involves oligodendrocyte precursor maturation arrest, hypomyelination, and an aberrant organization of existing myelin. Other similar studies have shown that IUGR fetuses exhibit reduced synaptogenesis and synaptic maturation, as well as reduced myelination, all of which are seen primarily in subareas of the hippocampus and associated efferent tracts. These neurodevelopmental changes are more pronounced in symmetric IUGR fetuses compared with asymmetric IUGR fetuses. Accordingly, altered hippocampal development involving synaptogenesis and myelination may represent a mechanism by which cognitive deficits manifest in human growth-restricted offspring in later life [109]. As a result of such changes in neuronal maldevelopment, animals with fetal growth restriction demonstrated deficits in gait, memory, object recognition, and spatial processing later in life, providing consistent evidence that adverse neurodevelopment in the IUGR fetal condition contributes to later-life mental and motor deficits.

Deficient fetal head growth, as determined by relative microcephaly at birth at any gestational age and reflecting the severity and duration of in utero growth failure, consistently predicts worse neurodevelopmental outcomes. Furthermore, a failure of head growth catch-up by 8 months of postnatal age predicts lower intelligence test scores at 3 years of age, which

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appears to be independent of environmental or other risks [110]. Large variations in measurements of SGA infants at follow-up are common when parents make the measurements. Also, some reports of the subsequent growth of infants with IUGR have included modifiers that might influence the outcome, such as asymmetric IUGR (with a low Ponderal index), which seems to persist as underweight for length despite catch-up growth in the first 6 months. Growth in length appears to be even more variable, particularly between term and preterm IUGR infants and whether catch-up growth was assessed. Decreased ossification also may predispose to catch-up in linear growth, although most studies have shown that IUGR/SGA infants are shorter even into adolescence [113]. Another factor that likely produces variation in growth outcomes in IUGR infants is the variability of response to insulin. At 6 months of age, SGA infants who had increased incremental linear growth demonstrated greater insulin secretion. Growth variation also might be linked to later evidence of glucose intolerance.

Postnatal Neurodevelopmental Outcome in Preterm IUGR/SGA Infants

The prognosis for neurodevelopmental outcome in preterm IUGR/SGA infants, while generally considered suboptimal [104,111,112], is more ambiguous and is easily confounded by other problems of preterm birth. Infants with IUGR have more developmental abnormalities and disabilities than gestational age–matched controls but not necessarily compared with weight-matched infants because the latter include preterm infants with problems specific to preterm birth. IUGR children born preterm with evidence of fetal circulatory redistribution are more severely affected. IUGR children born at 35 week's gestation or more score, on average, 0.5 SD lower than non-IUGR children across all neurodevelopmental assessments. IUGR children born at less than 35 weeks' gestation score approximately 0.7 SD lower than non-IUGR children across all neurodevelopmental assessments. IUGR children with evidence of fetal circulatory redistribution (preferential perfusion of the brain) have more severe neurodevelopmental impairments than those born IUGR alone.

Diffuse cerebral damage as a result of hypoxia probably accounts for the differences in expression of brain damage seen in preterm AGA and IUGR/SGA children. In general, growth restriction earlier in gestation leads to more cognitive disability in infants who were born preterm; thus infants with both preterm birth and early gestational growth restriction have a higher risk of neurodevelopmental deficits. Such infants are more likely to need special education at an earlier age as they reach school age.

Development and Intelligence Quotient

Most studies of restricted fetal growth document that insults at critical stages of development can produce persistent, lifelong failures in neurodevelopment. In rats, for example, undernutrition at a vulnerable period of brain development permanently decreases brain size, brain cell number, axonal length, dendritic arborization, and synapse formation, as well as later-life behavioral development, learning, and memory [2]. Not surprisingly, therefore, longer-term outcome studies have more often shown worse neurodevelopmental outcomes in IUGR/SGA infants with less than normal head circumferences [99]. Considerable variability has been noted among these studies, however, reflecting significant differences in the characteristics of the infants included in the studies, such as gestational age at birth, medical complications (presence and degree of asphyxia), and maternal problems (e.g., hypertension). Overall, late gestational IUGR of mild to moderate degree and without neonatal complications does not contribute to major adverse neurodevelopmental and cognitive outcomes. More recent evidence continues to document lower IQ scores and poorer neurodevelopmental outcome in IUGR infants with significant neonatal complications, although these neurodevelopmental and cognitive complications generally were found to be minor, with little or no CP and no severe hearing or visual impairments, unless the neonatal complications were severe.

Worse outcomes have been documented in symmetric IUGR infants, probably representing more chronic and severe IUGR or inclusion of other problems such as congenital infections. The majority of SGA infants with birth weights less than 1,000 g have catch-up growth of head circumference, although this is more likely in the asymmetric SGA group (85%) than in the symmetric group (73%) [114]. Normal head circumference usually is associated with a good outcome. When preterm infants with asymmetric or symmetric IUGR are compared with AGA infants,

asymmetric SGA infants have lower visuoauditory perception scores and social abilities scores at 18 months than normally grown infants, whereas symmetric SGA infants have deficits in all developmental areas except visuoauditory perception. Overall, however, there are more neurologic abnormalities in both asymmetric and symmetric groups relative to normally grown infants.

More recent studies using functional MRI show promise in sorting out the actual functional deficits specific to IUGR. This is an exciting area for research and clinical assessments, potentially allowing for determination of the impact of different degrees of IUGR, preterm versus term IUGR birth effects, impacts of related problems such as asphyxia or hypoglycemia, responses to treatment of the mother or fetus or neonate, and treatment after birth in the young child [115].

Follow-up of VLBW Infants Born SGA Following IUGR

Importantly, extrapolating results of follow-up to current VLBW populations is difficult because management of such neonates continues to change and improve. Exogenous surfactant has only been available commercially for around 25 years, and prenatal use of corticosteroids to accelerate fetal lung maturity increased considerably after the National Institutes of Health Consensus Conference in 1994 recommended their broad use in cases of anticipated preterm birth. As a result, certain complications of the VLBW infant (e.g., pneumothorax and intraventricular hemorrhage) have decreased, which could influence neurodevelopmental outcome. Finally, neonatal death or CP has decreased more in IUGR infants than in VLBW infants, and there is less neurodevelopmental impairment among the survivors [116].

Cerebral Palsy (CP). Most of the early follow-up studies of IUGR/SGA infants did not specifically address the issue of CP, although a low incidence was initially noted to be uncommon after uncomplicated IUGR. However, trends in the incidence of CP that have been followed over several years note that the rate of CP in IUGR/SGA infants is significantly increased compared with control infants born during the same years, in both late preterm and very preterm infants. More recent studies indicate a higher prevalence of CP in term IUGR infants [117], even up to a 10- to 30-fold increase in the risk of CP [118,119]. Furthermore, spastic CP increases with the degree of fetal growth restriction, worsening from values of lower than the 20th percentile weight for age and escalating greatly below the 3rd percentile.

Learning Deficits. While some studies have noted minimal differences in IQ tests and no differences in academic achievement when term IUGR/SGA and AGA infants were evaluated in later adolescence, most longer-term studies affirm the general association between IUGR and worse neurodevelopmental outcome. As with CP, most follow-up studies of IUGR infants have not extended into the school years. Most have shown a wide range of learning deficits, with learning deficits encountered in a third overall but up to half of preterm IUGR/SGA infants. Those with more chronic fetal growth restriction beginning in the first two trimesters do less well than those with later gestational onset of IUGR. Both cognitive ability (measured by IQ testing and reading comprehension) and motor ability are negatively associated with the degree of fetal growth restriction. When neurologic disorders are excluded, more IUGR/SGA children need special education at 9 years of age than those born AGA.

Most adults who were born SGA report that they are well adjusted, have a good health-related quality of life, and are socially satisfied with their lives [120]. Comprehensive neuropsychological evaluations at 9 years of age have been reported to show a lower IQ and relatively greater difficulties in creative problem solving, attention, and executive functions, as well as visuomotor organization and higher-order verbal skills, in children with a history of IUGR [121]. Socioeconomic conditions and other familial effects also contribute to outcome [122].

Consistently, restricted head circumference at birth and poor head growth are harbingers of frontal lobe–related suboptimal development and more severe intellectual disability [123]. Such studies also are confounded by the importance of perinatal complications as contributors to worse neurocognitive outcome among IUGR children [124]. The association of severe IUGR and reduced head circumference with poor neurodevelopmental outcomes, long-term neuropsychological problems, and difficulties in school is better understood in the context of severe reduction in cortical growth and a significant decrease in cell number in the future cortex of affected individuals, as well as discrete injuries to particular regions of the brain, such as the hippocampus.

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Effect of Fetal Malnutrition and IUGR on Disease in Adult Life

The consequences of IUGR reach far beyond the perinatal period. Many studies over the past three decades have clearly documented the relationship of IUGR, particularly when complicated by excessive growth of adipose tissue and body fat content, with the subsequent increased incidence of the metabolic syndrome (obesity, insulin resistance, and type 2 diabetes) and cardiovascular disease when these infants reach adult life [125]. Both hypertension and ischemic heart disease are increased in IUGR infants, and the risk of stroke also is increased [126]. Barker et al. first suggested that undernutrition during fetal life alters the relationships between nutrient substrates and hormones, such as between glucose and insulin and between growth hormone and IGF [125]. Since IGF-1 is decreased in many growth-restricted fetuses, and since fetal undernutrition may predispose to insulin resistance in various tissues and organs later in life [127,128], these infants also become obese (primarily increased visceral adiposity), insulin resistant, glucose intolerant, and diabetic as adults [129,130]. Fetal skeletal muscle growth is particularly reduced in IUGR fetuses that have placental insufficiency and are relatively hypoxic because blood and nutrients are preferentially shunted to vital organs. As a result, IUGR infants suffer from lifelong reductions in muscle mass (sarcopenia)[131], reducing their capacity for glucose disposal. This may be augmented by persistence of inadequate insulin secretion from the reduced numbers of pancreatic islet β-cells, which fail in response to the overstimulated pancreas from the Western diet over the lifespan. Reduced concentrations of IGF also have been associated with arterial wall thickening, in particular, abdominal aortic intima-media thickness, a marker for atherosclerosis [132,133]. While the IUGR fetus may represent successful adaptation to nutritional deprivation in utero, such adaptation may lead to an increased incidence of cardiovascular disease and related metabolic problems in adulthood [134]. Encouragingly, it has been estimated from a cohort of over 13,000 men and women that increasing birth weight and minimizing accelerated postnatal growth could reduce diabetes risk by 57% and the incidence of hypertension and coronary heart disease by 25% and 40%, respectively [135].

Prevention

Although outcome in the "nonasphyxiated," normally grown fetus appears to be good, the potential for developing fetal hypoxia-ischemia in the growth-restricted fetus is high. Indeed, the risk of intrauterine demise drives many obstetric decisions, primarily for early delivery. For this reason, a number of techniques have been used with the intent to improve placental perfusion.

Some specific interventions are showing promise for improving outcomes in IUGR fetuses, such as maternal hyperoxygenation. Several attempts have been made in situations where fetal hypoxia has been documented by cordocentesis to use maternal oxygen therapy to produce maternal hyperoxygenation and secondarily improve fetal oxygenation. However, few studies used randomized controls and did not provide enough evidence to evaluate adequately the benefits and risks of maternal oxygen therapy.

Another approach, which has been tested in a randomized, placebo-controlled, double-masked trial, is the use of low-dose aspirin [136]. Women were chosen on the basis of previous fetal growth restriction and/or fetal death or abruptio placentae. The benefits of low-dose aspirin were greater in patients with two or more previous poor outcomes. More recent evaluation of low-dose aspirin showed no evidence of improved uteroplacental or fetoplacental hemodynamics. Other experimental approaches are attempting to increase fetal nutrition, particularly of amino acids, by increasing uterine blood flow with vasodilators such as sildenafil [137] or increasing placental and fetal growth with maternal growth hormone [138]. Other studies, however, have documented that efforts to enhance energy supply to the fetus, such as with glucose alone, may cause more harm than good [139].

Several studies have assessed the role of dietary supplementation to correct specific deficiencies [140]. Correcting maternal undernutrition with balanced energy and protein supplementation appears modestly successful [141]. It also is possible, under certain severe adverse circumstances, such as complete lack of maternal capacity to tolerate any enteral feeding, to support adequate fetal growth using maternal intravenous nutrition. Extending this approach to other situations of less severe nutritional deprivation might allow supplemental parenteral nutrition to prevent fetal growth restriction, although there are too few

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studies with enough evidence to allow an adequate evaluation of nutrient supplementation [142]. There also is recent concern that too much energy provided to the fetus by increasing maternal energy intake, particularly of simple carbohydrates and sugars, might promote increased adiposity in the fetus, leading to obesity later in life [1,143,144].

Two analyses from the Cochrane Database of Systematic Reviews have shown insufficient evidence to demonstrate a conclusive effect of either plasma volume expansion or bed rest in hospital on fetal growth [145,146].

Determining the cause of IUGR is difficult but, if possible, is important in assessing the risk for IUGR in future pregnancies [147]. A good example would be the identification of thrombophilia, which may occur in 15–25% of Caucasian populations. Thrombophilia is exacerbated by pregnancy (an acquired hypercoagulable state) and can lead to vascular complications associated with IUGR [148].

Conclusion

Major advances have been made in our understanding of infants who are growth restricted in utero. Many of the factors that lead to IUGR have been recognized, and many of the women who are at risk of giving birth to such infants can be identified. In many cases, problems can be avoided by improving the intrauterine environment by improving maternal health through better access to healthcare during pregnancy, including improved care of chronic illness in the mother, maternal immunization, and improved counseling of pregnant women regarding smoking, use of alcohol, and drug abuse. We are still at the stage where attempts to prevent or correct fetal growth restriction through maternal nutritional supplemental strategies have been unsuccessful [1] because we do not have a firm understanding of the basic biology of cell, tissue, and organ growth regulation in the IUGR fetus in utero [149,150]. We have the potential to change the field by determining how and when pathways that regulate growth respond to nutrient and growth factor supplementation during critical windows of fetal development in an IUGR pregnancy.

Infants also can be classified according to the types of growth restriction present, and it is recognized that many of these infants do not thrive in a hostile intrauterine environment, do not tolerate the stresses of labor well, and do not have an appropriate transitional period from the fetal to the newborn state. IUGR infants also have markedly different problems in the neonatal period than do preterm infants of the same size or normally grown infants of the same gestational age. Unfortunately, many of these IUGR fetuses are not being identified early enough to alter these environments, and we are still late in responding to their problems in the neonatal period rather than anticipating and preventing them from developing in the fetal state. Unfortunately, this leaves fetal surveillance and early delivery of the fetus as the primary options for the management of the IUGR pregnancy.

Although significant strides have been made in our understanding of the problems of IUGR infants, we need to focus our attention on prevention, early detection, and appropriate management of their problems in order to produce the best outcome possible.

References

1. Rozance PJ, Brown LD, Thorn SR, et al. Intrauterine growth restriction and the small-for-gestational-age infant. In MacDonald MG, Seshia MMK, eds., *Avery's Neonatology: Pathophysiology and Management of the Newborn*, 7th edn. Philadelphia: Wolters Kluwer Health, 2015.
2. Smart J. Undernutrition, learning and memory: review of experimental studies. In Taylor TG, Jenkins NK, eds. *Proceedings of XII International Congress of Nutrition*. London: John Libbey, 1986: 74.
3. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, et al. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011; **117**: 618–26.
4. Simmons RA, Gounis AS, Bangalore SA, Ogata ES. Intrauterine growth retardation: fetal glucose transport is diminished in lung but spared in brain. *Pediatr Res* 1992; **32**: 59–63.
5. Poudel R, McMillen IC, Dunn SL, et al. Impact of chronic hypoxemia on blood flow to the brain, heart, and adrenal gland in the late-gestation IUGR sheep fetus. *Am J Physiol Regul Integr Comp Physiol* 2015; **308**: R151–62.
6. Castillo-Melendez M, Yawno T, Allison BJ, et al. Cerebrovascular adaptations to chronic hypoxia in the growth restricted lamb. *Int J Dev Neurosci* 2015; **29**:ii.
7. Toft PB, Leth H, Ring PB, et al. Volumetric analysis of the normal infant brain and in intrauterine growth retardation. *Early Hum Dev* 1995; **43**: 15–29.
8. Østgård HF, Løhaugen GC, Bjuland KJ, et al. Brain morphometry and cognition in young adults born small for gestational age at term. *J Pediatr* 2014; **165**: 921–7.

.008

9. Lager S, Powell TL. Regulation of nutrient transport across the placenta. *J Pregnancy* 2012; **2012**: 179827.
10. Gaccioli F, Aye IL, Roos S, et al. Expression and functional characterisation of system L amino acid transporters in the human term placenta. *Reprod Biol Endocrinol* 2015; **9**(13):57.
11. Lepercq J, Hauguel De Mouzo SJ. Leptin during pregnancy. *Gynecol Obstet Biol Reprod (Paris)* 2002; **31**: 167–72.
12. Symonds ME, Pope M, Sharkey D, Budge H. Adipose tissue and fetal programming. *Diabetologia* 2012; **55**: 1597–606.
13. Rosario FJ, Schumacher MA, Jiang J, et al. Chronic maternal infusion of full-length adiponectin in pregnant mice down-regulates placental amino acid transporter activity and expression and decreases fetal growth. *J Physiol* 2012; **15**(590): 1495–509.
14. Limesand SW, Jensen J, Hutton JC, Hay WW Jr. Diminished beta-cell replication contributes to reduced beta-cell mass in fetal sheep with intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol* 2005; **288**: R1297–305.
15. Rozance PJ, Anderson M, Martinez M, et al. Placental insufficiency decreases pancreatic vascularity and disrupts hepatocyte growth factor signaling in the pancreatic islet endothelial cell in fetal sheep. *Diabetes* 2015; **64**: 555–64.
16. Andrews SE, Brown LD, Thorn SR, et al. Increased adrenergic signaling is responsible for decreased glucose-stimulated insulin secretion in the chronically hyperinsulinemic ovine fetus. *Endocrinology* 2015; **156**: 367–76.
17. Fowden Al. The insulin-like growth factors and feto-placental growth. *Placenta* 2003; **24**(8–9): 803–12.
18. Ye P, Carson J, D'Ercole AJ. In vivo actions of insulin-like growth factor-I (IGF-I) on brain myelination: studies of IGF-I and IGF binding protein-1 (IGFBP-1) transgenic mice. *J Neurosci* 1995; **15**: 7344.
19. Abuzzahab MJ, Schneider A, Goddard A, et al. Intrauterine Growth Retardation (IUGR) Study Group. IFG-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* 2003; **349**(23): 2211–22.
20. Baumann MU, Schneider H, Malek A, et al. Regulation of human trophoblast GLUT1 glucose transporter by insulin-like growth factor I (IGF-I). *PLoS One* 2014; **9**(8):e106037.
21. Sferruzzi-Perri AN, Vaughan OR, Forhead AJ, Fowden AL. Hormonal and nutritional drivers of intrauterine growth. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 298–309.
22. Gressens P, Hill JM, Paindaveine B, et al. Severe microcephaly induced by blockade of vasoactive intestinal peptide function in the primitive neuroepithelium of the mouse. *J Clin Invest* 1994; **94**: 2020–7.
23. Nicolaides KH, Economides DL, Soothill PW. Blood gases, pH, and lactate in appropriate- and small-for-gestational-age fetuses. *Am J Obstet Gynecol* 1989; **161**: 996–1001.
24. Scholl TO, Hediger ML, Schall JI, et al. Maternal growth during pregnancy and the competition for nutrients. *Am J Clin Nutr* 1994; **60**: 183–8.
25. Klein JO, Baker CJ, Remington JS, et al. Current concepts of infection of the fetus and newborn infants. In Remington JS, Klein JO, Wilson CB, Baker CJ, eds., *Infectious Diseases of the Fetus and Newborn Infant*, 6th edn. Philadelphia: Elsevier Saunders, 2006: 1–25.
26. Kleigman RM. Intrauterine growth restriction. In Fanaroff AA, Martin RJ, Walsh MC, eds., *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*, 5th edn. Philadelphia: Mosby Elsevier, 2006: 221–306.
27. Ananth CV, Friedman AM. Ischemic placental disease and risks of perinatal mortality and morbidity and neurodevelopmental outcomes. *Semin Perinatol* 2014; **38**: 151–8.
28. Roos S, Powell TL, Jansson T. Placental mTOR links maternal nutrient availability to fetal growth. *Biochem Soc Trans* 2009; **37**: 295–8.
29. Lumey LH. Decreased birth weights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. *Paediatr Perinat Epidemiol* 1992; **6**: 240–53.
30. Catalano PM, McIntyre HD, Cruickshank JK, et al. HAPO Study Cooperative Research Group. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care* 2012; **35**: 780–6.
31. Hernandez TL, Van Pelt RE, Anderson MA, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. *Diabetes Care* 2014; **37**: 1254–62.
32. Crume TL, Shapiro AL, Brinton JT, et al. Maternal fuels and metabolic measures during pregnancy and neonatal body composition: the healthy start study. *J Clin Endocrinol Metab* 2015; **100**: 1672–80.
33. Ota E, Mori R, Middleton P, et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev* 2015; **2**(2): CD000230.
34. Butterworth RF. Maternal thiamine deficiency: still a problem in some world communities. *Am J Clin Nutr* 2001; **74**: 712–13.

35. Conti J, Abraham S, Taylor A. Eating behavior and pregnancy outcome. *J Psychosom Res* 1998; **44**: 465–77.
36. Many A, Fattal A, Leitner Y, et al. Neurodevelopmental and cognitive assessment of children born growth restricted to mothers with and without preeclampsia. *Hypertens Pregnancy* 2003; **22**: 25–9.
37. Manuck T, Branch DW, Lai Y, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Antiphospholipid antibodies and pregnancy outcomes in women heterozygous for factor V Leiden. *J Reprod Immunol* 2010; **85**: 180–5.
38. Triche EW, Hossain N. Environmental factors implicated in the causation of diverse pregnancy outcome. *Semin Perinatol* 2007; **31**: 240–2.
39. Blatt K, Moore E, Chen A, et al. Association of reported trimester-specific smoking cessation with fetal growth restriction. *Obstet Gynecol* 2015; **125**: 1452–9.
40. Kallen K. Maternal smoking during pregnancy and infant head circumference at birth. *Early Hum Dev* 2000; **58**: 197–204.
41. Carter RC, Jacobson JL, Sokol RJ, et al. Fetal alcohol-related growth restriction from birth through young adulthood and moderating effects of maternal prepregnancy weight. *Alcohol Clin Exp Res* 2013; **37**: 452–62.
42. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol* 1991; **77**: 361–4.
43. Frank DA, Bauchner H, Parker S, et al. Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *J Pediatr* 1990; **117**: 622–6.
44. Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risks of caffeine. *Teratology* 2001; **64**: 51–78.
45. Giussani DA, Salinas CE, Villena M. The role of oxygen in prenatal growth: studies in the chick embryo. *J Physiol* 2007; **585**: 911–17.
46. Milley JR. Ovine fetal leucine kinetics and protein metabolism during decreased oxygen availability. *Am J Physiol* 1998; **274**:e618–26.
47. Illsley NP, Caniggia I, Zamudio S. Placental metabolic reprogramming: do changes in the mix of energy-generating substrates modulate fetal growth? *Int J Dev Biol* 2010; **54**: 409–19.
48. Soria R, Julian CG, Vargas E, et al. Graduated effects of high-altitude hypoxia and highland ancestry on birth size. *Pediatr Res* 2013; **74**: 633–8.
49. Wilson MJ, Lopez M, Vargas M, et al. Greater uterine artery blood flow during pregnancy in multigenerational (Andean) than shorter-term (European) high-altitude residents. *Am J Physiol Regul Integr Comp Physiol* 2007; **293**: R1313–24.
50. Bennett A, Sain SR, Vargas E, Moore LG. The effect of heavy maternal workload on fetal growth retardation and preterm delivery: a study among southern Thai women. *J Occup Environ Med* 1998; **40**: 1013–21.
51. Tuntiseranee P, Geater A, Chongsuvivatwong V, Kor-anantakul O. The effect of heavy maternal workload on fetal growth retardation and preterm delivery: a study among southern Thai women. *J Occup Environ Med* 1998; **40**: 1013–21.
52. Koos BJ, Longo LD. Mercury toxicity in the pregnant woman, fetus, and newborn infant: a review. *Am J Obstet Gynecol* 1976; **126**: 390–409.
53. Albu AR, Horhoianu IA, Dumitrascu MC, Horhoianu V. Growth assessment in diagnosis of fetal growth restriction. *J Med Life* 2014; **5**(7): 150–4.
54. Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. *Cochrane Database Syst Rev* 2012; **6**:CD007113.
55. Businelli C, de Wit C, Visser GH, Pistorius LR. Ultrasound evaluation of cortical brain development in fetuses with intrauterine growth restriction. *J Matern Fetal Neonatal Med* 2014; **10**: 1–6.
56. Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2000; **15**: 209–12.
57. Flood K, Unterscheider J, Daly S, et al. The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study. *Am J Obstet Gynecol* 2014; **211**(288):e1–5.
58. Cruz-Martinez R, Tenorio V, Padilla N, et al. Risk of neonatal brain ultrasound abnormalities in intrauterine growth restricted fetuses born between 28 and 34 weeks: relationship with gestational age at birth and fetal Doppler. *Ultrasound Obstet Gynecol* 2015; **46**:389–90.
59. Girardi G. MRI-based methods to detect placental and fetal brain abnormalities in utero. *J Reprod Immunol* 2015; **2**:pii: S0165–0378(15)00094–7.
60. Marconi AM, Ronzoni S, Vailati S, et al. Neonatal morbidity and mortality in intrauterine growth restricted (IUGR) pregnancies is predicated upon prenatal diagnosis of clinical severity. *Reprod Sci* 2009; **16**: 373–9.
61. Marconi AM, Paolini CL, Zerbe G, Battaglia FC. Lactacidemia in intrauterine growth restricted (IUGR) pregnancies: relationship to clinical severity,

.008

oxygenation and placental weight. *Pediatr Res* 2006; **59**: 570–4.

62. Regnault TR, de Vrijer B, Galan HL, et al. Development and mechanisms of fetal hypoxia in severe fetal growth restriction. *Placenta* 2007; **28**: 714–23.
63. Salihagić-Kadić A, Medić M, Jugović D, et al. Fetal cerebrovascular response to chronic hypoxia: implications for the prevention of brain damage. *J Matern Fetal Neonatal Med* 2006; **19**: 387–96.
64. Figueras F, Eixarch E, Meler E, et al. Small-for-gestational-age fetuses with normal umbilical artery Doppler have suboptimal perinatal and neurodevelopmental outcome. *Eur J Obstet Gynecol Reprod Biol* 2008; **136**: 34–8.
65. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. *Paediatr Respir Rev.* 2015; **16**: 157–61.
66. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr* 2012; **161**: 787–91.
67. Hawdon JM, Aynsley-Green A, Ward Platt MP. Neonatal blood glucose concentrations: metabolic effects of intravenous glucagon and intragastric medium chain triglyceride. *Arch Dis Child* 1993; **68**: 255–61.
68. Limesand SW, Rozance PJ, Smith D, Hay WW Jr. Increased insulin sensitivity and maintenance of glucose utilization rates in fetal sheep with placental insufficiency and intrauterine growth restriction. *Am J Physiol Endocrinol Metab* 2007; **293**: E1716–25.
69. van Kempen AA, Ackermans MT, Endert E, et al. Glucose production in response to glucagon is comparable in preterm AGA and SGA infants. *Clin Nutr* 2005; **24**: 727–36.
70. Arya VB, Flanagan SE, Kumaran A, et al. Clinical and molecular characterization of hyperinsulinaemic hypoglycaemia in infants born small-for-gestational age. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F356–8.
71. Macko AR, Yates DT, Chen X, et al. Elevated plasma norepinephrine inhibits insulin secretion, but adrenergic blockade reveals enhanced β-cell responsiveness in an ovine model of placental insufficiency at 0.7 of gestation. *J Dev Orig Health Dis* 2013; **4**: 402–10.
72. Gatford KL, Simmons RA. Prenatal programming of insulin secretion in intrauterine growth restriction. *Clin Obstet Gynecol* 2013; **56**: 520–8.
73. Law TL, Korte JE, Katikaneni LD, et al. Ultrasound assessment of intrauterine growth restriction: relationship to neonatal body composition. *Am J Obstet Gynecol* 2011; **205**(255):e1–6.
74. Thorn SR, Regnault TRH, Brown LD, et al. Intrauterine growth restriction increases fetal hepatic gluconeogenic capacity and reduces hepatic and skeletal muscle mRNA translation initiation and nutrient sensing. *Endocrinology* 2009; **150**: 3021–30.
75. Thorn SR, Brown LD, Rozance PJ, et al. Increased hepatic glucose production in fetal sheep with intrauterine growth restriction is not suppressed by insulin. *Diabetes* 2013; **62**: 65–73.
76. Jain A, Agarwal R, Sankar MJ, et al. Hypocalcemia in the newborn. *Ind J Pediatr* 2010; **77**: 1123–8.
77. Bauer J, Masin M, Brodner K. Resting energy expenditure and metabolic parameters in small for gestational age moderately preterm infants. *Horm Res Paediatr* 2011; **76**: 202–7.
78. Glasser I, Sutten N, Schmeling M, Machan JT. A comprehensive study of umbilical cord blood cell developmental changes and reference ranges by gestation, gender and mode of delivery. *J Perinatol* 2015; **35**: 469–75.
79. Basha S, Surendran N, Pichichero M. Immune responses in neonates. *Exp Rev Clin Immunol* 2014; **10**: 1171–84.
80. Kempley S, Gupta N, Linsell L, et al. Feeding infants below 29 weeks' gestation with abnormal antenatal Doppler: analysis from a randomised trial. *Arch Dis Child Fetal Neonatal Ed*. 2014; **99**: F6–11.
81. Abdelmaaboud M, Mohammed A. Early versus late minimal enteral feeding in weeks preterm growth-restricted neonates with abnormal antenatal Doppler studies. *J Matern Fetal Neonatal Med* 2012 (epub ahead of print).
82. Leaf A, Dorling J, Kempley S, et al. Abnormal Doppler Enteral Prescription Trial Collaborative Group. Early or delayed enteral feeding for preterm growth-restricted infants: a randomized trial. *Pediatrics* 2012; **129**: e1260–8.
83. Pettigrew AG, Edwards DA, Henderson-Smart DJ. The influence of intra-uterine growth retardation on brainstem development of preterm infants. *Dev Med Child Neurol* 1985; **27**: 467–72.
84. Stanley OH, Fleming PJ, Morgan MH. Development of visual evoked potentials following intrauterine growth retardation. *Early Hum Dev* 1991; **27**: 79–91.
85. Scherjon S, Briët J, Oosting H, Kok J. The discrepancy between maturation of visual-evoked potentials and cognitive outcome at five years in very preterm infants with and without hemodynamic signs of fetal brain-sparing. *Pediatrics* 2000; **105**: 385–91.
86. Nijhuis IJ, ten Hof J, Nijhuis JG, et al. Temporal organization of fetal behavior from 24-weeks gestation

onwards in normal and complicated pregnancies. *Dev Psychobiol* 1999; **34**: 257–68.

87. Leventhal JM, Berg A, Egerter SA. Is intrauterine growth retardation a risk factor for child abuse? *Pediatrics* 1987; **79**: 515–19.
88. Watt J. Interaction and development in the first year. II. The effects of intrauterine growth retardation. *Early Hum Dev* 1986; **13**: 211–23.
89. Pallotto EK, Killbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clin Obstet Gynecol* 2006; **49**: 257–69.
90. Ortibus E, Lopriore E, Deprest J, et al. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. *Am J Obstet Gynecol* 2009; **200**(494): e1–8.
91. von Beckerath AK, Kollmann M, Rotky-Fast C, et al. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. *Am J Obstet Gynecol* 2013; **208**(130):e1–6.
92. Levine TA, Grunau RE, McAuliffe FM, et al. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review. *Pediatrics* 2015; **135**: 126–41.
93. Wang Y, Fu W, Liu J. Neurodevelopment in children with intrauterine growth restriction: adverse effects and interventions. *J Matern Fetal Neonatal Med* 2015; **23**: 1–9.
94. Murray E, Fernandes M, Fazel M, et al. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG* 2015; **122**: 1062–72.
95. Casey PH. Growth of low birth weight preterm children. *Semin Perinatol* 2008; **32**: 20–7.
96. Rogne T, Engstrøm AA, Jacobsen GW, et al. Fetal growth, cognitive function, and brain volumes in childhood and adolescence. *Obstet Gynecol* 2015; **125**: 673–82.
97. McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869–77.
98. Hack M. Effects of intrauterine growth retardation on mental performance and behavior outcomes during adolescence and adulthood. *Eur J Clin Nutr* 1998; **52**: S65–70.
99. Yerushalmy-Feler A, Marom R, Peylan T, et al. Electroencephalographic characteristics in preterm infants born with intrauterine growth restriction. *J Pediatr* 2014; **164**: 756–61.
100. Simić Klarić A, Kolundžić Z, Galić S. Language development inpreschool children born after asymmetrical intrautering growth retardation. *Eur J Paediatr Neurol* 2012; **16**: 132–7.
101. Ortigosa Rocha C, Bittar RE, Zugaib M. Neonatal outcomes of late-preterm birth associated or not with intrauterine growth restriction. *Obstet Gynecol Int* 2010; **2010**: 231842.
102. Fattal-Valevski A, Leitner Y, Kutai M, et al. Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. *J Child Neurol* 1999; **14**: 724–7.
103. De Jesus LC, Pappas A, Shankaran S, et al. Eunice Kennedy Shriver National Institute of Health and Human Development Neonatal Research Network. Outcomes of small for gestational age infants born at <27 weeks' gestation. *J Pediatr* 2013; **163**(55–60): e1–3.
104. Guellec I, Lapillonne A, Renolleau S, et al. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. *Pediatrics* 2011; **127**: e883–91.
105. Aucott SW, Donohue PK, Northington FJ. Increased morbidity in severe early intrauterine growth restriction. *J Perinatol* 2004; **24**: 435–40.
106. Christian P. Fetal growth restriction and preterm as determinants of child growth in the first two years and potential interventions. *Nestle Nutr Inst Workshop Ser* 2014; **78**: 81–91.
107. Baker J, Workman M, Bedrick E, et al. Brains versus brawn: an empirical test of Barker's brain sparing model. *Am J Hum Biol* 2010; **22**: 206–15.
108. Basilious A, Yager J, Fehlings MG. Neurological outcomes of animal models of uterine artery ligation and relevance to human intrauterine growth restriction: a systematic review. *Dev Med Child Neurol* 2015; **57**: 420–30.
109. Piorkowska K, Thompson J, Nygard K, et al. Synaptic development and neuronal myelination are altered with growth restriction in fetal guinea pigs. *Dev Neurosci* 2014; **36**: 465–76.
110. Hack M, Breslau N, Weissman B, et al. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med* 1991; **325**: 231–7.
111. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab*. 2008; **22**: 477–88.
112. Paz I, Seidman DS, Danon YL, et al. Are children born small for gestational age at increased risk of short stature? *Am J Dis Child* 1993; **147**: 337–9.

113. Bergvall N, Iliadou A, Johansson S, et al. Risks for low intellectual performance related to being born small for gestational age are modified by gestational age. *Pediatrics* 2006; **117**: e460–7.

114. Monset-Couchard M, de Bethmann O. Catch-up growth in 166 small-forgestational age premature infants weighing less than 1,000 g at birth. *Biol Neonate* 2000; **78**: 161–7.

115. de Bie HM, de Ruiter MB, Ouwendijk M, et al. Using fMRI to investigate memory in young children born small for gestational age. *PLoS One* 2015; **1**(10): e0129721.

116. Spinillo A, Gardella B, Preti E, et al. Rates of neonatal death and cerebral palsy associated with fetal growth restriction among very low birth weight infants: a temporal analysis. *BJOG* 2006; **113**: 775–80.

117. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. *Am J Obstet Gynecol* 2015; **213**: 779–88.

118. Blair EM, Nelson KB. Fetal growth restriction and risk of cerebral palsy in singletons born after at least 35 weeks' gestation. *Am J Obstet Gynecol* 2015; 212 (520):e1–7.

119. O'Callaghan ME, MacLennan AH, Gibson CS, et al. Epidemiologic associations with cerebral palsy. *Obstet Gynecol* 2011; **118**: 576–82.

120. Spence D, Alderdice FA, Stewart MC, et al. Does intrauterine growth restriction affect quality of life in adulthood? *Arch Dis Child* 2007; **92**: 700–3.

121. Geva R, Eshel R, Leitner Y, et al. Neuropsychological outcome of children with intrauterine growth restriction: a 9-year prospective study. *Pediatrics* 2006; **118**: 91–100.

122. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S. Birth characteristics and risk of low intellectual performance in early adulthood: are the associations confounded by socioeconomic factors in adolescence or familial effects? *Pediatrics* 2006; **117**: 714–21.

123. Leonard H, Nassar N, Bourke J, et al. Relation between intrauterine growth and subsequent intellectual disability in a ten-year population cohort of children in Western Australia. *Am J Epidemiol* 2008; **167**: 103–11.

124. Leitner Y, Fattal-Valevski A, Geva R, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. *J Child Neurol* 2007; **22**: 580–7.

125. Barker DJ, Gluckman PD, Godfrey KM, et al. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993; **341**: 938–41.

126. Gortner L. Intrauterine growth restriction and risk for arterial hypertension: a causal relationship? *J Perinat Med* 2007; **35**: 361–5.

127. Ong TP, Ozanne SE. Developmental programming of type 2 diabetes: early nutrition and epigenetic mechanisms. *Curr Opin Clin Nutr Metab Care* 2015; **18**: 354–60.

128. Duque-Guimarães DE, Ozanne SE. Nutritional programming of insulin resistance: causes and consequences. *Trends Endocrinol Metab* 2013; **245**: 525–35.

129. Forsén T, Eriksson J, Tuomilehto J, et al. The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 2000; **133**: 176–82.

130. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008; **359**: 61–73.

131. Sayer AA, Syddall H, Martin H, et al. The developmental origins of sarcopenia. *J Nutr Health Aging* 2008; **12**: 427–32.

132. Koklu E, Ozturk MA, Kurtoglu S, et al. Aortic intima-media thickness, serum IGF-I, IGFBP-3, and leptin levels in intrauterine growth-restricted newborns of healthy mothers. *Pediatr Res* 2007; **62**: 704–9.

133. Skilton MR, Evans N, Griffiths KA, et al. Aortic wall thickness in newborns with intrauterine growth restriction. *Lancet* 2005; **365**: 1484–6.

134. Bloomfield FH, Oliver MH, Harding JE. The late effects of fetal growth patterns. *Arch Dis Child Fetal Neonatal Ed* 2006; **91**: F299–304.

135. Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* 2002; **31**: 1235–9.

136. Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402–14.

137. Satterfield MC, Bazer FW, Spencer TE, Wu G. Sildenafil citrate treatment enhances amino acid availability in the conceptus and fetal growth in an ovine model of intrauterine growth restriction. *J Nutr* 2010; **140**: 251–8.

138. de Boo HA, Eremia SC, Bloomfield FH, et al. Treatment of intrautere growth restriction with maternal growth hormone supplementation in sheep. *Am J Obstet Gynecol* 2008; **199**(599):e1–9.

139. Rozance PJ, Limesand SW, Barry JS, et al. Glucose replacement to euglycemia causes hypoxia, acidosis, and decreased insulin secretion in fetal sheep with

intrauterine growth restriction. *Pediatr Res* 2009; **65**: 72–8.

140. Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York City. *Pediatrics* 1980; **65**: 683–97.

141. Ceesay SM, Prentice AM, Cole TJ, et al. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997; **315**: 786–90.

142. Gulmezoglu AM, Hofmeyr GJ. Maternal nutrient supplementation for suspected impaired fetal growth. *Cochrane Database Syst Rev* 2000; **2**: CD000148.

143. Catalano PM, Thomas AJ, Huston LP, Fung CM. Effect of maternal metabolism on fetal growth and body composition. *Diabetes Care*. 1998; **21**(Suppl. 2): B85–90.

144. Fernandez-Twinn DS, Ozanne SE. Mechanisms by which poor early growth programs type-2 diabetes, obesity and the metabolic syndrome. *Physiol Behav* 2006; **88**: 234–43.

145. Gulmezoglu AM, Hofmeyr GJ. Plasma volume expansion for suspected impaired fetal growth. *Cochrane Database Syst Rev* 2000; **2**: CD000167.

146. Gulmezoglu AM, Hofmeyr GJ. Bed rest in hospital for suspected impaired fetal growth. *Cochrane Database Syst Rev* 2000; **2**: CD000034.

147. Kinzler WL, Kaminsky L. Fetal growth restriction and subsequent pregnancy risks. *Semin Perinatol* 2007; **31**: 126–34.

148. Brenner B, Aharon A. Thrombophilia and adverse pregnancy outcome. *Clin Perinatol* 2007; **34**: 527–41.

149. Brown LD, Green AS, Limesand SW, Rozance PJ. Maternal amino acid supplementation for intrauterine growth restriction. *Front Biosci (Schol Ed)* 2011; **3**: 428–44.

150. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol* 2003; **27**: 302–10.

Chapter 8

Maternal Diseases that Affect Fetal and Neonatal Neurodevelopment

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Fetal brain development is highly sensitive to the effects of adverse intrauterine environmental conditions. Maternal disease states may contribute to abnormal fetal and neonatal neurodevelopment through direct and indirect mechanisms, including fetal growth restriction, medication exposure, endocrine abnormalities, preterm birth, infection, and alloimmune disease. This chapter includes a review of common maternal diseases in pregnancy and associated effects on neurodevelopment.

For the obstetric provider, care in the preconception period involves efforts to optimize maternal diseases in order to minimize effects on fetal development. Medication regimens are adjusted to the least teratogenic and best-studied option tolerated by the patient. Women are counseled on the known and unknown effects of the maternal disease and medication on pregnancy outcome, as well as the potential for worsening of disease secondary to pregnancy necessitating, in many cases, early delivery. During-pregnancy care from the obstetric provider includes both maternal disease surveillance and assessment of fetal growth and development, with particular consideration of the impact of maternal disease on fetal and neonatal outcome.

For the pediatric provider, the initial neonatal evaluation, approach to complications after birth, and childhood surveillance take into consideration potential effects (both acute and chronic) of maternal disease during the antepartum period.

Mechanisms of Brain Injury

Maternal disease may contribute to fetal *intrauterine growth restriction* (IUGR) through a variety of mechanisms including abnormal placental development (in the setting of chronic hypertension) and chronic hypoxia (from severe pulmonary disease). Prenatally diagnosed IUGR has been associated with poorer performance in neurodevelopmental testing in childhood relative to appropriately grown gestational age-matched children [1–3]. Whether growth restriction itself or the underlying maternal disease state contributes to neurodevelopmental deficits is not well understood and likely varies by disorder.

Medication and teratogen exposures can alter brain development and affect long-term cognitive function. While CNS development begins in the first weeks of gestation and is well underway by the end of the first trimester (12–13 weeks), the developing nervous system remains sensitive throughout gestation.

Multiple maternal disease states increase the risk for *preterm birth*, some due to an increased risk of spontaneous labor (e.g., maternal genitourinary infections) and others due to worsening maternal health prompting iatrogenic preterm delivery (e.g., chronic hypertension with superimposed preeclampsia). Prematurity is a risk factor for abnormal neurodevelopment in childhood [4,5].

Infection and inflammation also affects fetal neurodevelopment adversely. As a key example, children born prematurely with exposure to chorioamnionitis are at greater risk for cerebral palsy (CP) than those not exposed to infection [6].

Neurologic and Psychiatric Diseases

Seizure Disorders

Seizure disorders arise from multiple processes, including genetic abnormalities and history of trauma to the CNS. Based on research suggesting that women with untreated maternal seizure disorders are not at increased risk of having children with adverse neurodevelopmental sequelae, the presence of a seizure disorder is not thought to independently contribute to fetal and neonatal brain injury [7]. This subgroup of women with seizure disorders who do not require medication may have milder disease, however, and may be less likely to experience prolonged or frequent seizures, which are associated with maternal hypoxia and potential fetal injury.

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Women with seizure disorders are generally advised to continue antiepileptic medications in pregnancy due to a lower seizure threshold in pregnancy. Management of seizure disorders with a single agent is considered safer than treatment with multiple agents [8]. Currently, antiepileptic medications with the greatest safety profiles are carbamazepine [9] and lamotrigine [10]. Valproate should be avoided in pregnancy due to the association with deficits in verbal memory in childhood, lower IQ at 6 years of age, and problems with memory and executive functions [10,11]. A Cochrane review of prospective cohort studies comparing various antiepileptic regimens during pregnancy found that the developmental quotient of children exposed to valproate was significantly lower than that for children born to women without epilepsy ($p < 0.00001$) and to children born to women with untreated epilepsy ($p = 0.002$) [9].

Migraine Headaches

Maternal migraine headaches are not independently associated with adverse neurodevelopmental outcomes. Acute management of headaches commonly involves opioid analgesics, which are considered to be relatively safe in pregnancy but may lead to neonatal dependence with prolonged use. Ergot analogues should be avoided due to the risk of increased uterine tone (limiting fetal blood flow and oxygenation) and teratogenicity. Triptan use is generally avoided, although the rate of congenital anomalies and adverse pregnancy outcomes is thought to be no greater with the use of triptans prenatally [12]. The association between prenatal exposure to triptans and long-term neurodevelopmental outcomes is not yet known.

Depression and Anxiety

The association between prenatal exposure to mood disorders and neurodevelopmental outcome is compounded by multiple factors including the effects of ongoing maternal depression after delivery, social stressors, and antidepressant therapy [13]. Women with depression are more likely to deliver a small-for-gestational-age (SGA) neonate and to delivery prematurely [14]. Approximately 15–30% of neonates exposed to selective serotonin reuptake inhibitors (SSRIs) late in pregnancy present with *neonatal adaptation syndrome*, which manifests as tremors, agitation, hyper- or hypotonia, and occasionally seizures. This syndrome typically resolves within 2 weeks of birth and is not thought to have long-term sequelae [13]. Prenatal exposure to SSRIs or anxiolytics was not associated with diminished intelligence at 5 years of age within a large Danish cohort [15]. Studies present conflicting results with regard to other neurodevelopmental outcomes.

Alcohol

Alcohol is a teratogen that freely crosses the placenta and enters the fetal circulation. Exposed infants may develop signs of *fetal alcohol syndrome* – physical, mental, behavioral, and cognitive effects of prenatal alcohol exposure. Neurodevelopmental deficits seen in adolescence and adulthood include decreased IQ, poor socialization skills, and maladaptive behaviors (e.g., poor concentration, impulsivity, and anxiety) [16]. Currently there is not a safe level of prenatal alcohol consumption, and complete abstinence is recommended. There is thought to be a dose-response relationship between the quantity of alcohol intake and adverse pregnancy outcomes, including delivery of a SGA infant and preterm birth [17].

Tobacco

Prenatal nicotine exposure increases the risk for adverse pregnancy outcomes including SGA birth weight and spontaneous preterm delivery. Studies that have associated prenatal nicotine exposure to adverse neurodevelopmental outcomes (such as lower IQ and behavioral abnormalities) are countered by other analyses that demonstrate that once appropriate confounders and family characteristics are accounted for, the impact is neglible [18,19].

Substance Abuse

The study of prenatal substance abuse and neurodevelopmental outcome is invariably confounded by multiple factors prior to delivery and in childhood, including maternal psychiatric comorbidities, nutrition, parental bonding, and family characteristics and stability. A summary of the known short- and long-term effects of prenatal substance abuse on the exposed fetus is available elsewhere [20].

Cardiovascular Diseases

Hypertension

Hypertensive disorders seen in pregnancy include chronic hypertension, preeclampsia, and gestational

hypertension. In evaluating the potential association between prenatal exposure to elevated maternal blood pressure and neurodevelopmental outcome, consideration must be paid to both concurrent growth restriction and preterm delivery (both are seen more commonly with hypertensive disorders).

Hypertension is a significant risk factor for prenatal growth restriction. Maternal vascular diseases (e.g., chronic hypertension and long-standing diabetes) account for 25–30% of fetal growth restriction, presumably through decreased uteroplacental perfusion [21]. Among women with a hypertensive disorder in pregnancy, the presence of intrauterine growth restriction was associated with decreased quality of developmental outcomes (cognitive, visuospatial, and motor skills) compared with appropriately grown fetuses, with comparison groups that had similar mean gestational ages at birth [22].

In the absence of growth restriction or preterm delivery, prenatal exposure to a gestational hypertensive disorder may still adversely affect neurodevelopment, as evidenced by lower cognitive function testing in adulthood among male Danish conscripts born to mothers with gestational hypertension or preeclampsia among a cohort of appropriately grown infants born at term (19% versus 14%) [23]. In a case-control study of children born in California with autism, prenatal exposure to preeclampsia was significantly more common among children with autism than among healthy control children [24].

Commonly used antihypertensive medications in pregnancy include nifedipine (a calcium channel blocker) and labetalol (primarily a beta blocker). In a follow-up study at 18 months of children born to mothers enrolled in a randomized clinical trial of nifedipine use for hypertension between 12 and 34 weeks, there was no difference in the frequency of congenital anomalies, small size, or developmental delay [25]. In a prospective cohort of children prenatally exposed to labetalol, such exposure was not associated with neurocognitive deficits [26].

Congenital Heart Disease

With greater success in repairing congenital cardiac disease in the last several decades, more women are surviving to childbearing age. While many conditions are well tolerated in pregnancy, others such as pulmonary hypertension worsen in pregnancy, necessitating preterm delivery. Maternal cyanotic cardiac disease increases the risk for fetal growth restriction and preterm delivery [27]. Long-term outcome data in children exposed prenatally to maternal heart disease are limited.

Pulmonary Disease

Asthma

Asthma in pregnancy increases the risk for both preterm birth and delivery of a SGA infant [28]. Prenatal exposure to maternal asthma is not associated with developmental delay in childhood [29].

Cystic Fibrosis

Despite the theoretical influence of decreased maternal lung function and oxygenation on fetal growth and impaired nutrient intake, cystic fibrosis is not significantly associated with fetal growth restriction, possibly due to the increased co-occurrence of gestational diabetes [30]. Cystic fibrosis is, however, associated with spontaneous preterm labor [30].

Endocrine and Metabolic Disorders

Thyroid Disease

Untreated hypothyroidism adversely affects fetal neurologic development, particularly in early pregnancy [31]. Prior to the onset of fetal thyroid production in the second trimester, the fetus depends on transplacental passage of maternal thyroxine. Via animal models, we understand that maternal thyroid hormone availability (particularly T_4) plays a critical role in cerebral corticogenesis [32]. Endemic hypothyroidism is commonly seen in regions with limited iodine availability because iodine is a precursor to thyroid hormone production. The association between maternal iodine deficiencies and adverse neurodevelopmental was reported as early as 1915 [33]. Iodine replacement in deficient populations has been shown to improve neonatal neurologic outcomes, as was shown in a New Guinean cohort in which a trial of iodine replacement resulted in decreased "endemic cretinism" (diagnosed as retardation of motor milestones, "deaf-mutism," and mental deficiency) [34]. A similar study from a severely iodine-deficient area of China suggested that iodine replacement early in pregnancy was crucial to outcome because severe neurologic abnormalities were seen more commonly among children born to mothers who received iodine supplementation in the third trimester versus the first or second trimesters (9% versus

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2%, $p = 0.008$). Our practice of treating maternal hypothyroidism in pregnancy is supported by a case-control analysis in which children born to women with untreated disease had lower IQ scores at 8 years of age than children of women with normal thyroid-stimulating hormone (100 versus 107, $p = 0.005$) as well as an increase in the frequency of IQ ≤ 85 (19% versus 5%, $p = 0.007$) [35].

Diabetes

Uncontrolled diabetes in the preconception and embryonic period increases the risk of major congenital malformations. The increase in anomalies is attributed to the teratogenic effects of hyperglycemia in combination with excess free-oxygen radicals. The most common birth defects involve the CNS and cardiac, renal, and skeletal systems [36]. In the absence of a structural CNS abnormality, diabetes alone is not thought to contribute directly to poor cognitive function. Within a Danish cohort, offspring of women with type 1 diabetes were noted to obtain lower cognitive scores relative to offspring of healthy mothers, but this difference was no longer significant after consideration for gestational age at delivery and other known confounders [37]. Similarly, in a large population-based Swedish cohort, maternal prepregnancy diabetes was associated with lower offspring cognitive ability among nonsiblings but not within sibships [38].

Gestational diabetes, which has an onset in the latter half of pregnancy, is not associated with an increase in fetal malformations unless the mother has undiagnosed type 2 diabetes with poor glucose control prior to conception. Nor is gestational diabetes associated with poor cognitive function in adult offspring. Within a study comparing the cognitive function of offspring by screening glucose tolerance test levels, there was no significant difference in cognitive test scores after consideration for maternal age and education level and other predictors of cognitive function [39].

Fetal macrosomia occurs more frequently in the setting of maternal diabetes, particularly with poorly controlled disease. These larger fetuses are at greater risk for shoulder dystocia, which can lead to perinatal asphyxia.

In response to maternal hyperglycemia, fetal pancreatic insulin secretion is exaggerated in utero. When neonatal glucose levels fall after delivery, this exaggerated insulin secretion leads to neonatal hypoglycemia, which, if uncorrected, may manifest as hypoglycemic seizure. A history of neonatal hypoglycemia was associated with lower neuromotor and cognitive testing scores among a cohort of infants with abnormal postnatal brain MRI studies [40].

Phenylketonuria

Phenylketonuria is an autosomal recessive disorder of phenylalanine metabolism resulting in high serum levels of phenylalanine, which is a metabolic teratogen [41]. Phenylketonuria is managed with dietary modification limiting proteins, aspartame, and other sources of phenylalanine. During pregnancy, phenylalanine is actively transported to the fetus, with fetal levels 80% higher than maternal levels [42]. Exposure to high phenylalanine levels prenatally leads to significant neurodevelopmental abnormalities including microcephaly, developmental delay, seizure disorders, and autistic-like behaviors [41]. In a large case series of pregnancies affected by maternal phenylketonuria, mental retardation was reported in 92% of neonates with prenatal exposure to phenylalanine levels greater than 1,200 μmol/L [43]. Additional prenatal consequences include IUGR, congenital heart disease, and miscarriage. When maternal phenylalanine levels are well controlled prior to conception (goal range: 100–120 to 250–360 μmol/L), neonatal outcome are significantly improved [44]. Given the severity of these consequences, women with phenylketonuria are advised to delay conception until normalization of phenylalanine levels and to check levels regularly during pregnancy.

Hematologic and Autoimmune Disorders

Fetal and Neonatal Alloimmune Thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of intracranial hemorrhage among term newborns [45]. The condition results from incompatibility between parents for platelet-specific antigens. Fetal-maternal transfer of platelet antigens can lead to maternal development of platelet-specific antibodies that cross the placenta and cause fetal thrombocytopenia. Thrombocytopenia leads to intracranial hemorrhage in 10–20% of affected pregnancies, with the majority (75%) occurring prior to delivery [46]. Within an international registry of

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pregnancies with fetal intracranial hemorrhage caused by FNAIT, while 35% of children died within 4 days of delivery, the majority of infants survived with severe neurologic disability (53%) [47].

Rh Alloimmunization

Maternal alloimmunization to red blood cell antigens, most often those in the Rhesus system, results from antigen incompatibility between parents. Subsequent placental passage of antibodies leads to anemia from destruction of fetal red blood cells. The introduction of Rhogam for the prevention of maternal alloimmunization significantly decreased the incidence of fetal anemia and its associated sequelae (fetal hydrops and death). In the absence of fetal hydrops, fetal anemia requiring intrauterine transfusion is not associated with neurodevelopmental impairment [48].

Antiphospholipid Antibody Syndrome

Certain autoimmune disorders increase the likelihood of fetal growth restriction [49]. Antiphospholipid antibody syndrome, an autoimmune condition associated with poor pregnancy outcome and maternal venous and arterial thromboembolic disease, may lead to fetal growth restriction by limiting early placental invasion and activating coagulation and complement systems leading to fetoplacental vasculopathy [50].

Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune disorder associated with multiple adverse obstetric outcomes, including fetal growth restriction and preeclampsia [51], likely mediated through a combination of limited placental invasion early in pregnancy, renal dysfunction, and abnormal immune activation [52]. Greater risk is seen in the presence of lupus nephritis.

Women with lupus (and similar connective tissue disorders) are more likely to have anti-Ro/SSA and anti-La/SSB antibodies that cross the placenta and bind to fetal cardiomyocytes, causing permanent damage to the fetal atrioventricular node and surrounding tissue leading to congenital heart block. Children born with this condition may require pacemaker placement and in some cases heart transplant. The long-term developmental outcomes are not well described. Prenatal treatment of immune-mediated congenital heart block currently involves maternal administration of dexamethasone, a steroid medication that crosses the placenta [53]. Children exposed to dexamethasone prenatally for suspected congenital adrenal hyperplasia had comparable intelligence and long-term memory to age-matched controls but poorer verbal working memory, poorer self-perception of scholastic competence, and increased self-rated social anxiety [54].

Infection

Maternal bacterial and viral infections may increase the risk for several neuropsychiatric disorders such as schizophrenia, autism, and cognitive delays [55–57].

TORCH Infections

Toxoplasma gondii is a protozoan parasite that infects animal and humans. Humans acquire *Toxoplasma* through exposure to cat feces in contaminated dirt and through undercooked meat. Infected individuals are typically asymptomatic. Congenital *Toxoplasma* infection may cause adverse sequelae, particularly with first-trimester exposure, including deafness, seizures, and low intelligence [58]. Ultrasound findings suggestive of congenital toxoplasmosis include ventriculomegaly and diffuse intracranial calcifications.

Cytomegalovirus (CMV) is a double-stranded DNA virus transmitted through close contact, saliva, blood, and urine and via transplacental passage. Congenital CMV infections occur in 0.4–2.3% of infants (most commonly from a primary maternal infection) [59]. Prenatal ultrasound findings suggestive of fetal infection include microcephaly, ventriculomegaly, and intracranial calcifications. Long-term sequelae of congenital CMV infection includes deafness (from progressive sensorineural hearing loss) [60], delayed psychomotor development, and mental impairment [61,62]. Of congenitally infected infants who are asymptomatic at birth, approximately 10–15% develop clinical symptoms during the first 1–3 years of life.

Congenital varicella infection is associated with neurologic abnormalities, including mental retardation, microcephaly, hydrocephalus, and seizures [63]. Limb hypoplasia and cutaneous scars also may result.

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Chorioamnionitis

Fetal exposure to chorioamnionitis may contribute to fetal and neonatal brain injury, particularly in preterm infants. Risk factors for chorioamnionitis include preterm labor, prolonged rupture of membranes, and colonization with group B *Streptococcus*. Proposed mechanisms of fetal and neonatal brain injury with chorioamnionitis include neuronal loss and altered neuronal migration secondary to proinflammatory cytokines and decreased cerebral autoregulation in the setting of infection [64]. Perhaps the most severe long-term sequela of chorioamnionitis in children born preterm is cerebral palsy (CP) [6], a permanent movement disorder due to brain abnormalities that occurred during development of the fetal or infant brain. Confounding factors include neonatal infections contracted after delivery and necrotizing enterocolitis, which may also contribute to neonatal brain injury [64].

Antibiotic Exposure

Within a large birth cohort (195,909) from the United Kingdom, no associations were found between the use of any antibiotic class and CP or epilepsy [65]. While macrolides were associated with an increased risk of CP or epilepsy in comparison with penicillins, the study did not account for the indication of antibiotic use or gestational age at delivery. While penicillins are prescribed for many conditions during pregnancy (including minor urinary tract and skin infections), macrolides such as azithromycin and erythromycin are typically prescribed for preterm premature rupture of membranes, a condition that is independently associated with poor neurodevelopmental outcomes [66]. Further study is indicated to tease out the independent effects of gestational age and indications for treatment.

Conclusion

Certain maternal diseases may profoundly alter fetal development and contribute to adverse neurodevelopmental outcomes. Women with underlying medical conditions are advised to seek preconception counseling as well as prenatal care with an obstetric specialist in order to optimize control of maternal disease (prior to conception when feasible), evaluate and adjust medication regimens to limit teratogenic exposure and optimize pregnancy outcomes, and inform maternal expectations with regard to neonatal outcome. Communication between the obstetrician and the pediatrician at the time of delivery should include a review of maternal disease states in order to also allow for appropriate neonatal evaluation of potential sequelae.

References

1. Figueras F, Cruz-Martinez R, Sanz-Cortes M, et al. Neurobehavioral outcomes in preterm, growth-restricted infants with and without prenatal advanced signs of brain-sparing. *Ultrasound Obstet Gynecol* 2011; **38**: 288–94.
2. Levine TA, Grunau RE, McAuliffe FM, et al. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review. *Pediatrics* 2015; **135**: 126–41.
3. Murray E, Fernandes M, Fazel M, et al. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. BJOG 2015; **122**: 1062–72.
4. Johnson S, Evans TA, Draper ES, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Arch Dis Childhood Fetal Neonatal Ed* 2015; **100**: F301–8.
5. Serenius F, Kallen K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; **309**: 1810–20.
6. Wu YW, Colford JM, Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA* 2000; **284**: 1417–24.
7. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. *Drug Safety* 2010; **33**: 73–9.
8. Vajda FJ, Hitchcock AA, Graham J, et al. The teratogenic risk of antiepileptic drug polytherapy. *Epilepsia* 2010; **51**: 805–10.
9. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014; **10**: CD010236.
10. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; **12**: 244–52.
11. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav* 2013; **29**: 308–15.

.009

12. Marchenko A, Etwel F, Olutunfese O, et al. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. *Headache* 2015; **55**:490–501.

13. Stewart DE. Clinical practice: depression during pregnancy. *N Engl J Med* 2011; **365**: 1605–11.

14. Mei-Dan E, Ray JG, Vigod SN. Perinatal outcomes among women with bipolar disorder: a population-based cohort study. *Am J Obstet Gynecol* 2015; **212**(367): e1–8.

15. Eriksen HL, Kesmodel US, Pedersen LH, Mortensen EL. No association between prenatal exposure to psychotropics and intelligence at age five. *Acta Obstet Gynaecol Scand* 2015; **94**: 501–7.

16. Streissguth AP, Aase JM, Clarren SK, et al. Fetal alcohol syndrome in adolescents and adults. *JAMA* 1991; **265**: 1961–7.

17. Patra J, Bakker R, Irving H, et al. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA): a systematic review and meta-analyses. *BJOG* 2011; **118**: 1411–21.

18. Falgreen Eriksen HL, Kesmodel US, et al. Effects of tobacco smoking in pregnancy on offspring intelligence at the age of 5. *J Pregnancy* 2012; **2012**:945196.

19. Gilman SE, Gardener H, Buka SL. Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? *Am J Epidemiol* 2008; **168**: 522–31.

20. Behnke M, Smith VC, Committee on Substance A, Committee on F, Newborn. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013; **131**:e1009–24.

21. Creasy R, Resnik R, Iams J, et al. *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice*, 7th edn. New York: Elsevier Saunders, 2014.

22. Kronenberg ME, Raz S, Sander CJ. Neurodevelopmental outcome in children born to mothers with hypertension in pregnancy: the significance of suboptimal intrauterine growth. *Dev Med Child Neurol* 2006; **48**: 200–6.

23. Ehrenstein V, Rothman KJ, Pedersen L, et al. Pregnancy-associated hypertensive disorders and adult cognitive function among Danish conscripts. *Am J Epidemiol* 2009; **170**: 1025–31.

24. Walker CK, Krakowiak P, Baker A, et al. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatrics* 2015; **169**: 154–62.

25. Bortolus R, Ricci E, Chatenoud L, Parazzini F. Nifedipine administered in pregnancy: effect on the development of children at 18 months. *BJOG* 2000; **107**: 792–4.

26. Chan WS, Koren G, Barrera M, et al. Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database. *Hypertension in Pregnancy* 2010; **29**: 271–83.

27. Sawhney H, Suri V, Vasishta K, et al. Pregnancy and congenital heart disease: maternal and fetal outcome. *Aust NZ J Obstet Gynaecol* 1998; **38**: 266–71.

28. Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy: a population based study. *Eur J Epidemiol* 2000; **16**: 167–71.

29. Lyall K, Ashwood P, Van de Water J, Hertz-Picciotto I. Maternal immune-mediated conditions, autism spectrum disorders, and developmental delay. *J Autism Dev Disord* 2014; **44**: 1546–55.

30. Patel EM, Swamy GK, Heine RP, et al. Medical and obstetric complications among pregnant women with cystic fibrosis. *Am J Obstet Gynecol* 2015; **212**(98):e1–9.

31. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol* 2004; **151**(Suppl. 3): U25–37.

32. Lavado-Autric R, Auso E, Garcia-Velasco JV, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. *J Clin Invest* 2003; **111**: 1073–82.

33. Gyamfi C, Wapner RJ, D'Alton ME. Thyroid dysfunction in pregnancy: the basic science and clinical evidence surrounding the controversy in management. *Obstet Gynecol* 2009; **113**: 702–7.

34. Pharoah PO, Buttfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* 1971; **1**: 308–10.

35. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; **341**: 549–55.

36. Schaefer-Graf UM, Buchanan TA, Xiang A, et al. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am J Obstet Gynecol* 2000; **182**: 313–20.

37. Clausen TD, Mortensen EL, Schmidt L, et al. Cognitive function in adult offspring of women with type 1 diabetes. *Diabetic Med* 2011; **28**: 838–44.

38. Fraser A, Almqvist C, Larsson H, et al. Maternal diabetes in pregnancy and offspring cognitive ability:

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.009

sibling study with 723,775 men from 579,857 families. *Diabetologia* 2014; **57**: 102–9.

39. Clausen TD, Mortensen EL, Schmidt L, et al. Cognitive function in adult offspring of women with gestational diabetes–the role of glucose and other factors. *PloS One* 2013; **8**: e67107.
40. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. *J Pediatr* 2012; **161**: 88–93.
41. American Academy of Pediatrics CoG. Maternal phenylketonuria. *Pediatrics* 2008; **122**: 445–9.
42. Cetin I, Corbetta C, Sereni LP, et al. Umbilical amino acid concentrations in normal and growth-retarded fetuses sampled in utero by cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 253–61.
43. Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia: an international survey of the outcome of untreated and treated pregnancies. *N Engl J Med* 1980; **303**: 1202–8.
44. Rouse B, Azen C, Koch R, et al. Maternal Phenylketonuria Collaborative Study (MPKUCS) offspring: facial anomalies, malformations, and early neurological sequelae. *Am J Med Genet* 1997; **69**:89–95.
45. Pacheco LD, Berkowitz RL, Moise KJ Jr, et al. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. *Obstet Gynecol* 2011; **118**: 1157–63.
46. Pearson HA, Shulman NR, Marder VJ, Cone TE Jr. Isoimmune neonatal thrombocytopenic purpura: clinical and therapeutic considerations. *Blood* 1964; **23**: 154–77.
47. Tiller H, Kamphuis MM, Flodmark O, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. *BMJ Open* 2013; **3**.
48. Weisz B, Rosenbaum O, Chayen B, et al. Outcome of severely anaemic fetuses treated by intrauterine transfusions. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**: F201–4.
49. Copel JA, Bahtiyar MO. A practical approach to fetal growth restriction. *Obstet Gynecol* 2014; **123**: 1057–69.
50. Tong M, Viall CA, Chamley LW. Antiphospholipid antibodies and the placenta: a systematic review of their in vitro effects and modulation by treatment. *Hum Reprod Update* 2015; **21**: 97–118.
51. Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010; **5**: 2060–8.
52. Ostensen M, Clowse M. Pathogenesis of pregnancy complications in systemic lupus erythematosus. *Curr Opin Rheumatol* 2013; **25**: 591–6.
53. Friedman DM, Kim MY, Copel JA, et al. Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) study. *Am J Cardiol* 2009; **103**: 1102–6.
54. Hirvikoski T, Nordenstrom A, Lindholm T, et al. Cognitive functions in children at risk for congenital adrenal hyperplasia treated prenatally with dexamethasone. *J Clin Endocrinol Metab* 2007; **92**: 542–8.
55. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med* 2013; **43**: 239–57.
56. Atladottir HO, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. *Pediatrics* 2012; **130**: e1447–54.
57. Zerbo O, Iosif AM, Walker C, et al. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. *J Autism Dev Disord* 2013; **43**:25–33.
58. Roizen N, Swisher CN, Stein MA, et al. Neurologic and developmental outcome in treated congenital toxoplasmosis. *Pediatrics* 1995; **95**:11–20.
59. Demmler GJ, Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. *Rev Infect Dis* 1991; **13**: 315–29.
60. Foulon I, Naessens A, Foulon W, et al. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. *J Pediatr* 2008; **153**: 84–8.
61. Lanari M, Lazzarotto T, Venturi V, et al. Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics* 2006; **117**: e76–83.
62. Fowler KB, Stagno S, Pass RF, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992; **326**: 663–7.
63. Sauerbrei A, Wutzler P. The congenital varicella syndrome. *J Perinatol* 2000; **20**: 548–54.

.009

64. Chau V, McFadden DE, Poskitt KJ, Miller SP. Chorioamnionitis in the pathogenesis of brain injury in preterm infants. *Clin Perinatol* 2014; **41**: 83–103.

65. Meeraus WH, Petersen I, Gilbert R. Association between antibiotic prescribing in pregnancy and cerebral palsy or epilepsy in children born at term: a cohort study using the health improvement network. *PloS One* 2015; **10**: e0122034.

66. Manuck TA, Varner MW. Neonatal and early childhood outcomes following early vs later preterm premature rupture of membranes. *Am J Obstet Gynecol* 2014; **211**(308): e1–6.

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Chapter 9

Obstetric Conditions and Practices that Affect the Fetus and Newborn

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Placenta Previa

The implantation of the placenta over the cervical os or very near to it is known as *placenta previa*. Because the use of transvaginal ultrasonography allows for precise localization of the placental edge and the cervical os, the old characterization of previas as complete, partial, and marginal has been modified to eliminate the terms *partial* and *marginal* [1]. Instead, all placentas overlying the os to any degree are termed *previas*, those near to but not overlying the os are termed *low lying*, and the distance the placental edge measures from the os is reported for low-lying placentas [1].

Incidence

The incidence of placenta previa is about 1/200 singleton pregnancies at term [2,3]. In an unscarred uterus it has been reported to be 0.26%, and it increases almost linearly with the number of prior cesarean deliveries, up to 10% in patients with four or more prior cesareans [4]. Other risk factors include previous spontaneous and elective pregnancy terminations and previous uterine surgery [5]. Although the pathophysiology of placenta previa remains uncertain, there appears to be an association between endometrial damage and uterine scarring and subsequent previa.

Etiology and Risk Factors

The likelihood of placenta previa rises with multiparity [6], increasing maternal age, especially in women older than 35 years of age [2], and a history of prior cesarean deliveries [7]. Smoking during pregnancy can double the risk of this condition [8,9], and women of Asian origin have been reported to have an increased risk of a delivery complicated by placenta previa compared with Caucasian women [10].

Clinical Presentation and Diagnosis

The classic symptom of placenta previa is painless bright red vaginal bleeding in the second or third trimester. In fact, almost three-quarters of all women with placenta previa experience at least one episode of painless antepartum bleeding, which usually presents without warning. In most situations, the initial episode resolves spontaneously [11]. The antepartum diagnosis of placenta previa is based primarily on ultrasonographic visualization of the placental location and its relationship to the internal cervical os. Transvaginal sonography is more accurate than transabdominal sonography in making the diagnosis [12,13]. Transperineal [14] and translabial ultrasonography [15] may also provide good resolution of the internal os. Placenta previa has been diagnosed in 5% of patients undergoing ultrasound examination at between 16 and 18 weeks; 90% of these placentas are no longer identified as previas in the third trimester, however. This phenomenon has been called *placental migration*. In these patients, extra care is not required unless the diagnosis persists beyond 30 weeks of gestation or if the patient becomes symptomatic before that time. In general, the earlier in pregnancy the initial episode of bleeding occurs, the worse is the outcome of the pregnancy [16].

Management

Management of placenta previa varies according to the clinical situation. In preterm pregnancies with no active bleeding, expectant management is the general rule. Strict bed rest, blood transfusions as required, administration of corticosteroids to reduce the rate and severity of fetal respiratory distress syndrome, and the occasional use of tocolytic agents for inhibition of premature labor in the presence of vaginal bleeding are appropriate in the conservative aggressive management of this condition [17–19]. One of the most controversial issues is whether the mother

should be kept hospitalized after she has been stabilized. D'Angelo and Irwin reported an improved outcome in neonatal morbidity in these patients maintained in hospital [20], but Wing et al. noted that in selected patients, outpatient management may be safe and appropriate [21]. Anti-D immunoglobulin should be given after a bleeding episode if the patient is Rh negative. It is advisable to perform a scheduled cesarean delivery after determination of fetal pulmonary maturity: this approach significantly reduces overall neonatal morbidity and mortality [17]. Emergent and expeditious cesarean delivery, however, may be warranted in cases of persistent hemorrhage, failed tocolysis, fetal distress, or coagulopathy.

Complications

Major maternal complications of placenta previa are related to massive bleeding leading to hemorrhagic shock. Following placental removal, hemorrhage at the site of implantation may occur. Almost 7% of placenta previa patients have an abnormal placental attachment to the myometrium (see section on placenta accreta). If uterotonic medication, hemostatic sutures, and other conservative methods fail to control the hemorrhage, hysterectomy may be necessary.

Some investigators have reported a high incidence of fetal growth restriction with previa [22]. Others have not found this association after controlling for gestational age [23]. Fetal complications are highly correlated with gestational age at delivery. Despite tocolysis and transfusions to delay delivery, 44.4% deliver before 36 weeks [24].

The perinatal mortality due to placenta previa is increased three- to fourfold [25]. Crane et al., in a population-based retrospective cohort study of over 92,000 births in Nova Scotia, Canada, identified 305 cases of placenta previa [26]. The perinatal mortality rate in their patients was 2.3%, compared with 0.78% in control individuals. These investigators also noted no differences in birth weights after controlling for gestational age in the patients and controls. After controlling for potential confounders, neonatal complications associated with placenta previa included major congenital anomalies, respiratory distress syndrome, and anemia [26]. There is a significant correlation between antepartum maternal hemorrhage and the need for neonatal transfusion and between neonatal anemia and the amount of intrapartum maternal blood loss [16].

Summary

Placenta previa is a life-threatening condition for the mother and the fetus. Prompt diagnosis by ultrasound and treatment with strict bed rest, tocolysis, and blood transfusions are mainstays of care. A planned cesarean delivery as close to term as feasible and with documented fetal maturity is optimal. Emergent preterm delivery is frequently necessary, however.

Placental Abruption

The premature separation of the normally implanted placenta is known as *placental abruption*. Usually this phenomenon is accompanied by painful uterine contractions and a variable amount of vaginal bleeding. Bleeding may also be concealed behind the detached placenta.

Incidence

The incidence of placental abruption is between 5 and 7/1,000 births [27,28]. Ananth and Wilcox, evaluating 7,508,655 singleton births in the United States in the years 1995–6, found that abruption was encountered in 6.5/1,000 live births [29]. A perinatal mortality rate of 119/1,000 live births has been reported [29], and up to 14% of the fetuses that survive may have significant neurologic deficits [30].

Etiology and Risk Factors

Although the precise cause of placental abruption remains unknown, various risk factors have been identified. Many reports suggest that the incidence increases with advancing maternal age and parity [31,32], although other studies have been unable to confirm this association [33,34]. It has also been reported to be more common in African-American women than Caucasians and less frequent in Hispanic women [31]. There is a strong association of this condition with hypertension, either preexisting or pregnancy associated [28,35–37], with a threefold increased incidence of abruption with chronic hypertension and a fourfold increase with severe preeclampsia [38]. Women who smoke during their pregnancies also have an increased risk of abruption [39]. If one adds the effects of smoking and hypertension during pregnancy, the risk is increased even greater [28]. There is also an increased incidence of abruption with premature rupture of membranes [36], especially in patients who have recurrent bleeding episodes during the period of expectant management [40,41]. Studies have consistently documented placental

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abruption as a maternal reproductive risk associated with cocaine use [42–44]. Recent reports have also found an increased frequency of genetic thrombophilias in patients with placental abruption [45,46]. Placental abruption may also be present even in cases of minor trauma and may not be an immediately evident condition clinically [47,48]. Uterine leiomyomas may predispose to abruption, especially if they are located behind the placental implantation site [49]. A history of placental abruption may increase the risk of occurrence up to 10-fold in subsequent pregnancies [27]. Other risk factors associated with this condition include severe fetal growth restriction, chorioamnionitis, polyhydramnios, a short umbilical cord, sudden uterine decompression, external version, and diabetes [32,33,50].

Clinical Presentation and Diagnosis

Because of the wide variety of signs and symptoms associated with placental abruption, it is necessary to have a high index of suspicion to make an accurate diagnosis. The clinical spectrum ranges from asymptomatic states in which the diagnosis is made only after delivery on evaluation of the placenta to cases with fetal demise, maternal hypovolemic shock, and severe coagulopathy. The most common presentation, however, is an acute onset of vaginal bleeding accompanied by intermittent cramping or constant abdominal pain. Other findings that may be present are nonreassuring fetal status, frequent and intense contractions, preterm labor, and intrauterine fetal demise [51]. Ultrasound visualization of a clot occurs in only about 25% of the patients and appears to have little or no impact on course or management. The absence of these findings should not preclude the diagnosis. Ultrasound assessment and clinical inspection are both essential to rule out placenta previa and other causes of bleeding, however. In assessing a woman with placental abruption, the possibility of physical abuse or the use of cocaine must not be disregarded. Unless specific questions about these issues are posed, the precipitating cause of the abruption may not be identified [50].

Management

Once the diagnosis of placental abruption has been made, intravenous access, blood-product availability, and maternal hemodynamic stability must be secured. The next step in management will depend on gestational age and maternal and fetal statuses.

In preterm pregnancies without evidence of maternal or fetal compromise, expectant management may be considered. Tocolysis in this clinical situation is a matter of controversy [51–53]. Administration of steroids should be considered, in the hope of reducing the risk of fetal respiratory distress syndrome.

Expectant management generally is not a choice for most patients, and delivery is indicated because of maternal or fetal deterioration or both. Delivery is also indicated in viable, mature fetuses. If vaginal delivery is not imminent, cesarean section is the best approach. However, if the fetus has died or the mother is anticipated to deliver vaginally in the immediate future, labor can be pursued, provided that the mother does not continue to have deterioration of her clinical status. Cesarean delivery in the case of fetal demise should be reserved for maternal indications alone [20]. Rh-negative mothers with placental abruption require anti-D immunoglobulin to avoid Rh isoimmunization.

Complications

Most of the serious maternal complications of placental abruption are related to hypovolemia secondary to maternal hemorrhage, which may lead to acute renal and other organ failure. Almost 40% of cases of renal failure in pregnancy are secondary to placental abruption [54]. Abruption is also the most frequent cause of disseminated intravascular coagulation (DIC) in pregnancy. DIC may aggravate hemorrhagic problems, is found in about 30% of women with abruption, and may be severe enough to cause fetal demise [55]. With respect to the fetus, most of the complications result from prematurity and hypoxia. Low-birth-weight infants delivered after placental abruption tend to have low Apgar scores and are at increased risk of neonatal death and the development of intraventricular hemorrhage and cerebral palsy [56].

Summary

Placental abruption is an extremely dangerous condition for both the mother and the fetus, carrying significant morbidity and mortality for both. The diagnosis requires a high index of suspicion as well as prompt assessment of the fetal and maternal statuses. Whether expectant management or expeditious delivery is warranted depends on the severity of the condition and the gestational age at the time of diagnosis.

The route of delivery is dictated by the severity of the condition and the viability of the fetus.

Vasa Previa

Vasa previa is a rare condition in which the fetal blood vessels, unsupported by either the umbilical cord or placental tissue, traverse the fetal membranes of the lower segment of the uterus below the presenting part and directly over the cervix. This condition typically arises when the umbilical cord inserts into the placental membranes (velamentous cord insertion) near the cervix. It can also arise when a placenta previa or low-lying placenta "migrates" away from the lower uterine segment, leaving the cord insertion behind, attached only to membranes (velamentous insertion). If the fetal vessels between the umbilical cord and the main placental disk happen to traverse close to the cervix, a vasa previa would result. A vasa previa can also result from fetal vessels traversing over the cervix in their journey from the succenturiate lobe of a placenta to the main placenta disk or between two lobes of a bilobed placenta.

Incidence

It is difficult to estimate the true incidence of this condition because vasa previa is likely to be underreported. It has been estimated to occur in about ½,000 to 1/3,000 deliveries. Thus a relatively active obstetric service may expect one case per year [57].

Etiology and Risk Factors

Vasa previa has been associated with in vitro fertilization (IVF), multiple pregnancies, low-lying placentas, and multilobed or succenturiate placentas [58–60]. It is not clear why IVF appears to be associated with vasa previa [11,14,18]. A study of 100 placentas from IVF pregnancies revealed 14 cases of velamentous insertion among them [18]. This prevalence was higher than the prevalence of velamentous cord insertion in the general population, even after correcting for the higher prevalence of velamentous insertion in multiple pregnancies [18]. Similarly, in a recent study, Schachter et al. found an incidence of vasa previa at their institution of 1/293 IVF deliveries compared with a vasa previa rate of 1/6,068 total deliveries [11].

Clinical Presentation and Diagnosis

The usual clinical presentation of this condition is vaginal bleeding after either spontaneous or artificial rupture of membranes, leading to rupture of the velamentous vessels and fetal death from exsanguination. However, vessel rupture may occur independent of membrane rupture; therefore, this condition should be suspected in any patient with antepartum or intrapartum hemorrhage [61]. Occasionally, fetal heart rate abnormalities such as progressive severe variable decelerations, fetal bradycardia, or a sinusoidal pattern due to fetal anemia may be the only manifestations of vasa previa [62,63].Transabdominal and transvaginal ultrasound with color Doppler is the current method used for the antenatal diagnosis of vasa previa [64–68]. Pulsed-wave Doppler placed directly over vessels can help to distinguish between maternal and fetal pulsations. Three-dimensional ultrasound has also been reported as a useful diagnostic tool for this condition [69]. In situations where the source of vaginal bleeding is uncertain and maternal and fetal status are stable, hemoglobin denaturing tests such as the bedside Apt test may help to distinguish between fetal and maternal blood, thereby establishing the origin and therefore the acuity of the bleed.

Management

If the diagnosis of vasa previa has been made antenatally and there is no evidence of fetal compromise, the safest form of delivery would be by planned cesarean at between 34 and 36 weeks [70,71]. This is earlier than the 39 weeks that is generally recommended for elective cesarean delivery, but it mitigates the risk of membrane rupture and fetal exsanguination prior to delivery. Immediate delivery is mandatory in a viable pregnancy in the setting of bleeding from a vasa previa. The infant has a total blood volume of approximately 250 mL at term and is therefore very intolerant of blood loss. If the cervix is fully dilated and vaginal delivery can be accomplished rapidly, this becomes the route of choice [57]. Vaginal delivery is also indicated when the fetus is too immature to survive or when fetal demise has already occurred. An emergency cesarean delivery provides the most favorable outcome if performed immediately on recognition of the condition. Optimizing neonatal outcome requires rapid and aggressive neonatal resuscitative techniques. These include immediate basic and advanced life support measures and establishment of vascular access for fluids, blood, and blood component therapy [72]. Rh-negative patients should receive anti-D immunoglobulin when indicated. Because of the risk

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of unexpected and catastrophic hemorrhage from fetal vessels, admission to the hospital early in the third trimester may be reasonable. An alternative approach is to follow the pregnancy with serial transvaginal cervical length determinations, along with hospitalization should the patient experience contractions or spotting. It is unknown whether either plan would be successful in averting bad outcomes associated with unexpected premature rupture of membranes or preterm labor, but hospitalized patients theoretically might have a better chance. Elective cesarean delivery at between 34 and 36 weeks of gestation is reasonable when considering benefits and risks. Because of the potential for emergency preterm delivery, consideration should be given to administering steroids to promote fetal lung maturation.

Complications

Vasa previa is an obstetric condition that may have catastrophic consequences for the fetus. If unsuspected hemorrhage occurs from a vasa previa, immediate delivery and aggressive resuscitation of the newborn are mandatory, but this carries a high neonatal morbidity and mortality. Prenatal diagnosis by transabdominal and transvaginal ultrasound, with cesarean delivery before rupture of membranes, appears to dramatically improve the neonatal outcome. In women at increased risk (those with second-trimester low-lying placentas, pregnancies resulting from IVF, and accessory placental lobes), transvaginal color Doppler sonography of the region over the cervix should be considered if vasa previa cannot be excluded by transabdominal sonography. Neonates delivered after vasa previa diagnosed prenatally have a significantly higher chance of survival, higher Apgar scores, and a lower incidence of blood transfusions than cases not diagnosed prenatally.

Summary

Vasa previa is mainly a risk to the fetus. The fetal mortality rate ranges from 33% to 100% [64]. Complications are associated with bleeding from fetal vessels prior to and during labor and after rupture of membranes. In a recent review of 155 cases of vasa previa [57], the overall perinatal mortality was 36%. The only significant predictors of neonatal survival were prenatal diagnosis and gestational age at delivery. Of the patients who did not have prenatal diagnosis, intrapartum bleeding occurred in 41/94 (44%) [57]. The most striking finding was that when the diagnosis was made prenatally, more than 96% of infants survived, whereas more than half of all fetuses/infants died when there was no prenatal diagnosis. Among survivors when the diagnosis had not been made prenatally, 1- and 5-minute Apgar scores were very low (median 1 and 4, respectively). In addition, more than half the surviving neonates required blood transfusions when the diagnosis was not made prenatally.

Placenta Accreta

Placenta accreta is an abnormality in placental implantation in which the placental chorionic villi are attached to the myometrium instead of to the decidua basalis and the stratum spongiosum. Placenta accreta can be further specified as placenta increta where the villi invade into the myometrium and placenta percreta where the villi reach the uterine serosa and may invade surrounding structures such as the bladder or rectum.

Incidence

Once a rare occurrence in obstetrics with an incidence of less than 1/30,000 deliveries in the 1930s to 1950s, placenta accreta now occurs as often as 1/300 deliveries, largely as a result of an increase in rates of cesarean delivery [73].

Etiology and Risk Factors

The mechanism behind the abnormal placentation of placenta accreta is hypothesized to be a dysfunctional or absent decidua basalis, particularly in the scarred uterus. Risk factors identified for placenta accreta include any surgery that damages or transects the endometrium, such as uterine curettage, myomectomy, pelvic radiation, and endometrial ablation [74–76], advanced maternal age, smoking, IVF, multiparity, previa, and a short interval between a prior cesarean delivery and subsequent pregnancy [77–79].

The risk of accreta with prior cesarean delivery and the existence of a placenta previa has been shown to be 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more repeat cesarean deliveries, respectively [80].

Clinical Presentation and Diagnosis

The first clinical sign of placenta accreta is often the failure of placental separation to occur, usually at the time of repeat cesarean delivery, with attendant profuse hemorrhage. The intraoperative diagnosis of

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placenta percreta may be made by visualization of placental invasion through the uterine wall and/or into adjacent structures, with invasion of the bladder most common. Prenatal diagnosis of placenta accreta has gained much attention recently. Ultrasound serves as the mainstay for diagnosis, which can sometimes be made as early as the first trimester when a cesarean scar ectopic or lower uterine segment implantation is identified. Diagnosis of accrete in the second and third trimesters is more common, when a combination of transabdominal and transvaginal ultrasound with color and pulse Doppler will detect the turbulent lacunar blood flow and increased subplacental blood flow seen in most accretas. The use of these and other criteria in experienced centers has resulted in reported sensitivities and specificities as high as 80–90% [81,82]. MRI may also be helpful, particularly in cases where the placenta is posterior or there is suspected percreta [81,83].

Management

The mainstays of management include a planned cesarean delivery at an experienced center ("center of excellence" for placenta accreta) [84], usually between 34 and 36 weeks of gestation, individualized based on stability [84,85]. A lower threshold for delivery is often employed because specialty anesthesia and surgery teams, as well as blood products, may be required for intraoperative management of expected hemorrhage. Hysterectomy is the definitive treatment, although uterine preservation in rare circumstances has been described [86].

Complications

Fetal and neonatal effects of placenta accreta have not been well documented, but because most cases of placenta accreta occur in the setting of placenta previa, the attendant perinatal risks of placenta previa can be presumed to occur with placenta accreta. Although limited by its format as a questionnaire of practicing perinatologists, one review showed a 9% perinatal mortality rate, largely due to previable iatrogenic deliveries. The rising rate of cesarean delivery has prompted investigators to examine the potential increased maternal and fetal risks of repeat cesarean delivery, particularly in the setting of placenta previa. A recent large study of patients undergoing cesarean delivery for placenta previa showed an increase in adverse maternal outcome as the number of prior cesarean deliveries rose; adverse perinatal outcomes and gestational age at delivery, however, remained unrelated to the number of prior cesarean deliveries [87].

Summary

Placenta accreta is a maternally life-threatening condition of abnormal placentation growing in incidence, largely related to an increased rate of cesarean delivery. Although prenatal imaging techniques such as ultrasound and MRI do not have perfect sensitivity and specificity for predicting placenta accreta, these tests, when coupled with a high index of suspicion in patients most at risk, can provide invaluable information and therefore allow the practitioner to prepare adequately for massive hemorrhage and surgical intervention at the time of delivery.

Miscellaneous Cord and Placental Abnormalities

The presence of a short umbilical cord at delivery historically has been associated with increasing the predictive value of low Apgar scores for subsequent low IQ scores and neurologic abnormalities [88]. A recent large retrospective review of short cord diagnosed after delivery showed an association between short cord in nonanomalous singleton pregnancies and maternal labor and delivery complications, as well as death within the first year, among term infants [89]. Variation exists, however, in the reference standards for diagnosis of short cord, and the inability to reliably diagnose the entity in the antenatal period limits the utility of the predictive power of the diagnosis. The diagnosis has utility mainly in postnatal life, where there is a suggestion that neonates born with short umbilical cords may benefit from increased monitoring.

Postnatally diagnosed marginal cord insertion, often defined as a placental cord insertion within 1–2 cm of the placental edge, has classically been associated with reduced birth weight [90]. Recent advances in Doppler ultrasound have allowed the diagnosis to be made in the antenatal period; a recent retrospective review, however, failed to show an association between marginal cord insertion and increased risks of growth restriction and preterm delivery [91].

Postnatally diagnosed velamentous cord insertion has also been associated with low birth weight,

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preterm delivery, low Apgar scores, and abnormal fetal heart rate patterns [92]. Doppler ultrasound has also allowed for the antenatal diagnosis of velamentous cord insertion, with recent data suggesting an association between antenatally diagnosed velamentous insertions into the lower third of the uterus and intrapartum heart rate abnormalities [93].

References

1. Reddy UM, Abuhamad AZ, Levine D, Saade GR; Fetal Imaging Workshop Invited Participants. Fetal imaging: executive summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for MaternalFetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging workshop. *J Ultrasound Med* 2014; **33**: 745–57.
2. Iyasu S, Saftlas AK, Rowley DL, et al. The epidemiology of placenta previa in the United States, 1979 through 1987. *Am J Obstet Gynecol* 1993; **168**: 1424–9.
3. Cresswell JA, Ronsmans C, Calvert C, Filippi V. Prevalence of placenta praevia by world region: a systematic review and meta-analysis. *Trop Med Int Health* 2013; **18**: 712–24.
4. Clark SL, Koonings PP, Phelan JP. Placenta previa/accreta and prior cesarean sections. *Obstet Gynecol* 1985; **66**:89–92.
5. Ananth CV, Smulian JC, Vintzileos AM. The association of placenta previa with history of cesarean delivery and abortion: a metaanlysis. *Am J Obstet Gynecol* 1997; **177**: 1071–8.
6. Babinszki A, Kerenyi T, Torok O, et al. Perinatal outcome in grand and great grand multiparity: effects of parity on obstetric risk factors. *Am J Obstet Gynecol* 1999; **181**: 669–74.
7. Ananth CV, Smulian JC, Vintzileos AM. The association of placenta previa with history of cesarean delivery and abortion: a metaanalysis. *Am J Obstet Gynecol* 1997; **177**: 1071–8.
8. Williams MA, Mittendorf R, Lieberman E, et al. Cigarette smoking during pregnancy in relation to placenta previa. *Am J Obstet Gynecol* 1991; **165**:28–32.
9. Handler AS, Mason ED, Rosenberg DL, et al. The relationship between exposure during pregnancy to cigarette smoking and cocaine use and placenta previa. *Am J Obstet Gynecol* 1994; **170**: 884–9.
10. Schachter M, Torbin Y, Arieli S, et al. In vitro fertilization is a risk factor for vasa previa. *Fertil Steril* 2002; **78**: 642–3.
11. Love CD, Wallace EM. Pregnancies complicated by placenta previa: what is appropriate management? *Br J Obstet Gynaecol* 1996; **103**: 864–7.
12. Farine D, Fox HE, Jakobson S, et al. Is it really a placenta previa? *Eur J Obstet Gynecol Reprod Biol* 1989; **31**: 103–8.
13. Smith RS, Lauria MR, Comstock CH, et al. Transvaginal ultrasonography for all placentas that appear to be low lying or over the internal cervical os. *Ultrasound Obstet Gynecol* 1997; **9**: 22–4.
14. Hertzberg BS, Bowie JD, Carroll BA, et al. Diagnosis of placenta previa during the third trimester: role of transperineal sonography. *AJR Am J Roetgenol* 1992; **159**: 83–7.
15. Dawson WB, Dumas MD, Romano WM, et al. Translabial ultrasonography and placenta previa: does measurement of the os-placenta distance predict outcome? *Ultrasound Med* 1996; **15**: 441–6.
16. McShane PM, Heyl PS, Epstein MF. Maternal and perinatal morbidity resulting from placenta previa. *Obstet Gynecol* 1985; **65**: 176–82.
17. Cotton DB, Read JA, Paul RH, et al. The conservative aggressive management of placenta previa. *Am J Obstet Gynecol* 1980; **137**: 687–95.
18. Besinger RE, Moniak CW, Paskiweicz LS, et al. The effect of tocolytic use in the management of symptomatic placenta previa. *Am J Obstet Gynecol* 1995; **172**: 1770–5.
19. Chamberlain G, Steer P. ABC of labour care: obstetric emergencies. *BMJ* 1999; **318**: 1342–5.
20. D'Angelo LJ, Irwin LF. Conservation management of placenta previa: a cost-benefit analysis. *Am J Obstet Gynecol* 1984; **149**: 320–6.
21. Wing DA, Paul RH, Millar LK. Management of the symptomatic placenta previa: a randomized, controlled trial of inpatient versus outpatient expectant management. *Am J Obstet Gynecol* 1996; **175**: 806–11.
22. Brar HS, Platt LD, De Vore GR, et al. Fetal umbilical velocimetry for the surveillance of pregnancies complicated by placenta previa. *Reprod Med* 1988; **33**: 741–4.
23. Wolf EJ, Mallozi A, Rodis JF, et al. Placenta previa is not an independent risk factor for a small for gestational age infant. *Obstet Gynecol* 1991; **77**: 707–9.
24. Ananth CV, Demisse K, Smulian JC, Vintzileos AM. Placenta previa in singleton and twin births in the United States, 1989 through 1998: a comparison of risk factor profiles and associated conditions. *Am J Obstet Gynecol* 2003; **188**: 275–81.
25. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-

based study in the United States, 1989 through 1997. *Am J Obstet Gynecol* 2003; **188**: 1299–304.

26. Crane JM, van den Hof MC, Dodds L, et al. Neonatal outcomes with placenta previa. *Obstet Gynecol* 1999; **93**: 541–4.
27. Kåregård M, Gennser G. Incidence and recurrence rate of abruptio placentae in Sweden. *Obstet Gynecol* 1986; **67**: 523–8.
28. Ananth CV, Smulian JC, Vintzileos AM. Incidence of placental abruption in relation to cigarette smoking and hypertensive disorders during pregnancy: a meta-analysis of observational studies. *Obstet Gynecol* 1999; **93**: 622–8.
29. Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. *Am J Epidemiol* 2001; **153**: 332–7.
30. Abdella TN, Sibai BM, Hays JM, et al. Perinatal outcome in abruptio placentae. *Obstet Gynecol* 1984; **63**: 365–70.
31. Pritchard JA, Cunningham FG, Pritchard SA, et al. On reducing the frequency of severe abruptio placentae. *Am J Obstet Gynecol* 1991; **165**: 1345–51.
32. Kramer MS, Usher RH, Pollack R, et al. Etiologic determinants of abruptio placentae. *Obstet Gynecol* 1997; **89**: 221–6.
33. Krohn M, Voig L, McKnight B, et al. Correlates of placental abruption. *Br J Obstet Gynaecol* 1987; **94**: 333–40.
34. Toohey JS, Keegan KA, Morgan MA, et al. The "dangerous multipara": fact or fiction? *Am J Obstet Gynecol* 1995; **172**: 683–6.
35. Ananth CV, Savitz DA, Williams MA. Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. *Obstet Gynecol* 1996; **88**: 309–18.
36. Ananth CV, Savitz DA, Bowes WA, et al. Influence of hypertensive disorders and cigarette smoking on placental abruption and uterine bleeding during pregnancy. *Br J Obstet Gynaecol* 1997; **104**: 572–8.
37. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development network of maternal–fetal medicine units. *N Engl J Med* 1998; **339**: 667–71.
38. Ananth CV, Berkowitz GS, Savitz DA, et al. Placental abruption and adverse perinatal outcomes. *JAMA* 1999; **282**: 1646–51.
39. Misra DP, Ananth CV. Risk factor profiles of placental abruption in first and second pregnancies: heterogeneous etiologies. *J Clin Epidemiol* 1999; **52**: 453–61.
40. Gonen R, Hannah ME, Milligan JE. Does prolonged premature rupture of the membranes predispose to abruptio placentae? *Obstet Gynecol* 1989; **74**: 347–50.
41. Major CA, de Veciana M, Lewis DF, et al. Preterm premature rupture of membranes and abruptio placentae: is there an association between these pregnancy complications? *Am J Obstet Gynecol* 1995; **172**: 672–6.
42. Bingol N, Fuchs M, Diaz V, et al. Teratogenicity of cocaine in humans. *J Pediatr* 1987; **110**: 93–6.
43. Hoskins IA, Friedman DM, Frieden FJ, et al. Relationship between antepartum cocaine abuse, abnormal umbilical artery Doppler velocimetry, and placental abruption. *Obstet Gynecol* 1991; **78**: 279–82.
44. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol* 1992; **79**: 778–89.
45. Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999; **340**: 50–2.
46. Gherman RB, Goodwin TM. Obstetric implications of activated protein C resistance and factor V Leiden mutation. *Obstet Gynecol Surv* 2000; **55**: 117–22.
47. Kettel LM, Branch DW, Scott JR. Occult placental abruption after maternal trauma. *Obstet Gynecol* 1988; **71**: 449–53.
48. Stafford PA, Biddinger PW, Zumwalt RE. Lethal intrauterine fetal trauma. *Am J Obstet Gynecol* 1988; **159**: 485–9.
49. Rice JP, Kay HH, Mahony BS. The clinical significance of uterine leiomyomas in pregnancy. *Am J Obstet Gynecol* 1989; **160**: 1212–16.
50. Nimrod CA, Oppenheimer LW. *Medicine of the Fetus and Mother*, 2nd edn. Philadelphia: Lippincott-Raven, 1999: 1498–501.
51. Hurd WW, Miodovnik M, Hertzberg V, et al. Selective management of abruptio placentae: a prospective study. *Obstet Gynecol* 1983; **61**: 467–73.
52. Combs CA, Nyberg DA, Mack LA, et al. Expectant management after sonographic diagnosis of placental abruption. *Am J Perinatol* 1992; **9**: 170–4.
53. Towers CV, Pircon RA, Heppard M. Is tocolysis safe in the management of third trimester bleeding? *Am J Obstet Gynecol* 1999; **180**: 1572–8.
54. Grunfeld JP, Pertuiset N. Acute renal failure in pregnancy: 1987. *Am J Kidney Dis* 1987; **9**: 359–62.
55. Shaw KJ. Abruptio placentae. In Mishell DR, Brenner DR, eds., *Management of Common Problems in*

Obstetrics and Gynecology, 3rd edn. Boston: Blackwell, 1994: 211–15.

56. Spinillo A, Fazzi E, Stronati I, et al. Early morbidity and neurodevelopmental outcome in low birth weight infants born after third trimester bleeding. *Am J Perinatol* 1994; **11**:85–90.
57. Oyelese Y, Catanzarite V, Prefumo F, et al. Vasa previa: the impact of prenatal diagnosis on outcomes. *Obstet Gynecol* 2004; **103**: 937–42.
58. Englert Y, Imbert MC, Van Rosendael E, et al. Morphological anomalies in the placentae of IVF pregnancies: preliminary report of a multicentric study. *Hum Reprod* 1987; **2**: 155–7.
59. Burton G, Saunders DM. Vasa praevia: another cause of concern in in vitro fertilization pregnancies. *Aust NZ J Obstet Gynaecol* 1988; **28**: 180–1.
60. Oyelese KO, Schwarzler P, Coates S, et al. A strategy for reducing the mortality rate from vasa previa using transvaginal sonography with color Doppler. *Ultrasound Obstet Gynecol* 1998; **12**: 377–9.
61. Carp HJ, Mashiach S, Serr DM. Vasa previa: a major complication and its management. *Obstet Gynecol* 1979; **53**: 273–5.
62. Cordero DR, Helfgoftt AW, Landy HJ, et al. A non-hemorrhagic manifestation of vasa previa: a clinico-pathologic case report. *Obstet Gynecol* 1993; **82**:698–700.
63. Antoine C, Young BK, Silverma F, et al. Sinusoidal fetal heart rate pattern with vasa previa in twin pregnancy. *J Reprod Med* 1982; **27**: 295–300.
64. Oyelese KO, Turner M, Lees C, et al. Vasa previa: an avoidable obstetric tragedy. *Obstet Gynecol Surv* 1999; **54**: 138–45.
65. Harding JA, Lewis DF, Major CA, et al. Color flow Doppler: a useful instrument in the diagnosis of vasa previa. *Am J Obstet Gynecol* 1990; **163**: 1566–8.
66. Meyer WJ, Blumenthal L, Cadkin A, et al. Vasa previa: prenatal diagnosis with transvaginal color Doppler flow imaging. *Am J Obstet Gynecol* 1993; **169**: 1627–9.
67. Hata K, Hata T, Fujiwaki R, et al. An accurate antenatal diagnosis of vasa previa with transvaginal color Doppler ultrasonography. *Am J Obstet Gynecol* 1994; **171**: 265–7.
68. Clerici G, Burnelli L, Lauro V, et al. Prenatal diagnosis of vasa previa presenting as amniotic band: "a not so innocent amniotic band." *Ultrasound Obstet Gynecol* 1996; **7**: 61–3.
69. Lee W, Kirk JS, Comstock CH, et al. Vasa previa: prenatal detection by three-dimensional ultrasonography. *Ultrasound Obstet Gynecol* 2000; **16**: 384–7.
70. Oyelese Y, Chavez MR, Yeo I, et al. Three-dimensional sonographic diagnosis of vasa previa. *Ultrasound Obstet Gynecol* 2004; **24**: 211–5.
71. Robinson BK, Grobman WA. Effectiveness of timing strategies for delivery of individuals with vasa previa. *Obstet Gynecol* 2011; **117**: 542–9.
72. Schellpfeffer MA. Improved neonatal outcome of vasa previa with aggressive intrapartum management: a report of two cases. *J Reprod Med* 1995; **40**: 327–32.
73. Publications Committee, Society for Maternal-Fetal Medicine. Placenta accreta. *Am J Obstet Gynecol* 2010; **203**: 430–9.
74. Gyamfi-Bannerman C, Gilbert S, Landon MB, et al. Risk of uterine rupture and placenta accreta with prior uterine surgery outside of the lower segment. *Obstet Gynecol* 2012; **120**: 1332–7.
75. Norwitz ER, Stern HM, Grier H, Lee-Parritz A. Placenta percreta and uterine rupture associated with prior whole body radiation therapy. *Obstet Gynecol* 2001; **98**: 929–31.
76. Hare AA, Olah KS. Pregnancy following endometrial ablation: a review article. *J Obstet Gynaecol* 2005; **25**: 108–14.
77. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. *Am J Obstet Gynecol* 2005; **192**: 1458–61.
78. Wax JR, Seiler A, Horowitz S, Ingardia CJ. Interpregnancy interval as a risk factor for placenta accreta. *Conn Med* 2000; **64**: 659–61.
79. Esh-Broder E, Ariel I, Abas-Bashir N, et al. Placenta accreta is associated with IVF pregnancies: a retrospective chart review. *BJOG* 2011; **118**: 1084–9.
80. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol* 2006; **107**: 1226–32.
81. Berkley EM, Abuhamad AZ. Prenatal diagnosis of placenta accrete: is sonography all we need? *J Ultrasound Med* 2013; **32**: 1345–50.
82. Comstock CH, Bronsteen RA. The antenatal diagnosis of placenta accreta. *BJOG* 2014; **121**: 171–81.
83. D'Antonio F, Iacovella C, Palacios-Jarquemada J, et al. Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014; **44**: 8–16
84. Silver RM, Fox KA, Barton JR, et al. Center of excellence for placenta accreta. *Am J Obstet Gynecol* 2015; **212**: 561–8.
85. Robinson BK, Grobman WA. Effectiveness of timing strategies for delivery of individuals with placenta previa and accreta. *Obstet Gynecol* 2010; **116**: 835–42.

86. Sentilhes L, Ambroselli C, Kayem G, et al. Maternal outcome after conservative management of placenta accreta. *Obstet Gynecol* 2010; **115**: 526–34.

86. Riggs JC, Jahshan A, Schiavello HJ. Alternative conservative management of placenta accreta: a case report. *J Reprod Med* 2000; **45**: 595–8.

87. Grobman WA, Gersnoviez R, Landon MB, et al. Pregnancy outcomes for women with placenta previa in relation to the number of prior cesarean deliveries. *Obstet Gynecol* 2007; **110**: 1249–55.

88. Naeye RL. Umbilical cord length: clinical significance. *J Pediatr* 1985; **107**: 278–81.

89. Krakowiak P, Smith EN, de Bruyn G, et al. Risk factors and outcomes associated with a short umbilical cord. *Obstet Gynecol* 2004; **103**: 119–27.

90. Rolschau J. The relationship between some disorders of the umbilical cord and intrauterine growth retardation. *Acta Obstet Gynaecol Scand Suppl* 1978; **72**:15–21.

91. Liu CC, Pretorious DH, Scioscia AL, et al. Sonographic prenatal diagnosis of marginal placental cord insertion: clinical importance. *J Ultrasound Med* 2002; **21**: 627–32.

92. Heinonen S, Ryynaenen M, Kirkinen P, et al. Perinatal diagnostic evaluation of velamentous and umbilical cord insertion: clinical, Doppler, and ultrasonic findings. *Obstet Gynecol* 1996; **87**: 112–17.

93. Hasegawa J, Matsuoka R, Ichizuka K, et al. Velamentous cord insertion into the lower third of the uterus is associated with intrapartum fetal heart rate abnormalities. *Ultrasound Obstet Gynecol* 2006; **27**: 425–9.

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Chapter 10

Fetal and Neonatal Injury as a Consequence of Maternal Substance Abuse

H. Eugene Hoyme and Melanie A. Manning

Introduction

Substance abuse, both legal and illegal, is widely prevalent in our society, and women in their childbearing years are not immune to this public health concern. In addition to the many problems substance abuse causes for these women, it may also place the children they are carrying at risk for lifelong sequelae. According to the 2013 US National Survey on Drug Use and Health, 5.4% of all pregnant women reported current illicit drug use, 9.4% reported alcohol use, and 15.4% reported cigarette use [1]. In 2015, the Centers for Disease Control and Prevention (CDC) reported that 1 in 10 pregnant women aged 18–44 years reported consuming alcohol, and 1 in 33 reported binge drinking in the past 30 days [2]. In other words, one-third of pregnant women in the United States who consume alcohol engage in binge drinking, the most risky maternal alcohol consumption pattern for the developing fetus. However, the actual number of children who have been exposed to drugs and alcohol in utero may be even higher because pregnant women often underreport substance use [3]. The purpose of this chapter is to describe the fetal and neonatal effects of various legal and illegal sensorium-altering substances ingested by pregnant women.

Drug Distribution in Pregnancy

It is important to first understand general principles of drug distribution during pregnancy, including the roles of the placenta and breast in biotransformation and secretion. The characteristics that favor transport of a drug across the lipoprotein barriers between the circulation and the central and peripheral nervous systems include high lipid solubility, minimal ionization at physiologic pH, low protein binding, and low molecular weight. High lipid solubility may result in storage of such substances in maternal body fat with subsequent release and transfer into fetal lipid stores during pregnancy. These same characteristics also enable drugs to cross the placenta readily and enter the fetal circulation. Drugs with a lower molecular weight (<500 g/mol) cross the placenta readily, whereas drugs with molecular weights between 600 and 1,000 g/mol cross at a slower rate. A few drugs with a high molecular weight (>1,000 g/mol), such as heparin and insulin, do not cross the placenta in any appreciable amount [4,5]. Deposition and retention of drugs in placental tissue, while limiting acute fetal exposure during maternal binges, may result in chronic long-term exposure to low levels of the same substance or its metabolites. Because the activity levels of certain fetal hepatic enzyme systems critical to drug metabolism are suboptimal, concentrations of such substances may be higher in the fetus than in the mother. Fetal organs such as the kidney also may be relatively inefficient at drug excretion, producing higher serum levels. Fetal swallowing of amniotic fluid saturated with active drugs and metabolites results in continued exposure. The umbilical cord and its vessels, along with the vessels present on the surface of the placenta, provide yet another potential route of absorption of drugs and metabolites present in amniotic fluid [6]. Cutting the umbilical cord at birth does not fully protect the newborn from maternally ingested substances. Drugs stored in fetal fat can be released over time, resulting in continued exposure of the neonate over the first hours, days, weeks, or months of life. High lipophilicity enables these same substances to pass into breast milk, resulting in continued neonatal exposure.

General Effects of Substance Abuse during Pregnancy

Substance-abusing women often do not seek access to prenatal care or lack access to healthcare and are therefore at high risk for serious adverse health effects, including withdrawal, malnutrition, iron- and/or folate-deficiency anemia, and parenterally transmitted

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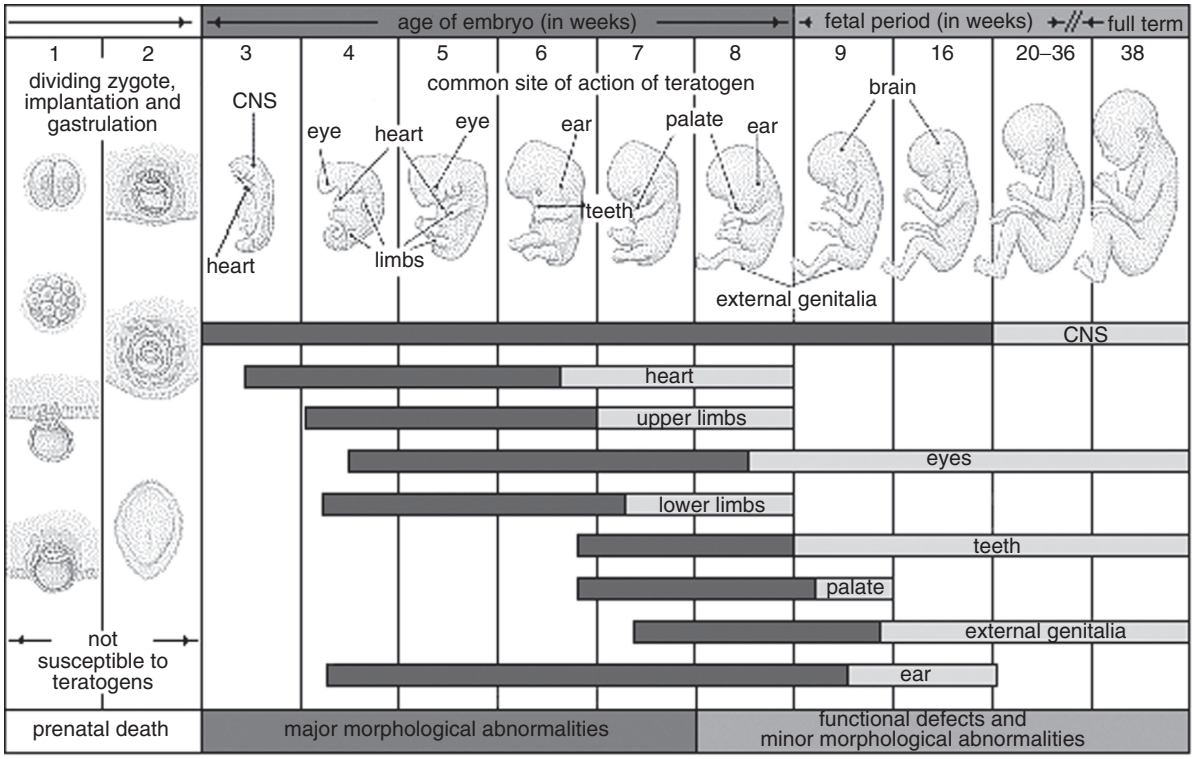


Figure 10.1 Malformations by organ system as a function of gestational timing. Note that the embryo is not susceptible to teratogenic damage during days 0–10 after conception. (Adapted from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology,* 8th edn. Philadelphia: Saunders, 2008, with permission.) (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

diseases such as bacterial endocarditis, human immunodeficiency (HIV) virus infection, and hepatitis B virus infection. Pregnancy further increases the health risks faced by these women.

Fetal effects of maternal substance abuse depend on many variables. Most agents to which the mother and the fetus are exposed during gestation are not harmful; however, many substances are known human teratogens (drugs, chemicals, infectious agents, and other physical and environmental agents that cause structural and/or neurobehavioral disabilities postnatally). The specific substance used by the mother may have profound effects on the fetus that are readily apparent during pregnancy or shortly after birth, subtle influences manifested during school-age years, or no detectable consequences. The dose of the substance ingested and the duration of exposure during pregnancy also play an important role. Heavy use of any drug over a long period of time places the fetus at greater risk than light use over a similar time frame. Binge use (high intake of a drug over a relatively short period of time) is also potentially toxic to the fetus. Similarly, the timing of ingestion during pregnancy helps to determine fetal and neonatal effects (Figure 10.1). Use during the first trimester, a period critical for organogenesis, may result in malformations of organs rapidly undergoing morphogenesis. The exception is the first 10–14 days of gestation, prior to implantation of the embryo, during which no recognizable teratogenic effects are observed. This is likely due to an "all or none" phenomenon in which if an embryo undergoes significant damage, implantation (and recognizable pregnancy) will not occur; conversely, if implantation does occur following the exposure, it implies absence of significant adverse effects. Use in later trimesters may unduly influence processes such as synapse formation in the CNS, which may produce neurobehavioral abnormalities or result in the neonatal abstinence syndrome. The genetic constitution of both mother and fetus is likewise important in that drug metabolism by enzyme systems is under genetic control, and inherited enzymatic defects may greatly

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potentiate the deleterious effects of various ingested substances [7].

Exposure to substances of abuse in utero may be associated with lifelong consequences. The effects of fetal exposure to human teratogens can present in the neonatal period and may be incompatible with long-term survival. Other, more subtle alterations in morphogenesis may present months or even years after birth as neurodevelopmental delay or similar abnormalities. Clamping of the umbilical cord produces an abrupt cessation of drug administration and may result in withdrawal as newborn blood levels fall. Continuing exposure of the neonate to substances of abuse, such as via breastfeeding, may produce a state of prolonged intoxication.

Methodologic Limitations

Many methodologic problems exist with studies performed on substance-abusing women and their children [8]. Because many women abuse more than a single substance during pregnancy, identification of a population of women and neonates exposed to a single substance is difficult at best. Small selective sample sizes and the lack of suitable control groups are problems that plague many clinical investigations; such studies tend to focus on those with the most intense exposures, who are most likely to exhibit detectable effects. Concomitant use of multiple drugs may produce an additive harmful effect when compared with use of a single substance. Investigators are also faced with an inherent inability to document the frequency and dose of drug exposure. Illicit drugs are not regulated for purity and are often adulterated or "cut" with other substances, making dose ascertainment problematic, even in those who apparently have limited their exposure to a single drug. While elicitation of a drug-use history is a vital component of any obstetric or neonatal evaluation, it has been shown in multiple studies that patient historical recall alone grossly underestimates prenatal substance abuse. Therefore, historical data must be accompanied by analysis of maternal and neonatal body fluids or tissues. Analysis of urine is capable of detecting only relatively recent (hours to days) exposure. Neonatal meconium analysis, while more sensitive than urine analysis, is useless in the detection of drug exposure very early in gestation because meconium is formed beginning at approximately 16 weeks' gestation. Maternal hair or nail analysis may provide the best information regarding timing of exposure, dose ingested, and duration of exposure, but it requires the cooperation of the mother. Neonatal hair may be lacking in sufficient quantity to allow study and also is not present early in gestation (fetal hair begins to appear at approximately 9 weeks' gestation). Selection of only the most severely affected cases for presentation in the literature and ignorance of negative studies are common. The presence of numerous confounding variables such as poor nutrition, poverty, previous obstetric history, and lack of access to prenatal and pediatric care greatly complicates any study of the effects of maternal substance abuse. In utero exposure and subsequent biologic predisposition are complicated by environmental influences, which are reflected in the multihit model of neurologic handicap [9]. Follow-up studies are hampered by high attrition rates and bias toward better-performing outcomes. Thus, while many of these substances are associated with adverse maternal, fetal, and neonatal outcomes, it is impossible to state that a cause-and-effect relationship exists for most of the drugs ingested by pregnant women.

Substances of Abuse

Ethanol

The adverse effects of ethanol on the developing fetus were described independently by Lemoine et al. in 1968 [10] and by Jones et al. in 1973 [11]. As with most malformation syndromes, the most severely affected children were described first, with the associated pattern of malformation termed *fetal alcohol syndrome* [11]. As physicians became more familiar with the clinical presentation of children prenatally exposed to alcohol, it became clear that the associated disabilities represent a spectrum from mild to severe (fetal alcohol spectrum disorders [FASD]). In 1996, the Institute of Medicine (IOM) described four distinct diagnostic categories within FASD: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) [12].

Prenatal exposure to ethanol is the leading cause of preventable developmental disabilities in the world. Recent school-based studies in the United States estimate the prevalence of FASD to be much higher than previously thought. May et al. recently recorded combined rates of FAS and PFAS of 10.9–25.2/1,000 (1.1–2.5%) in a Rocky Mountain community [13], whereas the complete continuum of FASD (including

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ARND) was observed to be 24–48/1,000 (2.4–4.8%) in a community in the Northern Plains [14]. In the mixed-race population of the Western Cape Province in South Africa, the highest prevalence rates of FASD in the world have been documented, 135.1–207.5/1,000 (13.5–20.8%) [15]. The World Health Organization (WHO) is currently planning prevalence studies in several countries in Europe, Asia, Africa, and North America, which should lead to global data about the frequency of this continuum of disabilities [16].

The high prevalence of FASD produces an immense burden to society in financial terms, unrealized productivity, and human suffering. In the United States, annual cost estimates have ranged from $74.6 million in 1984 [17] to $4.0 billion in 1998 [18]. In 2007, the estimated annual cost of FASD in Canada was CAD $5.3 billion [19]. The soaring prevalence and burden of FASD in children recently led the American Academy of Pediatrics to stress the following: no amount of alcohol intake during pregnancy can be considered safe, there is no safe trimester to drink alcohol, all forms of alcohol pose a similar risk, and binge drinking poses a dose-related risk to the fetus [20].

A number of diagnostic systems have been proposed that allow for clinical diagnosis of the continuum of disabilities associated with prenatal alcohol exposure [21–27]. In 2005, Hoyme et al. described specific clinical guidelines that allowed for assigning diagnoses within the 1996 IOM classification [21]. The Hoyme system recently has been updated to include a precise definition of documented prenatal alcohol exposure; more specific neurobehavioral criteria for diagnosis of fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorders; and revised diagnostic criteria for alcohol-related birth defects [28]. The Canadian diagnostic methodology has also recently been revised to simplify the terminology of FASD [27].

The recently published National Institute on Alcohol Abuse and Alcoholism (NIAAA) consensus diagnostic guidelines (updated Hoyme system) retain the four diagnostic categories originally proposed by the IOM in 1996. *Fetal alcohol syndrome* (FAS) denotes a specific pattern of malformation, with or without a confirmed history of maternal alcohol abuse during pregnancy, including: a persistent pattern of growth deficiency (length and/or weight); two of the three specific minor anomalies of the face associated with the teratogenic effects of ethanol (short palpebral fissures, smooth philtrum, and/or thin vermilion border of the upper lip); CNS structural or neurophysiologic abnormalities; and a defined array of neurobehavioral or cognitive deficits. Children with PFAS (with or without documented prenatal alcohol exposure) display the facial characteristics of FAS, specific neurocognitive deficits, and either the growth or documented CNS anomalies. ARBD represents a specific pattern of major anomalies in children in whom their prenatal alcohol exposure is consistent with the developmental pathogenesis of the birth defect, and ARND represents a group of children with documented prenatal alcohol exposure who exhibit the typical neurodevelopmental profile of FASD but who display normal structural development and normal growth [28]. It is perhaps this last group of children who represent the most difficult diagnostic challenge. The recently revised diagnostic criteria are set forth in Table 10.1 [28], and a typically affected child with FAS is shown in Figure 10.2.

Just as the intoxicating effects of ethanol on adults vary directly with blood levels, the effects seen in the newborn undoubtedly reflect the variability in dose, timing of exposure during gestation, frequency of exposure, and the genotype of mother and fetus.

Both ethanol and its primary metabolite acetaldehyde are teratogenic to numerous organ systems, but the primary target of ethanol teratogenesis is the developing brain. CNS abnormalities, especially involving midline structures, are a prominent component of FAS [29]. A number of structural brain anomalies have been observed in imaging studies in animals and human subjects with FASD. Although no specific anatomical region of the brain is preferentially affected, malformations resulting from migration abnormalities, changes in the size and shape of the corpus callosum, cerebellar vermis hypoplasia, and hypoplasia of the basal ganglia and hippocampus have been documented [30,31]. Neuroimaging studies have also documented that in addition to an overall reduction in brain size and specific structural malformations, prominent brain shape abnormalities have been observed, with narrowing in the parietal region and reduced brain growth in portions of the frontal lobe [31].

Multiple mechanisms by which ethanol and its metabolites impair normal development have been implicated. The levels of glucuronyl transferase and alcohol dehydrogenase activity are decreased in the fetus compared with maternal levels [32]. Catabolism

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Table 10.1 Updated Clinical Guidelines for Assigning Diagnoses within the Fetal Alcohol Spectrum Disorders (FASD) Continuum [28]

(I) Diagnostic criteria for FAS or PFAS (with or without confirmed maternal alcohol exposure). *FAS requires* **all** *features A–D; PFAS requires A and B.*

(A) A characteristic pattern of minor facial anomalies, including two or more of the following:
1. Short palpebral fissures (≤10th percentile)
2. Thin vermilion border of the upper lip (score 4 or 5 on lip/philtrum guide[a])
3. Smooth philtrum (score 4 or 5 on lip/philtrum guide[a])

(B) Neurobehavioral impairment
1. For children ≥3 years of age (a or b):
   a. With cognitive impairment:
      i. Global impairment (general conceptual ability ≥ 1.5 SD below the mean or performance IQ or verbal IQ or spatial IQ ≥ 1.5 SD below the mean)
      OR
      ii. Cognitive deficit in at least one neurobehavioral domain ≥ 1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual spatial impairment)
   b. With behavioral impairment *without* cognitive impairment:
      i. Behavioral deficit in at least one domain ≥ 1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
2. For children < 3 years of age:
   a. Developmental delay ≥ 1.5 SD below the mean

(C) A pattern of prenatal and/or postnatal growth deficiency
1. Height and or/weight ≤ 10th centile[a]

(D) Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including one or more of the following:
1. Head circumference ≤ 10th percentile[a]
2. Structural brain anomalies
3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)

(II) Diagnostic criteria for alcohol-related effects (ARND and ARBD). *A diagnosis in these categories requires a confirmed history of prenatal alcohol exposure.*

- **Alcohol-related neurodevelopmental disorder (ARND)**[b]

(A) Neurobehavioral impairment
1. For children ≥ 3 years of age (a or b):
   a. With cognitive impairment:
      i. Evidence of global impairment (general conceptual ability ≥ 1.5 SD below the mean or performance IQ or verbal IQ or spatial IQ ≥ 1.5 SD)
      OR
      ii. Cognitive deficit in at least two neurobehavioral domains ≥ 1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual spatial impairment)
   b. With behavioral impairment *without* cognitive impairment:
      i. Evidence of behavioral deficit in at least two domains ≥ 1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)

- **Alcohol-related birth defects (ARBD)**

(A) Requires one or more specific major malformations demonstrated in animal models and human studies to be the result of prenatal alcohol exposure: *cardiac:* atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; *skeletal:* radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; *renal:* aplastic/hypoplastic/dysplastic kidneys, "horseshoe" kidneys/ureteral duplications; *eyes:* strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; *ears:* conductive hearing loss, neurosensory hearing loss

Abbreviations: FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; ARBD = alcohol-related birth defects; ARND = alcohol-related neurodevelopmental disorder.

[a] Racially normed anthropometric growth charts and lip/philtrum guides should be used, if available.

[b] A diagnosis of ARND cannot be reliably made in children ≤ 3 years of age.

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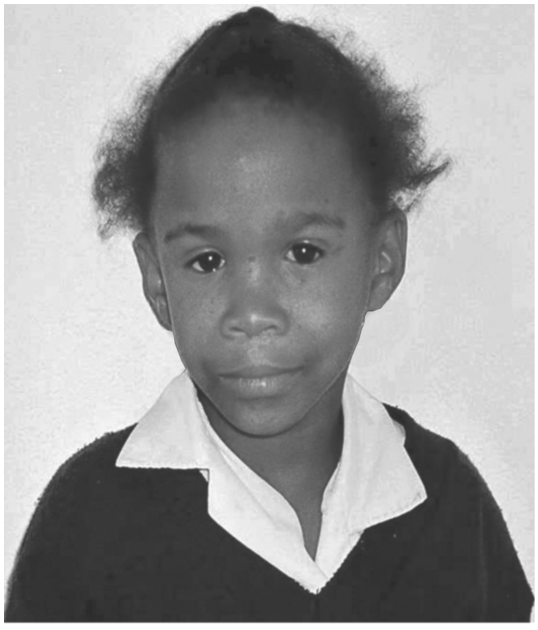


Figure 10.2 Typically affected child with fetal alcohol syndrome. Short palpebral fissures, a smooth philtrum, and a thin vermilion border of the upper lip are evident.

is delayed, resulting in higher fetal than maternal ethanol concentrations, thereby potentiating teratogenic risk. Events such as neuronal migration depend on the developmentally regulated expression and function of cell adhesion molecules (CAMs); CAMs are also expressed in osteoblasts and appear to play a role in bone formation. Ethanol has been shown to alter the migration of neurons into the cortex in animal models and suppress the expression of CAMs in tissue culture in a dose-dependent fashion [33]. Ethanol also alters the levels of endogenous retinoids and the expression of retinoic acid receptors in rats, producing cardiac anomalies similar to those seen in vitamin A teratogenesis [34].

Some studies have revealed that ethanol inhibits cell division and protein synthesis. Quantitative decreases in brain DNA and delays in the appearance of messenger RNA (mRNA) for various developmentally regulated CNS proteins have been detected in rat pups [35]. Delayed neuronal migration and proliferation have been documented in rats exposed to ethanol in utero [36]. The incidence of germinal matrix and intraventricular hemorrhage is increased in ethanol-exposed premature human neonates [37]. This may be indicative of an ethanol-induced alteration in the developmental biology of the germinal matrix, the site of both neuroblastogenesis and glioblastogenesis. Ethanol may also stimulate cell proliferation and thereby inhibit terminal neuronal differentiation and synapse formation [38]. Studies indicate that ethanol can impair gene expression at the transcriptional level, disrupting the temporal and spatial patterns of differential gene expression and potentially having a profound impact on eventual structure and function. Investigations in experimental animals have also documented that alcohol downregulates many early developmental genetic pathways in the embryo (e.g., *Shh, Pax6*, and *Fgf8*), thus leading to many of the observed changes in structure and function [39–41]. Finally, recent studies have documented persistent postnatal epigenetic markers in infants exposed to alcohol prenatally [42–44].

Functional abnormalities such as mental retardation, hypotonia, irritability, and poor coordination are observed in patients with FAS. Exposure to ethanol in utero has been shown quantitatively and temporally to alter the development of numerous neurotransmitters, including the serotonergic, cholinergic, dopaminergic, and glutamatergic systems, as well as to alter the activity of membrane-bound receptors for various neurotransmitters [45].

Prenatal ethanol exposure is associated with amblyopia, astigmatism, and other visual defects in humans. Animal studies in rats indicate that ethanol produces both macroscopic and microscopic changes in the optic nerves, including a gross decrease in cross-sectional diameter; cytostructural maldevelopment of glial cells, neurons, and myelin; and abnormalities in various organelles [46]. External ear anomalies and sensorineural hearing loss have also been described [47].

Associated cardiovascular abnormalities include atrial septal defect, ventricular septal defect, and anomalies of the great vessels. Myocardial ultrastructural changes, including decreased myofibrillar density and dysplasia, have been produced in rats exposed to ethanol prenatally [48]. The genitourinary system may also be involved, and hydronephrosis is a common finding. Murine embryos exposed to ethanol show excessive cell death in the region of the mesonephric duct proximal to the cloaca and in neural crest cells proximal to the posterior neuropore [49]. This is followed by abnormalities in the location of the ureterovesicle junction, leading to ureteral obstruction and hydronephrosis. Other common anomalies include hirsutism, cleft lip and palate, nail hypoplasia,

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pectus excavatum, diastasis recti, hypospadius, and camptodactyly, among other anomalies [50].

Prenatal and postnatal growth restriction is demonstrated as decreased weight, length, and head circumference [51]. Animal data indicate that prenatal ethanol exposure reduces fetal concentrations of insulin-like growth factor 1 (IGF-1) as well as the concentration of IGF-binding proteins later in life [52]. Ethanol has also been shown to reduce the secretion of IGF-2 from explanted fetal rat organs [53]. Such studies indicate that this may be but one mechanism by which prenatal ethanol exposure results in both short- and long-term alterations in growth and development. Lactase activity in the small intestine of rat pups exposed to transplacental ethanol is decreased in comparison with controls, and this may represent another factor contributing to the growth retardation seen in this syndrome [54].

Women giving birth to infants with FAS typically use more ethanol and use it earlier in gestation. While it is clear that daily consumption of more than ~1.5 oz (42 g) of absolute ethanol (the equivalent of three beers) greatly increases the risk of alcohol-induced teratogenicity, there is no uniform fetal response to a particular dose of ethanol: therefore, there is no amount of alcohol that can be considered entirely safe for a pregnant woman to consume. The American Medical Association, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the Surgeon General recommend that women who are attempting to conceive or who are already pregnant should not drink ethanol in any amount.

Ethanol withdrawal has been described in neonates born to chronically intoxicated mothers. Given the potent teratogenic effects of ethanol, it may be difficult to determine whether such manifestations represent true withdrawal or are manifestations of the CNS effects of FAS.

Maternal ethanol abuse complicates breastfeeding in several ways [55]. Lactation is impaired and the let-down reflex is inhibited by ethanol. Ethanol is readily secreted in breast milk, and acute neonatal intoxication can result. The motor capabilities of infants at 1 year of age regularly exposed to ethanol in breast milk have been shown to be significantly impaired [56]. Investigators have shown that the facial characteristics and other stigmata of FAS persist beyond the neonatal and infancy periods. It has also become apparent that children with a history of prenatal exposure but lacking the typical stigmata at birth may develop signs and symptoms over time. Longitudinal follow-up of neonates with prenatal ethanol exposure is necessary [57].

The neurodevelopmental deficits seen in the FAS persist into adulthood. Affected individuals manifest an inability to stay on task and poor memory, and they are at increased risk for attention-deficit disorder with hyperactivity [58]. Their comprehension, judgment, and reasoning are also impaired, making it difficult for them to anticipate the consequences of their actions. Because of mood lability, social interaction is impaired; this may accentuate feelings of withdrawal and depression [28,59].

Tobacco

While the prevalence of smoking has declined in the general population, it remains a major health problem. This is true of women of childbearing age, especially smokers who do not quit when they become pregnant. A Canadian study reported that one-third of women smoked before pregnancy, and of those, over two-thirds still smoked at the time of delivery [60]. Another focused American study found that ~16% of women smoked before pregnancy, with nearly 50% quitting before entering prenatal care and about 5% quitting after entering prenatal care [61]. A recent US report indicated that ~22% of women of reproductive age smoke, with 12% continuing to smoke during pregnancy [62,63].

Tobacco leaves, when burned, liberate thousands of compounds, including toxins (e.g., carbon monoxide and hydrogen cyanide), trace elements (e.g., lead, nickel, and cadmium), and carcinogens. Carbon monoxide avidly binds to hemoglobin, competitively inhibiting oxygen from being taken up in the pulmonary capillaries. At atmospheric partial pressures, this results in essentially irreversible displacement of oxygen. Carboxyhemoglobin levels in pregnant women who smoke are many times those of nonsmokers [64]. Increased maternal carboxyhemoglobin implies increased fetal carboxyhemoglobin, impaired oxygen content and delivery, and fetal hypoxemia [65]. Neonates born to mothers who smoke tobacco have elevated levels of erythropoietin in umbilical cord blood and increased numbers of nucleated red blood cells in peripheral circulation; both of these results indicate a response to hypoxemia [66]. Cyanide acts in a similar manner by binding to the iron moiety

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of both hemoglobin and mitochondrial cytochrome oxidase, inhibiting oxygen uptake and delivery as well as cellular respiration. Cyanide is also capable of inhibiting carbonic anhydrase, resulting in decreased carbon dioxide excretion. Chronic fetal hypoxemia results in intrauterine growth restriction and a small-for-gestational-age (SGA) neonate. Newborns so affected are at risk for sequelae such as hypoxic-ischemic encephalopathy, polycythemia, and pulmonary hypertension.

Nicotine is excreted primarily by the kidneys, although the lungs and liver are also sites of metabolism. Nicotine crosses the placenta and accumulates in the amniotic fluid and fetus to the extent that fetal levels exceed those seen in the mother [67].

There is common belief, particularly among pregnant adolescents, that smoking will allow for an easier (quicker, less painful) vaginal delivery. Studies have shown that mothers who smoke deliver neonates weighing 200–300 g less than gestational-age-matched controls; this appears to be due to a difference in fat-free mass [68]. Maternal smoking during pregnancy is now a well-known risk for low-birth-weight (LBW) infants [69]. Smoking mothers are two times more likely to have a LBW infant, and maternal smoking during pregnancy is responsible for 20–30% of all LBW infants [69]. Studies have indicated a dose-response relationship between weight and length at birth and prenatal exposure to tobacco [70]. One study showed third-trimester cigarette consumption to be a strong predictor of birth-weight percentile; for each additional cigarette smoked per day during the third trimester, a 27-g reduction in birth weight was seen [71]. Another series revealed less severe growth restriction in neonates born to mothers who quit smoking during pregnancy compared with women who continued to smoke [72]. A large multicenter study estimated the low birth weights attributable to prenatal smoking at 5.6%, greater than the risk attributable to other drugs such as alcohol and cocaine [73,74]. The pathophysiology of the intrauterine growth restriction seen in offspring of smoking mothers is multifactorial. Uterine artery vasoconstriction and decreased substrate delivery to the fetus may play a role [75]. Cigarette smoking may also alter the bioavailability of certain nutrients such as folate, zinc, and vitamins, producing relative maternal and fetal deficiencies. While gross placental size is not affected by smoking, structural changes in the cytoarchitecture at the placental-lacunar interface have been described [76,77]. Epidermal growth factor plays an important role in implantation, placental growth and endocrine function, and other aspects of fetoplacental development. Alterations in epidermal growth factor receptor autophosphorylation have been described and may represent another mechanism by which smoking may impair fetal growth [78]. It is also possible that embryonic and fetal cell number and size are diminished by premature termination of cell division, abnormal differentiation, alterations in neuronal synapse formation, or an as yet undetermined mechanism [79].

The existence of a tobacco embryopathy is unclear. Associations between smoking and certain birth defects, such as cleft lip and cleft lip/palate, were suggested in the past but considered controversial [80]. Recent studies have further investigated the contribution of prenatal tobacco exposure to a number of birth defects. A systematic review and meta-analysis suggested smoking to be moderately associated with an increased risk of congenital heart defects (CHDs), with the highest risk being for septal defects [63]. Another large study found that infants born to mothers who smoked in the first trimester were more likely to have a CHD, with an adjusted odds ratio (aOR) of 1.16 [81]. The investigators observed the highest association with pulmonary valve anomalies (aOR = 1.48), pulmonary artery anomalies (aOR = 1.71), and atrial septal defects (aOR = 1.22). The study concluded that maternal smoking may account for 1.4% of all CHDs. Another meta-analysis reported significant positive associations with maternal smoking and a number of defects: cardiovascular, musculoskeletal, limb reduction, missing/extra digits, clubfoot, facial/orofacial clefts, eye, gastrointestinal, gastroschisis, anal atresia, hernia, undescended testes, and craniosynostosis [82].

Most of the studies assessing the risk of placenta previa associated with maternal smoking have reported a positive association, with aORs ranging from 1.28 to 7.42 [83]. The evidence for an association between smoking during pregnancy and placental abruption is more compelling than in the case of placenta previa. A consensus opinion now exists that prenatal smoking is a major factor in the causation of placental abruption. The aORs for the association between prenatal smoking and placental abruption range from 1.4 to 4.0 [84]. A causal relationship between smoking and abruption is also supported by the observed impact of interventions. In the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders

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and Stroke, women who stopped smoking early in pregnancy showed a risk of abruption that was similar to that of those women who never smoked [85]. The causative mechanism may involve a chronic inflammatory process that triggers a chain of responses (increased oxidative stress, vascular reactivity, etc.) leading finally to increased necrosis, apoptosis, and destruction of the extracellular matrix at the maternal-fetal interface [86]. Cytotrophoblast (CTB) proliferation and differentiation are also affected by maternal smoking. CTB expression of three molecules that govern cellular responses to oxygen tension (von Hippel–Lindau tumor suppressor protein, hypoxia-inducible transcription factors, and vascular endothelial growth factor A) is dysregulated, leading in essence to a pathologically hypoxic environment [87].

Other adverse perinatal outcomes proven by epidemiologic studies to be associated with maternal smoking include placenta accreta, preterm birth, and stillbirth [88–91]. One recent meta-analysis found that maternal smoking was significantly associated with a 47% increase in the odds of stillbirth [92]. In another meta-analysis, maternal smoking was associated with an increased risk of stillbirth in high-income countries and was found to contribute to 20% of stillbirths in disadvantaged populations [93].

Intrauterine exposure to tobacco may have serious consequences for the fetus and neonate extending beyond the immediate newborn period. Alterations in cerebral blood flow have been documented in animal models [94], as has impairment of central chemoreception [95]. Prenatal tobacco exposure decreases arousal to auditory stimuli and may increase the risk of obstructive sleep apnea [96]. Maternal smoking during pregnancy is also a risk factor for sudden infant death syndrome (SIDS) [97]. Brainstem gliosis has been found in a number of autopsies of victims of SIDS; this histologic finding is consistent with repetitive hypoxemia, possibly secondary to abnormalities in the control of respiration [98]. Exposed infants demonstrate excitability and hypertonicity [69] as well as impaired speed of executive attention [99]. Maternal smoking also appears to have adverse effects on early intellectual function [100,101]. These effects, which include lower IQ, cognitive impairment, and behavior problems (attention-deficit/hyperactivity disorder [ADHD], aggression, rule breaking, externalizing, social problems), have now been shown to extend from infancy through childhood into adulthood [69,73,102–106].

Nicotine, cotinine, and other substances found in tobacco are secreted in breast milk. Levels in the neonate correlate with those seen in the mother. Nicotine has been shown to impair lactation and decrease the supply of breast milk. Nicotine also has been associated with neonatal emesis, respiratory problems such as frequent upper respiratory tract infections and reactive airway disease, and a potential increased risk of childhood cancer [107]. The effects on the newborn of the many other substances found in tobacco and secreted in breast milk are currently unknown. This is especially concerning because many women who quit smoking during pregnancy are likely to start again after delivery, feeling that the danger to their newborn no longer exists. All mothers should be counseled as to the potential risks presented by tobacco products secreted in breast milk and those found in environmental smoke [108].

The consumption of smokeless tobacco ("chew," "chaw," "dip"), while primarily a male activity in the population at large, is described in females in certain ethnic groups. Animal studies indicate that ingestion of this form of tobacco increases the risk of intrauterine growth restriction, decreased bone ossification, and embryonic demise [109]. While more studies are indicated, smokeless tobacco use in pregnancy is being associated with preterm delivery, stillbirth, and growth restriction [110,111]. One study found an increased incidence of oral clefts with snuff use during pregnancy [112], whereas another study found an increased risk of neonatal apnea [113]. A new concern in the primarily younger generation is the use of electronic cigarettes ("e-cigarettes" or "e-cigs"). These devices are electronic nicotine delivery systems consisting of a power source (battery) and heating element (atomizer) that vaporizes a solution ("e-liquid") contained in a cartridge [114,115]. These vapors contain various compounds, including nicotine, propylene glycol, diethylene glycol, glycerin, and flavorings [114,116]. E-cigarettes are often used as a smoking-cessation tool because there is no combustion of tobacco products, which is felt to be the most harmful part of cigarette smoke [117]. There have yet to be adequate studies investigating the long-range health effects of these products, which at this time are not fully regulated by the Food and Drug Administration (FDA). Studies of in utero nicotine exposure in animal models show association with adverse effects on the lungs, cardiovascular system, and brains of exposed offspring [116], implying that

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similar effects could be seen in humans. There are misconceptions by pregnant women that these alternative methods of nicotine replacement are not harmful, but there is yet to be conclusive evidence of their safety, especially in pregnancy [117].

The dangers of environmental tobacco smoke exposure ("secondhand smoke," "passive or involuntary smoking") are coming to light. As much as 50% of nonsmoking pregnant women may be exposed to secondhand smoke, and fetal exposure to nicotine and its metabolites may remain significant even in these cases [118]. Fetal exposure to environmental smoke appears to increase the risk of poor developmental outcome. In one study, infants exposed to secondhand smoke prenatally demonstrated a decrease in mental developmental index scores [119]. In another study, children between the ages of 6 and 9 years exposed to environmental smoke in utero were found to perform at a level inferior to those born to nonsmoking mothers but superior to those born to smoking mothers [120]. Behavior problems, particularly externalizing behaviors, in children exposed to secondhand smoke prenatally also have been described [121]. Paternal smoking with subsequent maternal passive inhalation of side-stream smoke has also been associated with intrauterine growth restriction [122,123]. An increased risk of respiratory tract disease (recurrent infection, reactive airway disease), impaired pulmonary development, otitis media, and lung cancer in later life has been associated with the inhalation of environmental tobacco smoke [123]; however, most of these studies are retrospective in nature, and prospective, well-controlled analyses are lacking. One of the most alarming findings to date is that smoking in the same room as an infant increases the risk of SIDS in a dose-dependent fashion [124]. The WHO and other international groups have continued to review evidence linking secondhand smoke and SIDS, and it is now accepted by many that tobacco exposure is the most common preventable cause of SIDS [125].

Marijuana

Delta-9-tetrahydrocannabinol (D-9-THC) is the major active metabolite derived from the plant *Cannabis sativa* (over 60 similar cannabinoid compounds are present). *Marijuana* is the term applied to the dried leaves, stems, and seeds of this plant. Although its legal use is becoming more frequent as state laws are relaxed, it is the most frequently abused of all illicit drugs in the United States, and its use by women in their childbearing years is extremely common. Other derivatives of marijuana include hashish and hashish oil. While oral consumption is possible, smoking is the usual route of ingestion, and this results in the absorption of a much greater proportion of active drug [126]. Burning or heating marijuana, hashish, and hashish oil allows for the inhalation of smoke containing D-9-THC and rapid absorption across the pulmonary epithelium. Marijuana smoke contains more carcinogens, irritants, and particulates than tobacco smoke [127]. Marijuana cigarettes ("joints") may be adulterated with other substances such as cocaine and phencyclidine (PCP) to produce a more intense high. Intoxication may also be seen in those exposed to secondhand smoke.

Prolonged, arrested labor has been reported with acute marijuana intoxication. While no teratogenic effects have been directly linked to prenatal marijuana use, the adulteration of cigarettes with other drugs of abuse may raise the potential risk. Frequent marijuana use during pregnancy has been shown to be associated with a small decrease in birth weight, although this decrease does not reach statistical significance in all studies and in and of itself probably carries little clinical significance [128]. A 1997 meta-analysis of 10 studies concluded that there was inadequate evidence to suggest that marijuana reduces birth weight at the amount typically consumed by pregnant women [129]. However, frequent use (>4 times/week) was associated with a 131-g decrease in birth weight. The effect of prenatal marijuana exposure on long-term growth remains unclear [130].

Reported effects on neonatal behavior of in utero marijuana exposure include prolongation of the startle response, tremors, irritability, poor state regulation, and altered visual and auditory responses [131]. Continued exposure of the neonate to marijuana after birth is experienced by breastfeeding newborns because D-9-THC is excreted in breast milk.

Reports of the effects of prenatal exposure to marijuana on neurobehavioral development during childhood are contradictory [132–134]. Although controversial, some studies indicate that marijuana exposure during pregnancy may affect learning and memory in children over time [135,136]. Marijuana exposure during development may also result in increased likelihood of drug experimentation later in life. Exposed rats exhibited decreased levels of D2 receptor expression and binding in the nucleus

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accumbens (NAc), a key reward center, and increased sensitivity to the rewarding properties of opiates [137]. Others have shown that exposure to THC during a period equivalent to midgestation in humans resulted in increased heroin-seeking behavior in offspring [138]. While these and other animal studies are compelling, further study in human populations is necessary to completely delineate the behavioral effects of prenatal cannabis exposure.

Cocaine

Cocaine, or benzoylmethylecgonine, is one of several alkaloids found in the leaves of *Erythroxylon coca*, which grows primarily in Peru, Ecuador, and Bolivia; raw leaves contain approximately 0.5–2% cocaine [139]. The major metabolite of cocaine is benzoylecgonine. In addition to its local anesthetic and vasoconstrictor properties, it blocks presynaptic catecholamine reuptake, resulting in catecholamine accumulation at postsynaptic receptors and pronounced CNS stimulation. Benzoylmethylecgonine hydrochloride ("coke," "snow," "lady," "gold dust") is produced in the form of crystals, granules, and powder. Cocaine base ("freebase") is formed by the extraction of cocaine from the hydrochloride salt with the use of alkaline solutions and subsequent recrystallization employing highly flammable solvents. Cocaine hydrochloride mixed with water and sodium bicarbonate and then hardened in a microwave oven results in a free-alkaloid form ("crack," "rock"). Smoking crack allows for rapid diffusion and entry into the blood and CNS, producing high serum levels and short, very intense highs. Because cholinesterase activity is low in pregnancy as well as in the fetal and neonatal periods, pregnant women who abuse cocaine and their newborns may be exposed to high levels for protracted periods of time. The placenta binds cocaine and its metabolites and thus may effectively serve as a depot for drug release during pregnancy [140].

The perinatal literature is replete with case reports of fetal and neonatal problems attributed to prenatal cocaine exposure. The biologically plausible pathogenetic mechanism underlying these many and varied effects is suspected to be a disruption of blood flow, either globally to the uteroplacental unit or locally within specific fetal organs [141]. Although plausible, population studies of women using cocaine during pregnancy have failed to demonstrate a "cocaine embryopathy" accompanying embryonic or fetal vascular disruption. Some studies have reported negative effects on cognitive development [142], whereas others claim that these findings are correlated with other factors, such as polydrug use and the quality of the child's environment [143].

Several epidemiologic studies have confirmed the negative effects of maternal cocaine use on birth weight, length, and head circumference, even after adjustments for tobacco, alcohol, or other drug use, nutritional indicators, and various sociodemographic factors [144,145]. Studies also have confirmed dose-response effects of cocaine exposure on fetal growth. For example, a retrospective cohort study in a New York City hospital found a 27-g decrement in birth weight with each log unit increase in cocaine concentration in maternal hair at delivery, adjusted for gestation, smoking, and alcohol consumption [146].

Cocaine use is associated with premature labor, premature rupture of membranes, advanced cervical dilation at admission, and a shortened latency period to labor and delivery [147,148]. In addition, maternal cocaine ingestion appears to carry an increased risk of placenta previa, abruptio placentae, uterine rupture, and precipitous delivery [149,150]. The incidence of spontaneous abortion and fetal demise is also higher in the cocaine-exposed population.

Neonatal effects of prenatal cocaine exposure primarily reflect focal disruption of vascular flow. Prenatal cocaine exposure is associated with an increased risk of necrotizing enterocolitis in both premature and term newborns [151]. Pregnant rats injected with cocaine delivered newborns with mesenteric vascular thrombosis and focal areas of inflammation, hemorrhage, and necrosis in their gastrointestinal tract [152].

Various CNS manifestations have been described in neonates, infants, and children born to cocaine-abusing women. Discrete anatomic lesions such as cerebral artery infarction have been detected in exposed neonates [153]. An increased incidence of intracranial hemorrhage has been described; this is felt to be due at least in part to an increase in mean arterial blood pressure and cerebral blood flow velocity [154]. Periventricular leukomalacia, thought to be secondary to in utero cerebral ischemia, has also been associated with prenatal cocaine exposure [155]. However, not all studies reveal an association between prenatal cocaine exposure and structural brain abnormalities [156]. Seizures have also been described

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in neonates after receiving a transplacental cocaine bolus shortly before birth and after passive inhalation of environmental crack smoke [157]. Alterations in both respiratory control and sleep regulation in the fetus and neonate have been described in human and animal studies. Cocaine-exposed term newborns have been shown to have increased apnea and periodic breathing in comparison with controls [158]. Abnormal sleep and awake state transition has been found in infants exposed to cocaine [159]. Direct intravascular administration of cocaine to fetal sheep suppresses low-voltage electrocortical activity and increases catecholamine levels [160]. Fetal sleep state regulation is in part controlled by norepinephrine, which normally decreases in active fetal sleep. Transplacentally acquired cocaine elevates norepinephrine levels and decreases active sleep. Tryptophan and serotonin also function as regulators of the sleep-wake cycle; cocaine has been found to interfere with tryptophan uptake and serotonin biosynthesis [161]. The effects of these alterations on the developmental biology of the CNS are unknown. Abnormalities in respiratory control and sleep-state regulation increase the risk of SIDS. However, it is not clear that cocaine-exposed neonates are at an increased risk of SIDS because studies have produced conflicting results [162,163].

Numerous developmental studies have been performed on children exposed to cocaine prenatally. Studies have shown poor on-task performance, fine-motor deficits, impaired habituation, low threshold for overstimulation, inability to self-regulate, and cognitive and motor developmental delay at 1.5–2 years [164,165]. Other studies indicate a dose-response effect of prenatal cocaine exposure on assessments of growth and behavior [166,167].

The lay press was quick to sensationalize the cocaine epidemic and the purported effects of this drug on the unborn. Despite limited evidence generated by studies complicated by all the problems outlined earlier, "crack babies" were labeled as irrevocably damaged and a burden to society. A more scientific analysis of the available data fails to substantiate the universality and inevitability of these early claims. A meta-analysis published in 2001 stated that there was no convincing evidence that in utero exposure to cocaine and its metabolites results in developmental defects in children aged 6 and younger [168].

No definitive withdrawal syndrome from in utero cocaine exposure has been described in neonates; it is uncertain whether the signs observed in some neonates prenatally exposed to cocaine represent true withdrawal or are secondary to the direct effects of the drug still present in the newborn. These signs typically appear in the first 24–48 hours after birth and peak in intensity by 72 hours [169]. The most frequently observed findings include tachycardia, tachypnea, hypertension, irritability, exaggerated Moro response, impaired visual tracking, increased tremulousness, abnormal sleep patterns, increased generalized motor tone, and feeding abnormalities, including poor suck and emesis [170].

Cocaine is excreted in breast milk up to 36 hours after the last dose, representing another potential route of neonatal exposure. Cases of neonatal intoxication marked by irritability, vomiting, diarrhea, tachycardia, tachypnea, hypertension, and tremulousness in breastfed newborns have been described [171]. One case described an 11-day-old breastfeeding neonate who developed apnea and seizures after ingesting cocaine used as a topical anesthetic for maternal nipple soreness [172].

Opioids

Opiate refers to a drug derived from opium, the dried milky exudate of the opium poppy, *Papaver somniferum*. An opioid is a natural or synthetic substance that produces opium- or morphine-like effects when ingested. *Narcotic* is the nonspecific term applied to any drug derived from opium or similar compounds capable of inducing analgesia, sedation, and sleep and that will cause dependence with repeated use. Opioids may be ingested orally or inhaled; they may also be injected intravenously, intramuscularly, and subcutaneously. One opioid is heroin; its lipid solubility is greater than that of morphine, allowing it to enter the CNS more rapidly and producing a quicker, more intense high.

Despite the frequency of fetal exposure to opioids, no consistent teratogenic effects have been observed. Most studies of prenatal opioid, heroin, or methadone use show higher rates of low birth weight, preterm birth, and intrauterine growth restriction, although few have controlled for associated risk factors. A meta-analysis estimated a 483-g reduction in birth weight and a relative risk for low birth weight of 3.81 associated with any opiate use during pregnancy [173].

Endogenous opioid peptides and opioid receptors are expressed transiently in the developing mammalian

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brain [174]. The significance of this developmentally regulated process and the effects that fetal opioid exposure have on this phenomenon are unknown at this time. Methadone delays pulmonary surfactant synthesis by an unknown mechanism and places the newborn at higher risk of respiratory distress syndrome and the need for assisted ventilation [175]. Unlike methadone, heroin accelerates pulmonary surfactant synthesis; exposed neonates have a decreased risk of respiratory distress.

Maternal withdrawal implies fetal withdrawal. While the addicted mother manifests the typical signs and symptoms of opioid withdrawal, the fetus experiences hypoxia and in response may pass meconium. Chronic fetal hypoxia produces pulmonary vascular remodeling and increased vascular reactivity, predisposing the newborn to pulmonary hypertension after birth. Both meconium aspiration and pulmonary hypertension increase neonatal morbidity and mortality. Chronic intrauterine hypoxia also increases the risk of hypoxic-ischemic encephalopathy and fetal demise. Because of the significant maternal, fetal, and neonatal sequelae, withdrawal in pregnancy should be treated promptly and appropriately.

A neonate exposed to opioids in utero is at risk of respiratory depression in the hours after birth. Naloxone (Narcan), an opioid antagonist, may be used to reverse respiratory depression in the newborn secondary to maternal opioid administration within 4 hours of delivery in the absence of a maternal history of opioid abuse. However, acute opioid reversal in a newborn chronically exposed in utero may produce withdrawal; thus naloxone should be used very judiciously on a case-by-case basis. It is preferable to support the neonate's respirations with positive-pressure ventilation and achieve a heart rate above 100 beats/minute prior to establishing the need for and administration of naloxone. Any neonate receiving naloxone should be monitored carefully in the hours to days after birth becauses the duration of action of many opioids is longer than that of naloxone.

Opioids appear to have effects that extend beyond the immediate newborn period. Neonates born to methadone-using mothers have been shown to have a decreased sensitivity to carbon dioxide during the first days of life in comparison with controls [176]. The risk of SIDS in babies born to opioid-abusing mothers is 5–10 times that of unexposed newborns (approximately 20–30/1,000 live births versus 2–3/1,000 in the general population) [177].

Once the umbilical cord is clamped, the newborn is disengaged from all that was once supplied by the mother and placenta. Neonates born to opioid-addicted mothers are at risk for withdrawal. Withdrawal in the newborn is characterized by CNS sign such as yawning, lacrimation, mydriasis, irritability, and seizures. While these effects are transitory, some may produce permanent nervous system injury if not treated appropriately (e.g., seizures). Heroin and methadone are the most commonly used opioids by pregnant women. Heroin has a relatively short half-life, and exposed newborns typically experience withdrawal soon after birth. Methadone is a synthetic opioid used in the treatment of maternal addiction and prevention of withdrawal signs and symptoms. The majority of neonates exposed to methadone in utero undergo withdrawal, usually showing signs within 1–2 days of birth. Withdrawal from methadone is typically more severe and longer in duration than that with other prenatally acquired opioids. Given the long half-life of this drug and the fact that methadone is present in low concentrations in breast milk, some neonates may not experience withdrawal until several weeks of age. While the presence of methadone in breast milk in levels approximating those found in serum may prevent or delay neonatal withdrawal, it may also result in intoxication, respiratory depression, and death in the breastfeeding newborn [178]. The American Academy of Pediatrics states that breastfeeding is contraindicated if the maternal dose of methadone exceeds 20 mg/day [179].

The long-term neurodevelopmental effects of prenatal exposure to opioids are unclear. Some studies suggest motor and cognitive impairments and ADHD at school age in children prenatally exposed to heroin [177,180–184]. However, long-term follow-up studies of cohorts of children prenatally exposed to opioids are lacking.

Sedative-Hypnotics

Sedative-hypnotics are drugs that cause CNS depression by stimulating or augmenting the activity of gamma-aminobutyric acid (GABA), which results in dopamine increase in the nucleus accumbens. This increase in dopamine is related to the experience of pleasure and reward. Their mode of action makes a sedative-hypnotic clinically useful as an anxiolytic or sleep inducer/maintainer. The two major categories of

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sedative-hypnotics are benzodiazepines (e.g., diazepam, lorazepam) and barbiturates (e.g., secobarbital, pentobarbital). Other nonbenzodiazepine, nonbarbiturate sedative-hypnotic agents include zolpidem, buspirone, methaqualone, gamma-hydroxybutyrate, and carisoprodol. Ethanol potentiates the absorption of these drugs and therefore may lead to overdose if used simultaneously. Because they can be ingested orally, they are common substances of abuse; they can also be administered intravenously or intramuscularly. As a class of drugs, these substances typically have long half-lives, and their effects may persist for days. They are metabolized by hepatic glucuronidases and excreted by the kidneys.

Benzodiazepine levels in fetal blood exceed those in maternal blood [185]. Fetal effects have included decreased beat-to-beat variability in heart rate pattern. While cleft lip and palate [186] and pyloric stenosis/alimentary tract atresia [187] have been described in exposed infants, no significant teratogenic effects or specific patterns of malformation have been observed in benzodiazepine-exposed pregnancies in larger population-based studies and reviews [187–192]. However, premature birth, low birth weight, and/or SGA in exposed infants are more consistent findings [187,191,193]. Reduced head circumference and cognitive deficits have been associated with in utero exposure to anticonvulsant barbiturates such as phenobarbital [194,195], although the association has not been reported in all studies [195]. While there is no strong evidence of a general sedative-hypnotic syndrome, certain heart defects (e.g., pulmonary valve stenosis) have been described with prenatal butalbital use [196].

Withdrawal in the neonate exposed to sedative-hypnotics is similar to that seen with opioids: at its most severe, hypothermia, hypotonia, and respiratory depression ensue [192,197]. Sedative-hypnotics are secreted in breast milk, and this route affords another possible route of intoxication, causing lethargy and sedation in exposed infants [192].

Sympathomimetics

Sympathomimetic drugs are stimulant compounds that mimic the effects of endogenous neurotransmitters of the sympathetic nervous system: catecholamines, epinephrine, norepinephrine, and dopamine. Their action stimulates neurotransmitter release at alpha, beta, dopaminergic, and serotonergic receptors [168]. Unlike catecholamines, these drugs retain their efficacy when ingested orally, readily enter the CNS, and are metabolized much more slowly than endogenous catecholamines, with large proportions excreted unchanged in urine. Many sympathomimetics can be obtained in over-the-counter medications, including phenylephrine, ephedrine, pseudoephedrine, and phenylpropanolamine. The most commonly abused sympathomimetics include amphetamine, methamphetamine ("meth"), and methylphenidate. The amphetamines are collectively known as "speed." Amphetamine and its derivatives, methamphetamine and methylenedioxymethamphetamine (MDMA), metabolize slowly and can be easily distributed to the CNS [198]. After amphetamine use, circulating norepinephrine and serotonin levels are increased, which produces vasoconstriction [199]. Routes of ingestion include oral consumption, nasal insufflation, inhalation of smoke (smokable methamphetamine hydrochloride is known as "ice"), and intravenous and subcutaneous injection. Metabolism occurs in the liver, and excretion is via the kidney.

Similar to cocaine, sympathomimetics may produce potent vasoconstriction and limit blood flow to various organs. (Amphetamine derivatives have even longer half-lives and more sympathomimetic properties than cocaine [198].) Uterine artery constriction results in relative placental insufficiency, decreased substrate delivery to the fetus, and risk of intrauterine growth restriction [199–202]. In addition, methamphetamine acts as a competitive inhibitor of serotonin and norepinephrine, whose transporters are expressed in the placenta and are thought to play a role in homeostasis of amniotic fluid and fetal circulation [203,204] as well as control of vasoconstriction of the placental vascular bed [205]. These sympathomimetic effects contribute to the development of gestational hypertension, preeclampsia, abruption, intrauterine fetal death, preterm labor/birth, and infant death [205–210]. Because the fetus has little CNS blood flow autoregulatory capacity, it is possible that the sympathomimetic-induced alterations in uterine and placental blood flow produce both uncompensated hypertensive spikes and hypotensive nadirs in the fetal circulation, predisposing the fetus to ischemic damage and reperfusion injury.

Methamphetamine is the third most commonly abused substance after alcohol and marijuana [208], with an estimated 5.2% of women using the substance at some point during their pregnancy [211]. Because

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methamphetamine crosses the placenta and blood-brain barrier, the potential for significant effects on a developing fetus is real. Animal studies reveal that prenatal amphetamine exposure is associated with structural and functional alterations in brain development [212–214]. In a study of CNS structure and neurocognitive function in methamphetamine-exposed children and controls, whole-brain volumes were comparable in each group. However, the meth-exposed children had a smaller putamen bilaterally, a smaller globus pallidus, a smaller hippocampus, and a smaller caudate bilaterally; no group differences in volumes were noted in the thalamus, midbrain, or cerebellum [215]. The reduction in these brain structures correlated with poorer performance on sustained attention and delayed verbal memory. These children scored lower on measures of visual motor integration, attention, verbal memory, and long-term spatial memory. There were no differences among the groups in motor skills, short-delay spatial memory, or measures of nonverbal intelligence [215]. Methamphetamine use in late gestation has been associated with neonatal intracranial lesions, including white matter cavitary lesions and intraventricular, subarachnoid, and subependymal hemorrhage [216]. While some studies reported an increased risk of fetal anomalies, such as oral clefting, heart defects, and gastroschisis [202,217–220] after prenatal methamphetamine exposure, other studies found no correlation [221,222]. At this point, there is no consistent pattern of malformation recognized with prenatal sympathomimetic exposure.

In addition to fetal growth effects of being SGA and having decreased birth weight [223,224], tremors, feeding difficulties, and irritability followed by prolonged periods of lethargy have been described in the first days of life in neonates exposed to methamphetamine in utero. Since methamphetamine persists for days in the neonate after clamping of the umbilical cord, it is possible that these signs represent drug toxicity rather than withdrawal [225], that is, no abstinence syndrome [226]. Improvements in neonatal stress and arousal were noted in exposed infants by 1 month of age [227]. While information regarding long-term follow-up of children exposed to methamphetamine prenatally is somewhat limited [228], reports are emerging that note a decrease in height growth trajectory [226,229], neurocognitive deficits [215,228,230,231], and attention/behavioral problems in this population [226,228,232,233].

Volatile Substances of Abuse

Volatile substances of abuse, or *inhalants*, are a diverse group of compounds that are inhaled from a container, soaked rag, or bag to achieve intoxicating properties [234,235]. They are primarily hydrocarbon derivatives: aromatic and aliphatic hydrocarbons such as those found in paint solvents, adhesives, and fuels; alkyl halides and nitrites present in aerosol propellants, refrigerants, cleaning fluids, and fuels; and ether and ketone components of fuels, solvents, oils, sealants, and plastics. These substances are ubiquitous, found in products such as lighter fluid, nail polish remover, rubber cement, hairspray, room fresheners, deodorants, glue, spray paint, and permanent markers [235]. Inhalants are common substances of abuse because they are readily accessible, legal, and relatively inexpensive, especially among those unable to afford more expensive illicit drugs [235–237]. Exposure to volatile compounds can also happen in the workplace, but abuse exposure is approximately 50 times greater than that allowed in a work setting [234].

The cellular action of inhaled solvents is thought to be shared with GABA receptors (e.g., benzodiazepines, barbiturates, alcohol), which results in a depressant effect [235]. Metabolism is primarily carried out in the liver, and metabolites are excreted in bile, urine, and exhaled gas. Gas chromatographic analysis of blood collected in a tube containing ethylenediaminetetraacetic acid or heparin can detect aliphatic hydrocarbons [235]. Obstetric/pregnancy complications can include preterm labor/delivery, placental abruption, premature rupture of membranes, and intrauterine growth restriction [234,238].

The teratogenic potential of many of these volatile chemicals is significant, especially in view of the fact that it is impossible to control the amount of exposure [239]. It should be noted, however, that the risk of problems is higher with abuse exposure than with occupational exposure [240]. Teratogenicity depends on the particular substance abused. Toluene embryopathy, that is, the effects on a developing fetus exposed to toluene, is well described and serves as an example. Toluene, an aromatic hydrocarbon found in paints and adhesives, readily crosses the placenta, but the fetus appears unable to metabolize toluene adequately [241]. Animal studies indicate that prenatal exposure to toluene results in intrauterine growth restriction and neurologic, cardiovascular, skeletal,

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and craniofacial abnormalities [242–246]. Reports in humans describe microcephaly, narrow bifrontal diameter, midface hypoplasia, developmental delay, and craniofacial abnormalities, including micrognathia, short palpebral fissures, ear anomalies, unusual scalp hair patterning, smooth philtrum, and thin upper lip [239,240,247,248]. Much phenotypic similarity exists in patients exposed in utero to toluene and those diagnosed with fetal alcohol spectrum disorders (FASDs) [247]. Similar to children exposed to alcohol prenatally, children with prenatal toluene exposure can demonstrate delays in growth and development as well as behavioral challenges (e.g., hyperactivity, attention deficit) [234,249]. Modeling the paradigm of FASDs, the term *fetal solvent syndrome* has been suggested to describe the constellation of physical and developmental effects attributed to prenatal solvent exposure [245,247–249]. While prenatal exposure to toluene results in a recognizable pattern of malformation, abuse of other inhalant chemicals during pregnancy may also result in serious fetal anomalies [250] that are as yet not fully characterized.

Screening

A maternal drug history is a mandatory part of any obstetric or neonatal history and physical examination. The history should be obtained in a nonthreatening manner and should review the use of over-the-counter medications, prescription drugs, tobacco, ethanol, and illicit drugs. When the concern of substance abuse is raised by the history or the examination of the mother, fetus, or neonate, the mother should be informed in a nonjudgmental manner. The physician should always be cognizant of the potential for spousal abuse when contemplating the manner in which this information is communicated to the father. Ideally, this is accomplished after obtaining maternal permission and with the support of social workers trained in substance abuse. Maternal self-reporting of substance abuse uniformly underestimates the actual frequency of in utero exposure [251]. In addition, it is recognized that drug use cuts across racial and socioeconomic boundaries [252]. Suspected substance abuse should be confirmed not only by elicitation on history but also by appropriate screening of selected maternal, fetal, and neonatal body fluids or tissues. Hospital policies vary, although permission of the mother is generally required for maternal screening, whereas neonatal testing is often considered implied when general consent to treat is provided on newborn admission.

Urine is the body fluid most frequently tested for substances of abuse. The kidney acts to concentrate drugs and their metabolites, producing higher concentrations in urine than in serum. Because of the lack of proteins and other cellular constituents that can interfere with the equipment used in assays, urine is relatively easy to analyze. Finally, urine offers the benefit of long-term stability if specimens are frozen. Screening tests commonly used include the fluorescence polarization immunoassay and the enzyme multiplication immunoassay technique. False-positive results depend on the extent of cross-reactivity with other substances. Positive results should be confirmed by more definitive methods such as gas chromatography/mass spectrometry. The most serious drawback in using urine to screen for intrauterine substance exposure lies in the fact that drugs and their metabolites are excreted quite quickly, usually within hours to several days after maternal ingestion. Therefore, the ability of a urine drug screen to detect any exposure occurring more than 48–72 hours preceding sampling is minimal. Other reasons for false-negative results include concentrations below the detectable limits of the assay and alterations in urinary pH affecting drug solubility [253].

Meconium is the first stool passed by the newborn. It is composed of swallowed amniotic fluid and secretions such as bile, vernix caseosa, epithelial cells, and other debris shed into the lumen of the fetal gastrointestinal tract starting early in the second trimester. Because of its appearance early in gestation, it functions as a reservoir for drugs delivered to the fetus via the umbilical cord and amniotic fluid and therefore provides a much better chronologic record of intrauterine drug exposure than does urine. Large quantities can easily be obtained in a noninvasive manner. However, it is a tenaciously thick fluid with abundant particulate matter that requires extensive processing before conventional screening methods can be employed. Whereas most hospitals in the United States offer urine toxicologic testing, fewer centers are currently testing meconium on a routine basis. In addition, the number of drugs capable of being detected in meconium is limited in comparison with urine. Nevertheless, its utility in increasing the yield of positive exposures for cocaine and other selected drugs is well documented [254].

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Fetal hair appears at approximately 8–9 weeks of gestation. As epidermal cells surrounding the dermal papillae divide, the hair shaft grows, and drugs and metabolites in the intrauterine environment are incorporated into the developing hair shafts. Like meconium, hair acts as a depot for drugs of abuse and provides a source for detection of drugs used early in gestation. The timing of exposure during gestation can be approximated by measuring the length of the hairs in the sample, incorporating the average rate of hair growth, and preserving the proximal-distal orientation of the hair strands [255]. Obviously, the longer the strands of hair obtained, the better is the historical assessment of substance exposure; therefore, it is best to obtain full-length hair. A core of hair approximately 5 mm in diameter is required. Because of the quantity of hair required, the mother is usually a much better source than the neonate. The hair is then washed and any drugs extracted [256]. Quantitative analysis is carried out by radioimmunoassay with a specific antibody or gas chromatography/mass spectrometry. While it is an extremely useful tool in the determination of prenatal drug exposure, hair analysis is not completely foolproof because various hair treatments may limit the amount of drug that can be extracted [257].

Serum may also be used for drug screening, although its use entails all the limitations of urine testing, including the inability to establish distant or chronic exposures.

Summary

With the exception of ethanol (FASD), tobacco, and toluene (toluene embryopathy), little is definitively known about the potential fetal and neonatal consequences of intrauterine drug exposure. While the many case reports and abundant anecdotal experience allow for the listing of numerous associations of the substances of abuse with various malformations, disruptions, and neurodevelopmental disabilities, few well-designed, controlled, prospective clinical studies with appropriate follow-up have been carried out. The further elucidation of embryopathic effects will require expansion of the concept of teratogenesis beyond gross morphologic abnormalities to include postnatal development (behavioral teratology). A lack of gross structural anomalies implies neither normal molecular structure nor normal physiologic function. Direct damage to DNA is but one mechanism by which drugs may affect the fetus. The cytoplasm is truly "where the action is," and it is in this dynamic milieu that drugs may exert their effects on transcription, mRNA stability, and other processes vital to normal cellular function. This is an especially important concept in view of the many neurobehavioral problems purportedly associated with prenatal substance abuse that occur in the absence of gross nervous system malformations. Further clinical studies, coupled with bench research at the molecular level, should provide a better understanding of the impact of prenatal drug use on the fetus.

The fetal and neonatal brain exhibits remarkable resilience. Although prenatal drug exposure may create vulnerability, it is clear that the majority of children, given appropriate care, stimulation, and follow-up can overcome such potential insults. It is also clear that the quality of the postnatal environment may be just as important as, if not more important than, the intrauterine environment in determining long-term outcome. Although children with prenatal drug exposure have been shown to attain a performance level equal to nonexposed peer groups, it is also true that such peer groups may function at levels below the national norm. This illustrates the profound effect other factors such as poverty and malnutrition can have on child development. It also illustrates how elimination of these other factors can positively affect the development of our youth.

The transition to an extrauterine existence is a difficult task. A baby must learn what actions elicit the desired responses from its parents. Caring for a newborn is a tremendous challenge, and parents must learn to interpret their baby's wants and needs and be able to respond appropriately. A neonate exposed to drugs in utero may be lethargic or irritable and thus unable to process stimuli from the outside world. Substance-abusing parents may be unable to care for themselves adequately, let alone their newborn. The potential for frustration, under- or overstimulation, neglect, and abuse is great. The importance of family support, beyond that provided by substance abuse programs, cannot be underestimated. Multidisciplinary assessment and intervention programs must be easily accessible to those most in need of their services. Intrauterine drug exposure, unlike many other hazards faced by the fetus and neonate, is potentially a preventable problem.

Finally, criminalization of drug use and legitimization of the concept of "fetal abuse" in regard to

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prenatal drug use is not the means to achieve adequate care for a mother and her unborn child. For physicians who have not experienced, either personally or professionally, a dependency disorder, it is difficult to understand how a woman can knowingly risk potential harm to her unborn child. We can only understand when we realize that these women, plagued by a society that not only reinforces their feelings of inadequacy but also convinces them that inadequacy is their fault, are ridden with guilt and self-deprecation and therefore easily succumb to the temporary but nevertheless real reprieve offered by illicit drugs.

References

1. Substance Abuse and Mental Health Services Administration. *2013 National Survey on Drug Use and Health: Summary of National Findings* (NSDUH Series H-48, HHS Publication No. [SMA] 14–4863). Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.
2. Tan CH, Denny CH, Cheal NE, et al. Alcohol use and binge drinking among women of childbearing age – United States, 2011–2013. *MMWR* 2015; **64**(37): 1042–6.
3. Kelly RH, Zatzick DF, Anders TF. The detection and treatment of psychiatric disorders and substance use among pregnant women cared for in obstetrics. *Am J Psychiatry* 2014; **158**(2): 213–9.
4. Briggs GG, Freeman RK,Yaffe SJ. Introduction. In *Drugs in Pregnancy and Lactation*, 9th edn. Philadelphia: Lippincott, Williams & Wilkins, 2011: xv–xxii.
5. Kraemer K. Placental transfer of drugs. *Neonatal Netw* 1997; **16**: 65–7.
6. Mahone PR, Scott K, Sleggs G, et al. Cocaine and metabolites in amniotic fluid may prolong fetal drug exposure. *Am J Obstet Gynecol* 1994; **171**: 465–9.
7. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics* 2004; **113**: 957–68.
8. Konijnenberg C. Methodological issues in assessing the impact of prenatal drug exposure. *Substance Abuse Res Treat* 2015; **9**(S2): 39–44.
9. Snodgrass SR. Cocaine babies: a result of multiple teratogenic influences. *J Child Neurol* 1994; **9**: 227–33.
10. Lemoine P, Harousseau H, Borteyru JP, et al. Les enfants des parents alcoholiques: anomolies observees a propos de 127 cas (The children of alcoholic parents: anomalies observed in 127 cases). *Quest Med* 1968; **25**: 476–82.
11. Jones KL, Smith DW, Ulleland CN, Streissguth AP. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1973; **301**(7815): 1267–71.
12. Stratton K, Howe C, Battaglia F, eds. *Institute of Medicine Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Washington: National Academy Press; 1996.
13. May PA, Keaster C, Bozeman R, et al. Prevalence and characteristics of fetal alcohol syndrome and partial fetal alcohol syndrome in a Rocky Mountain region city. *Drug Alcohol Depend* 2015; **155**: 118–27.
14. May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics* 2014; **134**(5): 855–66.
15. May PA, Blankenship J, Marais AS, et al. Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. *Alcohol Clin Exp Res.* 2013; **37**(5): 818–30.
16. Centre for Addiction and Mental Health C. Fetal alcohol spectrum disorders: how widespread are they in Canada? Available at: www.camh.ca/en/hospital/about_camh/newsroom/news_releases_media_advisories_and_backgrounders/current_year/Pages/Fetal-Alcohol-Spectrum-Disorders-How-Widespread-Are-They-in-Canada.aspx (accessed March 29, 2016).
17. Abel EL, Sokol RJ. A revised conservative estimate of the incidence of FAS and its economic impact. *Alcohol Clin Exp Res.* 1991; **15**(3): 514–24.
18. Harwood H. *Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Updated Methods and Data. Report Prepared by the Lewin Group*. Bethesda, MD:National Institute on Alcohol Abuse and Alcoholism, 2000.
19. Stade BC, Ali A, Bennett D, et al. The burden of prenatal exposure to alcohol: revised measurement of cost. *J Popul Ther Clin Pharmacol* 2009; **16**: e91–102.
20. Williams JF, Smith VC; Committee on Substance Abuse. Fetal alcohol spectrum disorders. *Pediatrics* 2015; **136**(5): e1395–406.
21. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 2005; **115**: 39–47.
22. Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. *Alcohol Alcohol* 2000; **35**: 400–10.
23. World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: WHO, 1992.
24. American Psychiatric Association. *A Diagnostic and Statistical Manual of Mental Disorders*, 5th edn.

16:22:13
.011

Arlington, VA: American Psychiatric Publishing, 2013: 798–801.

25. Centers for Disease Control and Prevention. *Fetal Alcohol Spectrum Disorders: Guidelines for Referral and Diagnosis*. Atlanta:CDC, 2004.
26. Chudley AE, Conry J, Cook JL, et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 2005; **172**: S1–21.
27. Cook JL, Green CR, Lilley CM, et al. Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan. *CMAJ* 2015; **188**(3): 191–7.
28. Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. *Pediatrics* 2016; **138**(2):pii: e20154256.
29. Swayze VW, Johnson VP, Hanson JW, et al. Magnetic resonance imaging of brain anomalies in fetal alcohol syndrome. *Pediatrics* 1997; **99**: 232–40.
30. Mattson SN, Schoenfeld AM, Riley EP. Teratogenic effects of alcohol on brain and behavior. *Alcohol Res Health* 2001; **25**(3): 185–91.
31. Spadoni AD, McGee CL, Fryer SL, Riley EP. Neuroimaging and fetal alcohol spectrum disorders. *Neurosci Biobehav Rev* 2007; **31**(2): 239–45.
32. Jacobson JL, Jacobson SW, Sokol RJ, et al. Effects of alcohol use, smoking and illicit drug use on fetal growth in black infants. *J Pediatr* 1994; **124**: 757–64.
33. Charness ME, Safran RM, Perides G. Ethanol inhibits neural cell-cell adhesion. *J Biol Chem* 1994; **269**: 9304–9.
34. DeJonge MH, Zachman RD. The effect of maternal ethanol ingestion on fetal rat heart vitamin A: a model for fetal alcohol syndrome. *Pediatr Res* 1995; **37**: 418–23.
35. Naus CCG, Bechberger JF. Effect of prenatal ethanol exposure on postnatal neural gene expression in the rat. *Dev Genet* 1991; **12**: 293–8.
36. Miller MW. Prenatal exposure to ethanol delays the schedule and rate of migration of neurons to rat somatosensory cortex. In *Fifth Congress of the International Society for Biomedical Research on Alcoholism (ISBRA)*. Denver: ISBRA, 1990.
37. Holzman C, Paneth N, Little R, et al. Perinatal brain injury in premature infants born to mothers using alcohol in pregnancy. *Pediatrics* 1995; **95**: 66–73.
38. Armant DR, Saunders DE. Exposure of embryonic cells to alcohol: contrasting effects during preimplantation and postimplantation development. *Semin Perinatol* 1996; **20**: 127–39.
39. Ahlgren SC, Thakur V, Bronner-Fraser M. Sonic hedgehog rescues cranial neural crest from cell death induced by ethanol exposure. *Proc Natl Acad Sci USA* 2002; **99**: 10476–81.
40. Peng Y, Yang PH, Ng SSM, et al. A critical role of *Pax6* in alcohol induced fetal microcephaly. *Neurobiol Dis* 2004; **16**: 370–6.
41. Chrisman K, Kenney R, Comin J, et al. Gestational ethanol exposure disrupts the expression of *Fgf8* and Sonic hedgehog during limb patterning. *Birth Defects Res A Clin Mol Teratol* 2004; **70**: 163–71.
42. Veazey KJ, Parnell SE, Miranda RC, Golding MC. Dose-dependent alcohol-induced alterations in chromatin structure persist beyond the window of exposure and correlate with fetal alcohol syndrome birth defects. *Epigenet Chromatin* 2015; **8**: 39.
43. Kleiber ML, Diehl EJ, Laufer BI, et al. Long-term genomic and epigenomic dysregulation as a consequence of prenatal alcohol exposure: a model for fetal alcohol spectrum disorders. *Front Genet* 2014; **5**: 161.
44. Mead EA, Sarkar DK. Fetal alcohol spectrum disorders and their transmission through genetic and epigenetic mechanisms. *Front Genet* 2014; **5**: 154.
45. Druse MJ, Kuo A, Tajuddin N. Effects of in utero ethanol exposure on the developing serotonergic system. *Alcohol Clin Exp Res* 1991; **15**: 678–84.
46. Pinazo-Duran MD, Renau-Piqueras J, Guerri C. Developmental changes in the optic nerve related to ethanol consumption in pregnant rats: analysis of the ethanol-exposed optic nerve. *Teratology* 1993; **48**: 305–22.
47. Church MW, Gerkin KP. Hearing disorders in children with fetal alcohol syndrome: findings from case reports. *Pediatrics* 1988; **82**: 147–54.
48. Syslak PH, Nathaniel EJH, Novak C, et al. Fetal alcohol effects on the postnatal development of the rat myocardium:an ultrastructural and morphometric analysis. *Exp Mol Pathol* 1994; **60**: 158–72.
49. Gage JC, Sulik KK. Pathogenesis of ethanol-induced hydronephrosis and hydroureter as demonstrated following in vivo exposure of mouse embryos. *Teratology* 1991; **44**: 299–312.
50. Autti-Rämö I, Fagerlund A, Ervalahti N, et al. Fetal alcohol spectrum disorders in Finland: clinical delineation of 77 older children and adolescents. *Am J Med Genet A* 2006; **140**: 137–43.
51. Day NL, Richardson G, Robles N, et al. Effect of prenatal alcohol exposure on growth and morphology of offspring at 8 months of age. *Pediatrics* 1990; **85**: 748–52.
52. Breese CR, D'Costa A, Ingram RL, et al. Long-term suppression of insulin-like growth factor-1 in rats after in utero ethanol exposure:relationship to somatic growth. *J Pharmacol Exp Ther* 1993; **264**: 448–57.
53. Mauceri HJ, Lee W, Conway S. Effect of ethanol on insulin-like growth factor-II release from fetal organs. *Alcohol Clin Exp Res* 1994; **18**: 35–41.

54. Guo W, Gregg JP, Fonkalsrud EW. Effect of maternal ethanol intake on fetal rabbit gastrointestinal development. *J Pediatr Surg* 1994; **29**: 1030–4.

55. American College of Obstetricians and Gynecologists. *Breastfeeding: Maternal and Infant Aspects* (Educational Bulletin Number 258). Washington, DC: ACOG, 2000.

56. Little RE, Anderson KW, Ervin CH, et al. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. *N Engl J Med* 1989; **321**: 425–30.

57. Graham JM, Hanson JW, Darby BL, et al. Independent dysmorphology evaluations at birth and 4 years of age for children exposed to varying amounts of alcohol in utero. *Pediatrics* 1988; **81**: 772–8.

58. Streissguth AP. The behavioral teratology of alcohol: performance, behavioral, and intellectual deficits in prenatally exposed children. In West JR, ed., *Alcohol and Brain Development*. New York:Oxford University Press, 1986: 3–44.

59. Streissguth AP, Aase JM, Clarren SK, et al. Fetal alcohol syndrome in adolescents and adults. *JAMA* 1991; **265**: 1961–7.

60. Kirkland SA, Dodds LA, Brosky G. The natural history of smoking during pregnancy among women in Nova Scotia. *CMAJ* 2000; **163**: 281–2.

61. Tong VT, England LJ, Dietz PM, Asare LA. Smoking patterns and use of cessation interventions during pregnancy. *Am J Prevent Med* 2008; **35**: 327–33.

62. Tong VT, Jones JR, Dietz PM, et al. Trends in smoking before, during, and after pregnancy: pregnancy risk assessment monitoring system (PRAMS), United States, 31 Sites, 2000–2005. *MMWR Surveill Summ* 2009; **58**: 1–29.

63. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and metaanalysis. *Pediatr Cardiol* 2013; **34**: 398–407.

64. Secker-Walker RH, Vacek PM, Flynn BS, et al. Smoking in pregnancy, exhaled carbon monoxide, and birth weight. *Obstet Gynecol* 1997; **89**: 648–53.

65. Visnjevac V, Mikov M. Smoking and carboxyhemoglobin concentrations in mothers and their newborn infants. *Toxicology* 1986; **5**: 175–7.

66. Jazayeri A, Tsibris JCM, Spellacy WN. Umbilical cord plasma erythropoietin levels in pregnancies complicated by maternal smoking. *Am J Obstet Gynecol* 1998; **178**: 433–5.

67. Jordanov JS. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on the 1st day of life. *Eur J Pediatr* 1990; **149**: 734–7.

68. Bernstein IM, Plocienik K, Stahle S, et al. Impact of maternal cigarette smoking on fetal growth and body composition. *Am J Obstet Gynecol* 2000; **183**: 883–6.

69. Law KL, Stroud LR, LaGasse LL, et al. Smoking during pregnancy and newborn neurobehavior. *Pediatrics* 2003; **111**: 1318–23.

70. Bardy AH, Seppälä T, Lillsunde P, et al. Objectively measured tobacco exposure during pregnancy: neonatal effects and relation to maternal smoking. *Br J Obstet Gynaecol* 1993; **100**: 721–6.

71. Bernstein IM, Mongeon JA, Badger GJ, et al. Maternal smoking and its association with birth weight. *Obstet Gynecol* 2005; **106**: 986–91.

72. Cliver SP, Goldenberg RL, Cutter GR, et al. The effect of cigarette smoking on neonatal anthropometric measurements. *Obstet Gynecol* 1995; **85**: 625–30.

73. Hermann M, King K, Weitzman M. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Curr Opin Pediatr* 2008; **20**: 184–90.

74. Bada HS, Das A, Bauer CR, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *J Perinatol* 2005; **25**: 631–7.

75. Resnik R, Brink GW, Wilkes M. Catecholamine-mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. *J Clin Invest* 1979; **63**: 1133–6.

76. Burton GJ, Palmer ME, Dalton KJ. Morphometric differences between the placental vasculature of non-smokers, smokers and ex-smokers. *Br J Obstet Gynaecol* 1989; **96**: 907–15.

77. Larsen LG, Clausen HV, Jonsson L. Stereologic examination of placentas from mothers who smoke during pregnancy. *Am J Obstet Gynecol* 2002; **186**: 531–7.

78. Gabrial R, Alsat E, Evain-Brion D. Alteration of epidermal growth factor receptor in placental membranes of smokers: relationship with intrauterine growth retardation. *Am J Obstet Gynecol* 1994; **170**: 1238–43.

79. Slotkin TA, McCook EC, Lappi SE, *et al.* Altered development of basal and forskolin-stimulated adenylate cyclase activity in brain regions of rats exposed to nicotine prenatally. *Dev Brain Res* 1992; **68**: 233–9.

80. Khoury MJ, Gomez-Frias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? *Am J Dis Child* 1989; **143**: 333–7.

81. Sullivan PM, Dervan LA, Reiger S, et al. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr* 2015; **166**: 978–84.

16:22:13
.011

82. Hacksaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update* 2011; **17**: 589–604.
83. Ananth CV, Savitz DA, Luther ER. Maternal cigarette smoking as a risk factor for placental abruption, placenta previa, and uterine bleeding in pregnancy. *Am J Epidemiol* 1996; **144**: 881–9.
84. Castles A, Adams K, Melvin CL, et al. Effects of smoking during pregnancy: five meta-analyses. *Am J Prevent Med* 1999; **16**: 208–15.
85. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. *Obstet Gynecol* 1980; **55**: 701–4.
86. Ananth CV, Getahun D, Peltier MR, et al. Placental abruption in term and preterm gestations: evidence for heterogeneity in clinical pathways. *Obstet Gynecol* 2006; **107**: 785–92.
87. Zdravkovic T, Genbacev O. McMaster MT, Fisher SJ. The adverse effects of maternal smoking on the human placenta: a review. *Placenta* 2005; **26A**: S81–6.
88. Usta IM, Hobeika EM, Musa AA, et al. Placenta previa-accreta: risk factors and complications. *Am J Obstet Gynecol* 2005; **193**: 1045–9.
89. Nabet C, Ancel PY, Burguet A, et al. Smoking during pregnancy and preterm birth according to obstetric history: French national perinatal surveys. *Paediatr Perinat Epidemiol* 2005; **19**: 88–96.
90. Salihu HM, Sharma PP, Getahun G. Prenatal tobacco use and risk of stillbirth: a case-control and bidirectional case–crossover study. *Nicotine Tobac Res* 2008; **10**: 159–66.
91. Varner MW, Silver RM, Rowland CJ, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet Gynecol* 2014; **123**: 113–25.
92. Marufu TC, Ahankari A, Coleman T, Lewis S. Maternal smoking and the risk of stillbirth: systemic review and meta-analysis. *BMS Public Health* 2015; **15**: 239–53.
93. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011; **377**: 1331–40.
94. Arbeille P, Bosc M, Vaillant MC, et al. Nicotine-induced changes in the cerebral circulation in ovine fetuses. *Am J Perinatol* 1992; **79**: 645–8.
95. Lei F, Yan X, Zhao F. Impairment of central chemoreception in neonatal rats induced by maternal cigarette smoke exposure during pregnancy. *PLoS One* 2015; **10**: e0137362.
96. Franco P, Groswasser J, Hassid S, et al. Prenatal exposure to cigarette smoking is associated with a decrease in arousal in infants. *J Pediatr* 1999; **135**: 34–8.
97. Hoffman HJ, Hillman LS. Epidemiology of the sudden infant death syndrome: maternal, neonatal, and postneonatal risk factors. *Clin Perinatol* 1992; **19**: 717–37.
98. Takashima S, Armstrong D, Becker LE, et al. Cerebral hypoperfusion in the sudden infant death syndrome, brainstem gliosis and vasculature. *Ann Neurol* 1978; **4**: 257–62.
99. Mezzacappa E, Buckner JC, Earls F. Prenatal cigarette exposure and infant learning stimulation as predictors of cognitive control in childhood. *Dev Sci* 2011; **14**: 881–91.
100. Drews CD, Murphy CC, Yeargin-Allsop M, et al. The relationship between idiopathic mental retardation and maternal smoking during pregnancy. *Pediatrics* 1996; **97**: 547–53.
101. Olds DL, Henderson CR, Tatelbaum R. Intellectual impairment in children of women who smoke cigarettes during pregnancy. *Pediatrics* 1994; **93**: 221–7.
102. Cornelius MD, De Genna NM, Leech SL, et al. Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers. *Neurotoxicol Teratol* 2011; **33**: 137–44.
103. Cornelius MD, Goldschmidt L, De Genna NM, Larkby C. Long-term effects of prenatal cigarette smoke exposure on behavior dysregulation among 14-year-old offspring of teenage mothers. *Matern Child Health J* 2012; **16**: 694–705.
104. Cornelius MD, Goldschmidt L, Day NL. Prenatal cigarette smoking: long term effects on young adult behavior problems and smoking behavior. *Neurotoxicol Teratol* 2012; **34**: 554–9.
105. Ernst M, Moolchan ET, Robisnon ML. Behavioral and neural consequences of prenatal exposure to nicotine. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 630–41.
106. Polanska K, Jurewicz J, Hanke W. Smoking and alcohol drinking during pregnancy as the risk factors for poor child neurodevelopment: a review of epidemiological studies. *Int J Occup Med Environ Health* 2015; **28**: 419–43.
107. John EM, Savitz DA, Sandler DP. Prenatal exposure to parents' smoking and childhood cancer. *Am J Epidemiol* 1991; **133**: 123–32.
108. Charlton A. Children and passive smoking: a review. *J Fam Pract* 1994; **38**: 267–77.
109. Paulson RB, Shanfeld J, Mullet D, et al. Prenatal smokeless tobacco effects on the rat fetus. *J Craniofac Genet Dev Biol* 1994; **14**: 16–25.
110. Inamdar AS, Croucher RE, Chokhandre MK, et al. Maternal smokeless tobacco use in pregnancy and adverse heatlh outcomes in newborns: a systematic review. *Nicotine Tobac Res* 2015; **17**: 1058–66.

.011

111. England LJ, Kim SY, Shapiro-Mendoza CK, et al. Effects of maternal smokeless tobacco use on selected pregnancy outcomes in Alaska Native women: a case-control study. *Acta Obstet Gynaecol Scand* 2013; **92**: 648–55.

112. Gunnerbeck A, Edstedt Bonamy AK, Wikstrom AK, et al. Maternal snuff use and smoking and the risk of oral cleft malformations: a population-based cohort study. *PLoS One* 2014; **9**: e84715.

113. Gunnerbeck A, Wikstrom AK, Edstedt Bonamy AK, et al. Relationship of maternal snuff and cigarette smoking with neonatal apnea. *Pediatrics* 2011; **128**: 503–9.

114. Weaver M, Breland A, Spindle T, Eissenberg T. Clinical case conference electronic cigarettes: a review of safety and clinical issues. *J Addict Med* 2014; **8**: 234–40.

115. Breland A, Spindle T, Weaver M, Eissenberg T. Science and electronic cigarettes: current data, future needs. *J Addict Med* 2014; **8**: 223–33.

116. Suter MA, Mastrobattista J, Sachs M, Aagaard K. Is there evidence for potential harm of electronic cigarette use in pregnancy? *Birth Defects Res A Clin Mol Teratol* 2015; **103**: 186–95.

117. Mark KS, Farquhar B, Chisolm MS, et al. Knowledge, attitudes, and practice of electronic cigarette use among pregnant women. *J Addict Med* 2015; **9**: 266–72.

118. Ostrea EM, Knapp DK, Romera A, et al. Meconium analysis to assess fetal exposure to nicotine by active and passive maternal smoking. *J Pediatr* 1994; **124**: 471–6.

119. Lee BO, Hong YC, Park H, et al. Secondhand smoke exposure during pregnancy and infantile development. *Environ Res* 2011; **111**: 539–44.

120. Makin J, Fried PA, Watkinson B. A comparison of active and passive smoking during pregnancy: long-term effects. *Neurotoxicol Teratol* 1991; **13**: 5–12.

121. Liu J, Leung PW, McCauley L, et al. Mother's environmental tobacco smoke exposure during pregnancy and externalizing behavior problems in children. *Neurotoxicology* 2013; **34**: 167–74.

122. Witschi H, Lundgaard SM, Rajini P, et al. Effects of exposure to nicotine and to sidestream smoke on pregnancy outcome in rats. *Toxicol Lett* 1994; **71**: 279–86.

123. Davis DL. Paternal smoking and fetal health. *Lancet* 1991; **337**: 123.

124. Klonoff-Cohen HS, Edelstein SL, Lefkowitz ES, et al. The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. *JAMA* 1995; **273**: 795–8.

125. Zhou S, Rosenthal DG, Sherman S, et al. Physical, behavioral, and cognitive effects of prenatal tobacco and postnatal secondhand smoke exposure. *Curr Probl Pediatr Adolesc Health Care* 2014; **44**: 219–41.

126. Selden BS, Clark RF, Curry SC. Marijuana. *Emerg Med Clin North Am* 1990; **8**: 8527–39.

127. Wu TC, Tashkin DP, Djahed B, et al. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med* 1988; **318**: 347–51.

128. Cornelius MD, Taylor PM, Geva D, et al. Prenatal tobacco and marijuana use among adolescents: effects on offspring gestational age, growth, and morphology. *Pediatrics* 1995; **95**: 738–43.

129. English DR, Hulse GK, Milne E, et al. Maternal cannabis use and birth weight: a meta-analysis. *Addiction* 1997; **92**: 1553–60.

130. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* 1999; **21**: 513–25.

131. Fried PA, Makin JE. Neonatal behavioral correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low risk population. *Neurotoxicol Teratol* 1987; **9**: 1–7.

132. Dahl RE, Scher MS, Williamson DE, et al. A longitudinal study of prenatal marijuana use: effects on sleep and arousal at age 3 years. *Arch Pediatr Adolesc Med* 1995; **149**: 145–50.

133. Fried PA. Prenatal exposure to marijuana and tobacco during infancy, early and middle childhood: effects and an attempt at synthesis. *Arch Toxicol Suppl* 1995; **17**: 233–60.

134. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodologic issues and findings. It's easy to throw the baby out with the bathwater. *Life Sci* 1995; **56**: 2159–68.

135. Campolongo P, Trezza V, Palmery M, et al. Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations. *Int Rev Neurobiol* 2009; **85**: 117–33.

136. Schneider M. Cannabis use in pregnancy and early life and its consequences: animal models. *Eur Arch Psychiatry Clin Neurosci* 2009; **259**: 383–93.

137. DiNieri JA, Wang X, Szutorisz H, et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry* 2011; **70**: 763–9.

138. Spano MS, Ellgren M, Wang X, Hurd YL. Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. *Biol Psychiatry* 2007; **61**: 554–63.

16:22:13
.011

139. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115**: 665–75.

140. Bailey DN. Cocaine and cocaethylene binding to human placenta in vitro. *Am J Obstet Gynecol* 1997; **177**: 527–31.

141. Jones KL. Developmental pathogenesis of defects associated with prenatal cocaine exposure: fetal vascular disruption. *Clin Perinatol* 1991; **18**: 139–46.

142. Singer LT, Arendt R, Minnes S, et al. Cognitive and motor outcomes of cocaine-exposed infants. *JAMA*. 2002; **287**(15): 1952–60.

143. Frank DA, Augustyn M, Knight WG, et al. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. *JAMA*. 2001; **285**(12): 1613–25.

144. Bandstra ES, Morrow CE, Anthony JC, et al. Intrauterine growth of full-term infants: impact of prenatal cocaine exposure. *Pediatrics* 2001; **108**: 1309–19.

145. Bateman DA, Chiriboga CA. Dose-response effect of cocaine on newborn head circumference. *Pediatrics* 2000; **106**: e33.

146. Kuhn L, Kline J, Ng S, et al. Cocaine use during pregnancy and intrauterine growth retardation: new insights based on maternal hair tests. *Am J Epidemiol* 2000; **152**: 112–19.

147. Dinsmoor MJ, Irons SJ, Christmas JT. Preterm rupture of the membranes associated with recent cocaine use. *Am J Obstet Gynecol* 1994; **171**: 305–9.

148. Kliegman RM, Madura D, Kiwi R, et al. Relation of maternal cocaine use to the risks of prematurity and low birth weight. *J Pediatr* 1994; **124**: 751–6.

149. Iriye BK, Bristow RE, Hsu CD, et al. Uterine rupture associated with recent antepartum cocaine abuse. *Obstet Gynecol* 1994; **83**: 840–1.

150. Macones GA, Sehdev HM, Parry S, et al. The association between maternal cocaine use and placenta previa. *Am J Obstet Gynecol* 1997; **177**: 1097–100.

151. Czyrko C, Del Pin CA, O'Neill JA, et al. Maternal cocaine abuse and necrotizing enterocolitis: outcome and survival. *J Pediatr Surg* 1991; **26**: 414–18.

152. Büyükünal C, Kiliç N, Dervisoglu S, et al. Maternal cocaine abuse resulting in necrotizing enterocolitis: an experimental study in a rat model. *Acta Paediatr* 1994; **396**: 91–3.

153. Chasnoff IJ, Bussey ME, Savich R, et al. Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; **108**: 456–9.

154. Singer LT, Yamashita TS, Hawkins S, et al. Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; **124**: 765–71.

155. Sims ME, Walther FJ. Antenatal brain injury and maternal cocaine use. *J Perinatol* 1989; **9**: 349–50.

156. Behnke M, Eyler FD, Conlon M, et al. Incidence and description of structural brain abnormalities in newborns exposed to cocaine. *J Pediatr* 1998; **132**: 291–4.

157. Mott SH, Packer RJ, Soldin SJ. Neurologic manifestations of cocaine exposure in childhood. *Pediatrics* 1994; **93**: 557–60.

158. Chen C, Duara S, Neto GS, et al. Respiratory instability in neonates with in utero exposure to cocaine. *J Pediatr* 1991; **119**: 111–13.

159. Tronick EZ, Frank DA, Cabral H, et al. Late dose-response effects of prenatal cocaine exposure on newborn neurobehavioral performance. *Pediatrics* 1996; **98**: 76–83.

160. Chan K, Dodd PA, Day L, et al. Fetal catecholamine, cardiovascular, and neurobehavioral responses to cocaine. *Am J Obstet Gynecol* 1992; **167**: 1616–23.

161. Knapp S, Mandell AJ. Narcotic drugs: effect on the serotonin biosynthetic systems of the brain. *Science* 1972; **177**: 1209–11.

162. Durand DJ, Espinoza AM, Nickerson BG. Association between prenatal cocaine exposure and sudden infant death syndrome. *J Pediatr* 1990; **117**: 909–11.

163. Bauchner H, Zuckerman B, McClain M, et al. Risk of sudden infant death syndrome among infants with in utero exposure to cocaine. *J Pediatr* 1988; **113**: 831–4.

164. Mayes LC, Granger RH, Frank MA, et al. Neurobehavioral profiles of neonates exposed to cocaine prenatally. *Pediatrics* 1993; **91**: 778–83.

165. Eisen LN, Field TM, Bandstra ES, et al. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton scale. *Pediatrics* 1991; **88**: 477–80.

166. Eyler FD, Behnke M, Conlon M, et al. Birth outcome from a prospective, matched study of prenatal crack/cocaine use. I. Interactive and dose effects on health and growth. *Pediatrics* 1998; **101**: 229–37.

167. Eyler FD, Behnke M, Conlon M, et al. Birth outcome from a prospective, matched study of prenatal crack/cocaine use. II. Interactive and dose effects on neurobehavioral assessment. *Pediatrics* 1998; **101**: 237–41.

168. Frank DA, Augustyn M, Knight WG, et al. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. *JAMA* 2001; **285**: 1613–25.

.011

169. Roland EH, Volpe JJ. Effect of maternal cocaine use on the fetus and newborn: review of the literature. *Pediatr Neurosci* 1989; **15**: 88–94.

170. Oro A, Dixon S. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr* 1987; **111**: 571–8.

171. Chasnoff IJ, Lewis DE, Squires L. Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; **80**: 836–8.

172. Chaney NE, Franke J, Waddington WB. Cocaine convulsions in a breast-feeding baby. *J Pediatr* 1988; **112**: 134–5.

173. Hulse GK, Milne E, English DR, et al. The relationship between maternal use of heroin and methadone and infant birth weight. *Addiction* 1997; **92**: 1571–9.

174. Barg J, Rius A, Bem WT, et al. Differential development of beta-endorphin and mu-opioid binding sites in mouse brain. *Dev Brain Res* 1992; **66**: 71–6.

175. Suguihara C, Bancalari E. Substance abuse during pregnancy: effects on respiratory function in the infant. *Semin Perinatol* 1991; **15**: 302–9.

176. Olson GD, Lees MH. Ventilatory response to carbon dioxide of infants following chronic prenatal methadone exposure. *J Pediatr* 1980; **96**: 983–9.

177. Bunikowski R, Grimmer I, Heiser A, et al. Neurodevelopmental outcome after prenatal exposure to opiates. *Eur J Pediatr* 1998; **157**: 724–30.

178. Smialek JE, Monforte JR, Aronow R, et al. Methadone deaths in children: a continuing problem. *JAMA* 1977; **238**: 2516–17.

179. Committee on Drugs, American Academy of Pediatrics. Transfer of drugs and other chemicals into human milk. *Pediatrics* 1989; **84**: 924–36.

180. Guo X, Spencer JW, Suess PE, et al. Cognitive brain potential alterations in boys exposed to opiates: in utero and lifestyle comparisons. *Addict Behav* 1994; **19**: 429–41.

181. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev* 2008; **84**: 29–35.

182. Hickey JE, Suess PE, Newlin DB, et al. Vagal tone regulation during sustained attention in boys exposed to opiates in utero. *Addict Behav* 1995; **20**: 43–59.

183. Ornoy A, Michailevskaya V, Lukashov I, et al. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. *Child Abuse Negl* 1996; **20**: 385–96.

184. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. *Dev Med Child Neurol* 2001; **43**: 668–75.

185. Idänpäan-Heikkilä JE, Jouppila PI, Puolakka JO, et al. Placental transfer and fetal metabolism of diazepam in early pregnancy. *Am J Obstet Gynecol* 1971; **109**: 1011–16.

186. Laegreid L, Olegärd R, Walström J, et al. Teratogenic effects of benzodiazepine use during pregnancy. *J Pediatr* 1989; **114**: 126–31.

187. Wikner BN, Stiller C-O, Bergman U, et al. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf* 2007; **16**: 1203–10.

188. Eros E, Czeizel AE, Rockenbauer M, et al. A population-based case control teratologic study of nitrazepam, medazepam, tofisopam, alprazolum and clonazepam treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2002; **101**: 147–54.

189. Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. *Gen Hosp Psychiatry* 2013; **35**: 3–8.

190. Ban L, West J, Gibson JE, Fiaschi L, et al. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. *PLoS One* 2014; **9**: e100996.

191. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. *Am J Obstet Gynecol* 2015; **212**: 428–41.

192. Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv* 2002; **53**: 39–49.

193. Kallen B, Reis M. Neonatal complications after maternal concomitant use of SSRI and other central nervous system active drugs during the second or third trimester of pregnancy. *J Clin Psychopharmacol* 2012; **32**: 608–14.

194. Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, *et al.* Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. *Acta Paediatr* 2000; **89**: 533–41.

195. Verrotti A, Scaparrotta A, Cofini M, et al. Developmental neurotoxicity and anticonvulsant drugs: a possible link. *Reprod Toxicol* 2014; **48**: 72–80.

196. Browne ML, Van Zutphen AR, Botto LD, et al. Maternal butalbital use and selected defects in the national birth defects prevention study. *Headache* 2014; **54**: 54–66.

16:22:13
.011

197. Rementeria JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. *J Pediatr* 1977; **90**: 123–6.

198. Izquierdo LA, Yonke N. Fetal surveillance in late pregnancy and during labor. *Obstet Gynecol Clin N Am* 2014; **41**: 307–15.

199. Ladhani NN, Shah PS, Murphy KE. Prenatal amphetamine exposure and birth outcomes: a systematic review and metaanalysis. *Am J Obstet Gyncol* 2011; **205**(219): e1–7.

200. Stek AM, Baker RS, Fisher BK, et al. Fetal responses to maternal and fetal methamphetamine administration in sheep. *Am J Obstet Gynecol* 1995; **173**: 1592–8.

201. Shah R, Diaz SD, Arria A, et al. Prenatal methamphetamine exposure and short-term maternal and fetal outcomes. *Am J Perinatol* 2012; **29**: 391–400.

202. Plessinger MA. Prenatal exposure to amphetamines: risks and adverse outcomes in pregnancy. *Obstet Gynecol Clin North Am* 1998; **25**: 119–38.

203. Ganapathy V, Ramamoorthy S, Leibach FH. Transport and metabolism of monoamines in the human placenta. *Trophoblast Res* 1993; **7**: 35–51.

204. Ganapathy VV, Prasad PD, Ganapathy ME, Leibach FH. Drugs of abuse and placental transport. *Adv Drug Deliv Rev* 1999; **38**: 99–110.

205. Wright TE, Schuetter R, Tellei J, Sauvage L. Methamphetamines and pregnancy outcome. *J Addict Med* 2015; **9**: 111–17.

206. Bottalico B, Larson I, Brodszicki J, et al. Norepinephrine transporter (NET), serotonin transporter (SERT), vesicular monoamine transporter (VMAT2) and organic cation transporters (OCT1, 2 and EMT) in human placenta from pre-eclamptic and normotensive pregnancies. *Placenta* 2004; **25**: 518–29.

207. Ganapathy V. Drugs of abuse and human placenta. *Life Sci* 2011; **88**: 926–30.

208. Gorman MC, Orme KS, Nguyen NT, et al. Outcomes in pregnancies complicated by methamphetamine use. *Am J Obstet Gynecol* 2014; **211**(429): e1–7.

209. Geary FH, Turnquest Wells MA. Management of the patient in labor who has abused substances. *Clin Obstet Gynecol* **56**: 166–72.

210. Ericksson M, Larsson C, Zetterström R. Amphetamine addiction and pregnancy. *Acta Obstet Gynaecol Scand* 1981; **60**: 253–9.

211. Arria AM, Derauf C, LaGasse LL, et al. Methamphetamine and other substance use during pregnancy: preliminary estimates from the infant development, environment, and lifestyle (IDEAL) study. *Matern Child Health J* 2006; **10**: 293–302.

212. Nasif FJ, Cuadra GR, Ramirez OA. Permanent alteration of cerebral noradrenergic system by prenatally administered amphetamine. *Brain Res Dev Brain Res* 1999; **112**: 181–8.

213. Tavares MA, Silva MC. Differential effects of prenatal exposure to cocaine and amphetamine on growth parameters and morphometry of the prefrontal cortex in the rat. *Ann NY Acad Sci* 1996; **801**: 256–73.

214. Tavares MA, Silva MC, Silva-Araujo A, et al. Effects of prenatal exposure to amphetamine in the medial prefrontal cortex of the rat. *Int J Dev Neurosci* 1996; **14**: 585–96.

215. Chang L, Smith LM, LoPresti C, et al. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res* 2004; **132**: 95–106.

216. Dixon SD, Bejar R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: incidence and clinical correlates. *J Pediatr* 1989; **115**: 770–8.

217. McElhatton PR, Pughe KR, Evans C, *et al*. Is exposure to amphetamine-like drugs in pregnancy associated with malformations? *J Toxicol Clin Toxicol* 2000; **38**: 195–6.

218. Torfs CP, Velie EM, Oechsli FW, et al. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* 1994:**50**: 44–53.

219. Holbrook BD, Rayburn WF. Teratogenic risks from exposure to illicit drugs. *Obstet Gynecol Clin North Am* 2014; **41**: 229–39.

220. Forrester MB, Merz RD. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986–2002. *J Toxicol Environ Health A* 2007; **70**: 7–18.

221. Little BB, Snell LM, Gilstrap LC. Methamphetamine abuse during pregnancy: outcome and fetal effects. *Obstet Gynecol* 1988; **72**: 541–4.

222. Oei J, Abdel-Latif ME, Clark R, et al. Short-term outcomes of mothers and infants exposed to antenatal amphetamines. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**: F36–41.

223. Nguyen D, Smith LM, LaGasse LL, et al. Intrauterine growth of infants exposed to prenatal methamphetamine: results from the infant development, environment, and lifestyle study. *J Pediatr* 2010; **157**: 337–9.

224. Smith LM, LaGasse LL, Derauf C, et al. The infant development, environment, and lifestyle study: effects

.011

of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics* 2006; **118**: 1149–56.

225. Oro AS, Dixon SP. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr* 1987; **111**: 571–8.

226. Smith LM, Diaz S, LaGasse LL, et al. Developmental and behavioral consequences of prenatal methamphetamine exposure: a review of the infant development, environment, and lifestyle (IDEAL) study. *Neurotoxicol Teratol* 2015; **51**: 35–44.

227. Kiblawi ZN, Smith LM, Diaz SD, et al. Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. *Subst Abus* 2014; **35**: 68–73.

228. Behnke M, Smith VC. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013; **131**: e1009–24.

229. Zabaneh R, Smith LM, LaGasse LL, et al. The effects of prenatal methamphetamine exposure on childhood growth patterns from birth to 3 years of age. *Am J Perinatol* 2012; **29**: 203–10.

230. Diaz SD, Smith LM, LaGasse LL, et al. Effects of prenatal methamphetamine exposure on behavioral and cognitive findings at 7.5 years of age. *J Pediatr* 2014; **164**: 1333–8.

231. Cernerud L, Eriksson M, Jonsson B, et al. Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. *Acta Paediatr* 1996; **85**: 204–8.

232. LaGasse LL, Derauf C, Smith LL, et al. Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age. *Pediatrics* 2012; **129**: 681–8.

233. Kwiatkowski MA, Roos A, Stein DJ, et al. Effects of prenatal methamphetamine exposure: a review of cognitive and neuroimaging studies. *Metab Brain Dis* 2014; **29**: 245–54.

234. Holbrook BD, Rayburn WF. Teratogenic risks from exposure to illicit drugs. *Obstet Gynecol Clin North Am* 2014; **41**: 229–39.

235. Anderson CE, Loomis GA. Recognition and prevention of inhalant abuse. *Am Fam Physician* 2003; **68**: 869–74.

236. Linden CH. Volatile substances of abuse. *Emerg Med Clin North Am* 1990; **8**: 559–78.

237. Scheeres JJ, Chudley AE. Solvent abuse in pregnancy: a perinatal perspective. *J Obstet Gynaecol Can* 2001; **24**: 22–6.

238. Geary FH, Turnquist Wells MA. Management of the patient in labor who has abuse substances. *Clin Obstet Gynecol* 2013; **56**: 166–72.

239. Jones HE, Balster RL. Inhalant abuse in pregnancy. *Obstet Gynecol Clin North Am* 1998; **25**: 153–67.

240. Hannigan JH, Bowen SE. Reproductive toxicology and teratology of abused toluene. *Syst Biol Reprod Med* 2010; **56**: 184–200.

241. Ghantous H, Danielsson BRG. Placental transfer and distribution of toluene, xylene, and benzene and their metabolites during gestation in mice. *Biol Res Pregnancy* 1986; **7**: 98–105.

242. Stoltenbeurg-Didinger G, Altenkirch H, Wagner M. Neurotoxicity of organic solvent mixtures: embryotoxicity and fetotoxicity. *Neurotoxicol Teratol* 1990; **12**: 585–9.

243. Gospe SM, Zhou SS. Prenatal exposure to toluene results in abnormal neurogenesis and migration in rat somatosensory cortex. *Pediatr Res* 2000; **47**: 362–8.

244. Gospe SM, Zhou SS. Toluene abuse embryopathy: longitudinal neurodevelopmental effects of prenatal exposure to toluene in rats. *Reprod Toxicol* 1998; **12**: 119–26.

245. Bowen SE, Hannigan JH. Developmental toxicity of prenatal exposure to toluene. *AAPS J* 2006; **8**: E419–24.

246. Bowen SE, Batis JC, Mohammadi MH, Hannigan JH. Abuse pattern of gestational toluene exposure and early postnatal development in rats. *Neurotoxicol Teratol* 2005; **27**: 105–16.

247. Pearson MA, Hoyme HE, Seaver LH, et al. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 1994; **93**: 211–15.

248. Arnold GL, Kirby RS, Langendoerfer S, Wilkins-Haug L. Toluene embryopathy: clinical delineation and developmental follow-up. *Pediatrics* 1994; **93**: 216–20.

249. Bowen SE. Two serious and challenging medical complications associated with volatile substance misuse: sudden sniffing death and fetal solvent syndrome. *Subst Use Misuse* 2011; **46**: 68–72.

250. Boynukalin FK, Baykal C. Prenatal diagnosis of multiple fetal anomalies in naphthalene-addicted pregnant women: a case report. *Clin Exp Obstet Gynecol* 2014; **41**: 217–18.

251. Schutzman DL, Frankenfield-Chernicoff M, Clatterbaugh HE, et al. Incidence of intrauterine cocaine exposure in a suburban setting. *Pediatrics* 1991; **88**: 825–7.

252. Chasnoff IJ, Landres HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. *N Engl J Med* 1990; **322**: 1202–6.

16:22:13
.011

253. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115**: 665–75.

254. Ryan RM, Wagner CL, Schultz JM, et al. Meconium analysis for improved identification of infants exposed to cocaine in utero. *J Pediatr* 1994; **125**: 435–40.

255. Saitoh M, Uzuka M, Sakamoto M. Rate of hair growth. *Adv Biol Skin* 1969; **9**: 183–201.

256. Baumgartner WA, Hill VA, Bland WH. Hair analysis for drug abuse. *J Forensic Sci* 1989; **34**: 1433–53.

257. Marques PR, Tippetts AS, Branch DG. Cocaine in the hair of mother-infant pairs: quantitative analysis and correlations with urine measurements and self report. *Am J Drug Alcohol Abuse* 1993; **19**: 159–75.

Chapter 11

Hypertensive Disorders of Pregnancy

Amy E. Judy, Maurice L. Druzin, and Deirdre J. Lyell

Introduction

Hypertensive disorders of pregnancy complicate up to 12–22% of all pregnancies and are the second leading cause of maternal death [1,2]. They also contribute significantly to neonatal morbidity and mortality.

The American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy (ACOG Task Force) separates hypertensive disease of pregnancy into four categories: (1) preeclampsia-eclampsia, (2) chronic hypertension, (3) chronic hypertension with superimposed preeclampsia, and (4) gestational hypertension [3]. This classification, initially proposed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [4], is an effort to create uniformity in diagnosis for diagnostic, management, and research purposes. While these classifications identify distinct signs and symptoms, hypertensive disorders of pregnancy may represent a spectrum of disease, and thus the distinctions between these classifications can be blurred. This chapter discusses chronic hypertension, gestational hypertension, and preeclampsia/superimposed preeclampsia, their known fetal effects, and treatment and intervention options.

The fetal and neonatal effects of hypertensive disorders of pregnancy result primarily from alterations in placental perfusion, iatrogenic prematurity, and effects of maternal medications. In addition, the *Barker hypothesis* postulates that the intrauterine environment may reprogram fetal physiology and place the fetus at risk later in life for specific adult diseases. Retrospective studies have correlated low birth weight (intrauterine growth restriction [IUGR]) with diverse adult diseases including hypertension, coronary artery disease, and type 2 diabetes [5]. It is unclear whether these correlations imply that adult diseases are related to the intrauterine environment or whether they reflect the multiple causes of IUGR and are markers for genetic heredity and/or childhood environment.

The most frequent neonatal sequela from hypertensive disorders of pregnancy is prematurity because definitive treatment of preeclampsia entails delivery of the newborn and the placenta. However, clinical sequelae of this disease will often continue into the postpartum period.

Hypertension in Pregnancy

In normal pregnancy, maternal blood pressure decreases early and generally reaches a nadir at approximately 22 weeks' gestation. Subsequently, blood pressure gradually increases, returning to near baseline by the end of the third trimester [6]. Thus, if a patient presents with hypertension in the second or third trimester without documented blood pressure measurements from prepregnancy or the first trimester, it may be impossible to know whether these elevated blood pressures represent a chronic or pregnancy-related condition. Distinguishing chronic hypertension, gestational hypertension, and preeclampsia is important because the diagnosis correlates strongly with the disease course and with maternal, fetal, and neonatal outcomes. Diagnosis, therefore, informs clinical management.

Chronic Hypertension

Chronic hypertension is defined as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) that is diagnosed prior to pregnancy or at less than 20 weeks' gestation (Table 11.1). Women previously diagnosed with hypertension or taking medications for hypertension are also considered to have chronic hypertension, even if blood pressure in early pregnancy is normal. Hypertension that is diagnosed after 20 weeks' gestation and does not resolve by 12 weeks postpartum is also classified as chronic hypertension [4,7].

Chronic hypertension affects both maternal and fetal physiology. Ideally, a woman with chronic

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Table 11.1 Classification of Hypertensive Disorders of Pregnancy

Chronic hypertension
Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg that is present before pregnancy or before 20 weeks' gestation or hypertension diagnosed after 20 weeks' gestation that does not resolve postpartum [3,4,7]
Gestational hypertension
Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg that is diagnosed after 20 weeks' gestation and is not associated with significant proteinuria (≥300 mg/24 h) or other systemic manifestations [3]
Preeclampsia
Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart after 20 weeks' gestation in a previously normotensive patient and significant proteinuria (≥300 mg/24 hs) *or* new onset of any of the following: • Thrombocytopenia (platelet count < 100,000/μL) • Renal insufficiency (serum creatinine > 1.1 mg/dL or creatinine 2× baseline) • Impaired liver function (serum transaminases 2× normal) • Pulmonary edema • Cerebral or visual symptoms
Superimposed preeclampsia
The development of preeclampsia (as defined earlier) in a woman with underlying chronic hypertension.

hypertension should be evaluated prior to pregnancy or early in pregnancy. First, she should be classified as having primary or secondary hypertension. Secondary causes of hypertension should be suspected if blood pressure is particularly high or particularly difficult to control (high doses of a single antihypertensive or multiple antihypertensives are needed). Secondary causes of hypertension include coarctation of the aorta, underlying renal disease, renal artery stenosis, pheochromocytoma, Cushing's disease, hyperthyroidism, malignant hypertension, and drug-induced hypertension. Secondary causes of hypertension are important to identify in order to treat or manage the underlying cause, in addition to treatment of the blood pressure itself. It is important to identify any end-organ effects of maternal hypertension, such as left ventricular hypertrophy or renal dysfunction, for risk stratification of the pregnancy and prevention of further end-organ damage [4,7]. A baseline assessment of serum creatinine and a 24-hour urine sample for protein quantification early in pregnancy are critical to distinguish worsening hypertension from superimposed preeclampsia. A baseline assessment of liver enzymes, platelet count, and uric acid can also be considered.

Chronic hypertension affects the fetus primarily by altering placental vessels and placental perfusion. Decidual vessels of women with chronic hypertension demonstrate microvascular changes similar to those seen in the renal arterioles of women with chronic hypertension [6]. These microvascular changes are thought to explain increased risks for placental abruption (threefold increased risk) [3] and IUGR (30–50%). Early abnormal placental vasculature/implantation may also be related to the pathogenesis of superimposed preeclampsia [6]. Up to one-third of women with chronic hypertension will have a SGA infant (<10th percentile), and two-thirds will have a preterm delivery. Approximately 20–25% of women with chronic hypertension will develop superimposed preeclampsia [6]. Women with chronic hypertension are more likely to have earlier and more severe preeclampsia. Most of the fetal morbidity associated with chronic hypertension is thought likely due to IUGR and superimposed preeclampsia [6].

The ACOG Task Force suggests ultrasound screening for fetal growth restriction among women with chronic hypertension and umbilical artery Doppler velocimetry assessment if fetal growth restriction is detected [3]. The ACOG Task Force suggests antenatal surveillance (nonstress testing, biophysical profile [BPP] or modified BPP) only in cases of "complicated" chronic hypertension – requiring medication, presence of fetal growth restriction, or superimposed preeclampsia [3,4]. Others perform routine antenatal testing in the third trimester. In the absence of other complications, delivery for women with chronic hypertension controlled by medications is recommended at 37–39 weeks and for women with hypertension controlled without medications at 38–39 weeks [3,8]. Earlier delivery should be dictated by nonreassuring fetal status, including intrauterine growth restriction, or superimposed preeclampsia. The route of delivery should be decided by usual obstetric indications.

Treatment of chronic hypertension in pregnancy is controversial. Expert opinion holds that women with baseline blood pressures of 140–179/90–109 mmHg and normal renal function are generally

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considered to be at low risk for maternal cardiovascular complications in the relatively short time frame of pregnancy [4], although little data exist to support this. Treatment of hypertension in pregnancy may be beneficial to the mother in the long term, especially when she has renal disease or left ventricular hypertrophy. However, meta-analyses have not demonstrated that treatment of mild to moderate chronic hypertension improves fetal outcomes or decreases maternal morbidity [3,9]. Further, there is concern that decreasing maternal blood pressure will decrease uterine-placental perfusion and impair fetal growth and development, with meta-analyses suggesting a higher incidence of SGA infants among women treated for mild chronic hypertension [10]. A recent randomized trial comparing "tight" (diastolic blood pressure ≤ 85 mmHg) to "less tight" (diastolic blood pressure 85–105 mmHg) control of chronic hypertension in pregnancy did not find a difference in perinatal outcomes between groups, although a higher incidence of development of severe hypertension (≥160/110 mmHg) was observed in women randomized to "less tight" control [10]. Thus the decision to treat chronic hypertension in pregnancy should weigh the risks and benefits to the mother and the fetus.

The ACOG Task Force recommends that antihypertensive therapy be initiated for women with severe chronic hypertension, with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 105 mmHg [3], and that blood pressure targets for these women be 120–160 mmHg systolic and 80–105 mmHg diastolic. For women with chronic hypertension and blood pressures below these thresholds, routine treatment is not recommended. However, in the presence of end-organ dysfunction, such as left ventricular hypertrophy or renal insufficiency, a lower treatment threshold may be considered [3,6].

Antihypertensive medications used to treat chronic hypertension in pregnancy include α-methyldopa, labetalol, and slow-release nifedipine [3]. None of these medications has been associated with teratogenesis. ACE inhibitors and angiotensin receptor blockers should not be used due to demonstrated teratogenicity (discussed later in this chapter) [3].

Gestational Hypertension

Gestational hypertension is defined as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) first diagnosed after 20 weeks' gestation that is *not* associated with significant proteinuria (≥300 mg/24-hour period) or other systemic findings. The blood pressure must be elevated in at least two measurements, taken 4 hours apart [3]. *Severe* gestational hypertension is defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg [12], and many obstetricians manage this condition in the same manner as preeclampsia with severe features. Gestational hypertension should be considered a transient diagnosis; if hypertension does not resolve in the first 12 weeks postpartum, then the diagnosis of chronic hypertension is given.

Gestational hypertension encompasses a heterogeneous group that includes women with true transient hypertension, women with undiagnosed chronic hypertension, and women with early/incompletely manifested preeclampsia. Given this heterogeneity, gestational hypertension may represent a benign or hazardous pregnancy condition. The course of the disease reflects individual underlying pathophysiology.

Identifying which women with gestational hypertension will have a morbid clinical course is a significant clinical problem. Anywhere from 15–60% of women with gestational hypertension will develop preeclampsia [13,14]. Traditionally, gestational hypertension was distinguished from preeclampsia based on the absence of proteinuria alone, leading some to incorrectly assume that the absence or presence of proteinuria distinguished perinatal risk. In fact, gestational hypertension without proteinuria also confers increased risk of maternal and perinatal complications compared with normotensive patients. One study reports that up to 19% of women with eclampsia had only gestational hypertension at the time of the seizure [15]. Both the degree of proteinuria and the degree of hypertension likely confer perinatal risk. Buchbinder et al. showed that women with severe gestational hypertension had higher rates of preterm delivery at less than 35 weeks (25% versus 8.4%) and SGA infants at less than the 10th percentile (20.8% versus 6.5%) compared with women who were normotensive or had mild gestational hypertension. In this study, multivariate analysis showed that severe hypertension was strongly associated with poor perinatal outcome, whereas proteinuria was not [12]. Woelkers et al. also found women with severe gestational hypertension to be at similar risk of adverse maternal and neonatal outcomes compared with women with "traditional" preeclampsia [16]. Other studies suggest that gestational hypertension may lead to

less maternal and neonatal morbidity than preeclampsia. North et al. reported that compared with women with gestational hypertension alone, women with preeclampsia were more likely to develop severe maternal hypertension (63.4% versus 26.5%, $p < 0.001$), deliver SGA infants at less than the 10th percentile (25.4% versus 20.5%, $p < 0.01$), and deliver at less than 37 weeks (35.2% versus 6%, $p < 0.0001$) [17].

Until more is understood about the pathophysiology of preeclampsia and superimposed preeclampsia, distinguishing gestational hypertension that is benign from that which is a harbinger of severe maternal or perinatal disease will remain a challenge. Earlier gestational age of onset and severe hypertension are associated with worse outcomes [12,13]. Therefore, careful monitoring and evaluation of all women with gestational hypertension should be performed, including frequent evaluation of maternal blood pressure, maternal symptoms, and fetal well-being. Maternal proteinuria, renal and hepatic function, and platelet count should be assessed frequently.

Preeclampsia and Superimposed Preeclampsia

Preeclampsia differs from chronic hypertension in that it is a syndrome specific to pregnancy. *Preeclampsia* is defined as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg two times 4 hours apart) occurring after 20 weeks in a previously normotensive patient *with* significant proteinuria (≥300 mg/24-hour urine collection) or other symptoms of systemic involvement [3]. *Superimposed preeclampsia* is the development of preeclampsia in a woman with preexisting chronic hypertension. Superimposed preeclampsia can be difficult to diagnose due to the similarity of signs between chronic hypertension and preeclampsia and is characterized by new onset of proteinuria, a sudden increase in preexisting proteinuria, or the development of severe signs/symptoms of preeclampsia in a woman with chronic hypertension (see Table 11.1) [3,7].

The incidence of preeclampsia is approximately 5% [18]. The incidence of severe features of preeclampsia is 0.9% [19]. Risk factors include nulliparity, African-American race, chronic hypertension, renal disease, connective-tissue disorders, pregestational diabetes, obesity, multiple gestations, and extremes of maternal age [6].

Table 11.2 Severe Features of Preeclampsia [3]

- Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on two occasions at least 4 hours apart while on bed rest (unless antihypertensive therapy has been initiated before this time)
- Thrombocytopenia (platelet count < 100,000/μL)
- Progressive renal insufficiency (serum creatinine > 1.1 mg/dL or a doubling of creatinine in the absence of other renal disease)
- Impaired liver function (serum transaminases 2× normal) or severe, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by other diagnoses or both
- Pulmonary edema
- New-onset cerebral or visual disturbances

The clinical features of preeclampsia are caused by vasospasm (increased systemic vascular resistance) and endothelial cell dysfunction (increased vascular permeability and platelet aggregation). Most often the disease course is mild, with mild hypertension and proteinuria. Severe cases are marked by uncontrollable hypertension, thrombotic microangiopathy (small-vessel thrombosis), and tissue edema leading to end-organ damage. End-organ damage can involve seizures (<1%), stroke (<1%), pulmonary edema (2–5%), renal insufficiency and hepatic failure (<1%), and thrombocytopenia/hemolytic anemia (10–20%) [20]. This syndrome also can affect the fetus, manifesting as intrauterine growth restriction (10–25%), oligohydramnios, and/or abruption (1–4%) [20]. Table 11.2 lists the severe features of preeclampsia.

Women with underlying medical disease, such as chronic hypertension, renal disease, or autoimmune disease, are at increased risk for developing preeclampsia earlier and in more severe forms [20]. The severity of illness in the mother and fetus are not always concordant.

Multiple theories for the pathogenesis of preeclampsia exist. The most prevalent theories have implicated (1) abnormal placental implantation and/or (2) abnormal maternal immunologic response to the placenta. A recent literature-substantiated hypothesis marries these theories and implicates maternal-fetal immune maladaptation as causing superficial placentation, with associated underperfusion and even hypoxia resulting in oxidative stress. Subsequent placental events may trigger a systemic inflammatory

response in the mother, which causes endothelial cell dysfunction and vasospasm [21]. Key players likely include the placental-derived antiangiogenic proteins soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin, which diffuse into the maternal sera. sFlt1 acts by reducing circulating placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), causing direct endothelial cell dysfunction and inhibiting vasodilation. Soluble endoglin (sEng) acts as a soluble inhibitor of transforming growth factor 1β (TGF-β1), potentially blocking the activation of endothelial nitric oxide synthase, resulting in vasospasm [21]. Placental pathology in pregnancies complicated by preeclampsia reveals changes similar to those seen with intrauterine growth restriction [22].

Why one pregnancy complicated by immune maladaptation and poor placentation manifests as maternal disease, another manifests as fetal disease, and still another manifests as both is unclear. Varying clinical presentation may result from the degree of placental damage, the extent of inflammatory reaction, and/or the maternal response to molecular mediators.

Treatment

Definitive treatment for preeclampsia is delivery of the placenta. Adjunctive interventions that diminish morbidity include seizure prophylaxis, treatment of severe hypertension to prevent maternal stroke, and glucocorticoids for fetal maturation.

Timing of Delivery

Controlling the timing of delivery is the best tool for limiting maternal and perinatal mortality. In cases of preeclampsia at term, a decision for delivery is easy. A decision to deliver a preterm infant is more difficult, and thus the extent of disease in the mother and the degree of prematurity of the fetus must be carefully weighed. Guidelines for timing of delivery are based on observational studies, randomized trials, and expert opinion [3,19,23].

Preeclampsia without severe features can be managed with close observation, similar to gestational hypertension, as long as maternal disease remains mild and fetal status remains reassuring [23]. Delivery is indicated when neonatal complications from prematurity are minimal, at ≥ 37 0/7 weeks [3]. In the late preterm period (>34 0/7 weeks), fetal growth restriction at less than the 5th percentile, persistent oligohydramnios, and persistent biophysical profile (BPP) ≤ 6/10 or nonreassuring fetal heart tracing are indications for early delivery [3].

Severe features of preeclampsia represent progressive deterioration in the mother, fetus, or both. Delivery must always be considered. Expectant management necessitates intensive maternal and fetal monitoring but may be considered in pregnancies between 24 0/7 and 34 0/7 weeks of gestation because it can decrease perinatal mortality and significantly increases gestational age at delivery [3,19]. Severe features that imply end-organ dysfunction are indications for delivery. These include the inability to control blood pressure below the stroke range (mean arterial pressure <140 mmHg) despite maximal antihypertensive medications, headache, eclampsia or other neurologic symptoms, right upper quadrant/epigastric pain with elevated liver enzymes, significantly elevated liver enzymes, pulmonary edema, acute renal failure/oliguria, thrombocytopenia <100,000/μL, and/or nonreassuring fetal status. Patients with stable, severe features of preeclampsia are generally delivered by 34 weeks due to the ongoing maternal and fetal risks. If severe features occur with a nonreassuring fetal status such as growth restriction at less than the 5th percentile, reversed umbilical artery Doppler velocimetry, or a nonreassuring fetal heart tracing, delivery is almost always indicated [3,19].

Preeclampsia that develops prior to viability is most often severe. Attempts to prolong gestation when preeclampsia develops prior to viability risk severe maternal morbidity and even mortality. Neonatal morbidity and mortality are also high [24]. Termination prior to viability is recommended in these rare cases [3].

Vaginal delivery is generally preferred. Cesarean delivery is appropriate in cases of severe maternal disease where an expedient induction and vaginal delivery appear unlikely, when vaginal delivery has not been achieved within 24 hours after initiating an induction of labor in cases of severe disease, and for the standard obstetric indications.

Eclampsia Prophylaxis

The incidence of eclampsia (seizures) with preeclampsia informs approaches to preventative treatment. Less than 1% of women with preeclampsia develop seizures in the absence of severe features,

whereas approximately 2–3% of patients with severe features of preeclampsia develop seizures [25].

Magnesium sulfate is the preferred antiepileptic, and its administration during labor and immediately postpartum is recommended for patients with preeclampsia with severe features [3]. Randomized, controlled trials have demonstrated that magnesium is superior to phenytoin, diazepam, and placebo for seizure prophylaxis in preeclampsia with severe features [7]. There is no consensus on the use of magnesium for preeclampsia without severe features, although guidelines from the recent American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy state that "it is suggested that magnesium sulfate not be administered universally" for these patients [3,7,25]. One large randomized, controlled trial demonstrated a number needed to treat of approximately 100 to prevent one eclamptic event among women with preeclampsia without severe features [26]. Ultimately, the decision to administer magnesium sulfate must be made by the responsible provider, with consideration of the entire clinical picture.

Antihypertensive Medications

Antihypertensive medication is used in women with severe hypertension to prevent cerebrovascular and cardiovascular complications. However, antihypertensive therapy given to women with preeclampsia does not alter rates of maternal disease progression, perinatal death, IUGR, or prematurity. Controlling severe hypertension, however, may prolong gestation, providing time for antenatal corticosteroid administration and decreasing the degree of prematurity. Treatment is recommended for sustained acute elevations in systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg [3]. The most commonly used antihypertensive medications are parenteral hydralazine, parenteral labetalol, and oral immediate-release nifedipine. Nitroprusside can be used when hypertension is refractory to other treatment.

Glucocorticoids for Fetal Lung Maturity

As discussed elsewhere in this book, antenatal corticosteroid administration to women at risk for preterm delivery between 24 and 34 weeks has been shown to reduce the incidence and severity of neonatal respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis. It has also been shown to decrease perinatal mortality. Glucocorticoids in the form of betamethasone or dexamethasone should be given to any woman with preeclampsia at less than 34 weeks because preterm delivery is likely.

Fetal and Neonatal Effects of Hypertensive Disease in Pregnancy

Fetal and neonatal effects of hypertensive disease in pregnancy are due primarily to placental insufficiency, iatrogenic prematurity, and drug effects of medications.

Placental Insufficiency

Hypertension and preeclampsia are associated with a vasculopathy in the placenta that often shares similarities. Similar features of the vasculopathy include shallow placental implantation and maternal spiral arteries that fail to become low resistance [22]. Cytotrophoblastic hyperplasia, thickening of the basement membrane, placental infarction, and chorionic villitis are also seen. These changes are associated with increased vascular resistance and decreased diffusion capacity in the placenta. Fetal consequences of placental vasculopathy include increased placental vascular resistance, IUGR (<10th percentile), increased cerebral blood flow (centralization), oligohydramnios, and placental abruption. Approximately one-third of IUGR is caused by uteroplacental insufficiency [27].

IUGR is associated with neonatal polycythemia, hyperbilirubinemia, hypoglycemia, hypothermia, and apneic episodes. Long-term follow-up suggests that SGA infants may have increased risks of adult hypertension and cardiovascular complications [27].

Iatrogenic Prematurity

An estimated 15–67% of pregnancies complicated by hypertensive disorders result in preterm delivery [20]. Most poor perinatal outcome results from complications of prematurity, including neonatal death, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis. There is a misconception that in utero "stress" associated with preeclampsia causes accelerated fetal maturation. Freidman et al. found no difference in the incidence of these complications when premature infants born to

preeclamptic mothers were compared with infants born to normotensive control mothers. This was also true when infants of mothers with severe preeclampsia or severe preeclampsia with IUGR were compared with infants of normotensive control mothers [28]. To the contrary, in early-term neonates (≥37 weeks), preeclampsia may actually be associated with increased rates of respiratory distress syndrome and intraventricular hemorrhage compared with infants of normotensive mothers [29].

Fetal Effects of Maternal Medications

Magnesium

Magnesium sulfate crosses the placenta, enters the fetal circulation, and may cause neonatal respiratory depression and hypotonia. In a study of neonates born at greater than 34 weeks' gestation, those exposed to magnesium sulfate were more likely to be hypotonic at birth and to have lower Apgar scores, but no additional complications were identified [30]. Some have reported higher rates of NICU admission and feeding difficulties [31]. These effects may be related to magnesium's action as a smooth muscle relaxant and appear to be transient. Magnesium has been shown to reduce the incidence of CP among exposed preterm neonates (24–31 weeks' 6 days gestation) compared with neonates receiving placebo [32,33]. Taken together, it is unlikely that magnesium given for eclampsia prophylaxis will adversely affect the fetus/neonate in the long term and may be beneficial for neonates delivered preterm.

Antihypertensive Medications

Antihypertensive medications used to treat chronic hypertension or preeclampsia with severe features in pregnancy include α-methyldopa, labetalol, hydralazine, and long-acting calcium channel blockers such as nifedipine. Antihypertensive medications used to treat acute hypertension related to severe gestational hypertension, preeclampsia, or superimposed preeclampsia include parenteral hydralazine, parenteral labetalol, and short-acting oral nifedipine. A complete discussion regarding indications for treatment was included earlier.

Chronic Management. Oral α-methyldopa, labetolol, and long-acting calcium channel blockers are used for chronic management of hypertension in pregnancy. A Cochrane systematic review including over 3,500 women found no significant differences in efficacy or safety in comparisons of labetalol versus calcium channel blockers or labetalol versus α-methyldopa [34]. While α-methyldopa was historically the drug of choice, without known decreases in uteroplacental blood flow or adverse long-term neonatal harm, it has fallen out of favor due to maternal side effects including occasional transaminitis. Although beta-blockers have been associated with growth restriction in meta-analyses, this effect may not be generalizable to all beta-blockers; studies of labetalol use in pregnancy have been reassuring; labetalol is commonly used [4]. Hydralazine is also used occasionally for chronic management but can be limited by maternal rebound tachycardia; it remains a preferred agent for acute management. Long-acting calcium channel blockers such as nifedipine are used with minimal side effects. Diuretics are controversial in pregnancy because of concerns that reduction in maternal blood volume will reduce uterine blood flow. However, a meta-analysis did not identify any detrimental effects of diuretic use in pregnancy [4]. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are contraindicated in pregnancy because of teratogenic concerns in all trimesters. Specific related anomalies are cardiac anomalies (risk ratio 3.72, 95% CI 1.89–7.30) and CNS anomalies (risk ratio 4.39, 95% CI 1.37–14.02) [35], in addition to well-documented concerns over in utero hypotension, fetal renal failure, and oliguria.

Acute Management. For women with preeclampsia with severe hypertension (sustained systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg), treatment with antihypertensive medication is recommended [3]. Parenteral hydralazine and labetalol are the most commonly use antihypertensive agents. Short-acting oral nifedipine is also used, though less commonly so [3,7]. Major perinatal morbidity (including admission to intensive care), neonatal hypotension, and complications from prematurity have not been shown to be different between hydralazine and other antihypertensive agents [34,36]. Specific concern exists with oral short-acting nifedipine because it has been associated with untoward fatal and nonfatal cardiovascular events in nonpregnant patients [4,19]. The risk-benefit ratio for use of nifedipine for acute, severe hypertension must be considered. However, in the absence of cardiovascular disease in the pregnant patient, it is considered an appropriate first-line oral alternative to intravenous medications, particularly when intravenous access is not available.

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Summary

Hypertensive disease in pregnancy is common, and it is responsible for significant maternal and neonatal morbidity. Distinguishing between chronic hypertension, gestational hypertension, and preeclampsia/superimposed preeclampsia is important because the diagnosis predicts associated morbidity and directs care. However, at times, distinguishing between these entities is impossible.

Management of all hypertensive disease in pregnancy includes close surveillance of both maternal and fetal health. Once preeclampsia develops, particularly in the preterm setting, its course is usually progressive and can accelerate. Appropriate timing of delivery, seizure prophylaxis, treatment of severe hypertension, and antenatal corticosteroid administration for fetal maturation are the mainstays of preeclampsia care. Expectant management of severe preeclampsia at between 24 and 34 weeks can significantly reduce perinatal morbidity and significantly extend gestation. Delivery is indicated when end-organ dysfunction is notable in the mother or the fetus. Hypertensive disease in pregnancy causes morbidity for the fetus/neonate via placental insufficiency, prematurity, and magnesium toxicity.

When more is understood about the pathophysiology of preeclampsia and its interaction with chronic hypertension, biochemical markers may become available to better predict which mothers and which fetuses are at most risk for morbidity.

References

1. Walker JJ. Pre-eclampsia. *Lancet* 2000; **356**: 1260–5.
2. Main EK, McCain CL, Morton CH, et al. Pregnancy related mortality in California: causes, characteristics, and improvement opportunities. *Obstet Gynecol* 2015; **125**: 938–47.
3. American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122**(5): 1122–31.
4. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; **183**: S1–22.
5. Rogers LK, Velten M. Maternal inflammation, growth retardation, and preterm birth: insights into adult cardiovascular disease. *Life Sci* 2011; **89**: 417–21.
6. Markham KB, Funai EF. Pregnancy-related hypertension. In Creasy RK, Resnik R, Iams JD, et al., eds., *Maternal-Fetal Medicine: Principles and Practice*, 7th edn. Philadelphia: Saunders, 2014: 856–81.
7. American Congress of Obstetricians and Gynecologists (ACOG). Diagnosis and Management of Preeclampsia and Eclampsia (American Congress of Obstetricians and Gynecologists Practice Bulletin Number 33), ACOG, Washington, DC, 2002 (reaffirmed 2012).
8. Spong CY, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol* 2011; **118**: 323–33.
9. Abalos A, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014; **2**: CD002252
10. Magee L.A., Elran E., Bull S.B., et al: Risks and benefits of beta receptor blockers for pregnancy hypertension: overview of the randomized trials. *Eur J Obstet Gynecol Reprod Biol* 2000; **88**: 15–26.
11. Magee LA, von Dadelszen P, Rey E, et al. The control of hypertension in pregnancy study (CHIPS) randomized controlled trial. *Pregnancy Hypertens* 2015; **5**: 2.
12. Buchbinder A, Sibai BM, Caritis S, et al. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. *Am J Obstet Gynecol* 2002; **186**: 66–71.
13. Saudan P, Brown MA, Buddle ML, et al. Does gestational hypertension become pre-eclampsia. *Br J Obstet Gynaecol* 1998; **105**: 1177–84.
14. Wu Y, Xiong X, Fraser WD, et al. Association of uric acid with progression to preeclampsia and development of adverse conditions in gestational hypertensive pregnancies. *Am J Hypertens* 2012; **25**: 711–17.
15. Sibai BM. Eclampsia. VI. Maternal-perinatal outcome in 254 consecutive cases. *Am J Obstet Gynecol* 1990; **163**: 1049–54.
16. North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of preeclampsia. *Br J Obstet Gynaecol* 1999; **106**: 767–73.
17. Woelkers D, Barton J, von Dadelszen P, et al. Rates of adverse outcomes are elevated in preterm patients with suspected hypertensive disorders without diagnostic criteria for preeclampsia. *Pregnancy Hypertens* 2015; **5**: 39.
18. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013; **170**: 1–7.
19. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. *Am J Obstet Gynecol* 2007; **196**: 514.e1–9.

20. Sibai BM. Pre-eclampsia. *Lancet* 2005; **365**: 785–99.
21. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology* 2009; **24**: 147–58.
22. Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. *Am J Obstet Gyncol* 2006; **195**: 40–9.
23. Sibai BM. Management of late preterm and early-term pregnancies complicated by mild gestational hypertension/pre-eclampsia. *Semin Perinatol* 2011; **35**: 292–6.
24. Bombrys AE, Barton JR, Nowacki EA, et al. Expectant management of severe pre-eclampsia at less than 27 weeks' gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. *Am J Obstet Gynecol* 2008; **199**: 247.e1–6.
25. Sibai, BM. Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. *Am J Obstet Gynecol* 2004; **190**: 1520–6.
26. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulfate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; **1**: 1877–90.
27. Resnik R, Creasy RK. Intrauterine growth restriction. In Creasy RK, Resnik R, Iams JD, et al., eds., *Maternal-Fetal Medicine: Principles and Practice*, 7th edn. Philadelphia: Saunders, 2014: 743–55.
28. Friedman SA, Schiff E, Kao L, et al. Neonatal outcome after preterm delivery for preeclampsia. *Am J Obstet Gynecol* 1995; **172**: 1785–92.
29. Mendola P, Mumford SL, Mannisto TI, et al. Controlled direct effects of preeclampsia on neonatal health after accounting for mediation by preterm birth. *Epidemiology* 2015; **26**: 17–26.
30. Riaz M, Porat R, Brodsky NL, et al. The effects of maternal magnesium sulfate treatment on newborns: a prospective controlled study. *J Perinatol* 1998; **18**: 449–54.
31. Greenberg MB, Penn AA, Whitaker KR, et al. Effect of magnesium sulfate exposure on term neonates. *J Perinatol* 2013; **33**: 188–93.
32. Rouse D, Hirtz DG, Thom E, et al. A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.
33. Constantine MM, Weiner SJ. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Obstet Gynecol* 2009; **114**: 354–64.
34. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2013; **7**: CD001449.
35. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; **354**: 2443–51
36. Magee LA, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003; **327**: 955–64.

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Chapter

12

Complications of Labor and Delivery

Samantha Do and Yair Blumenfeld

Introduction

Despite a common misconception among the general public, intrapartum events rarely lead to fetal injury. Approximately 70% of cases of neonatal encephalopathy are secondary to events arising prior to the onset of labor [1]. Moreover, the overall incidence of neonatal encephalopathy attributable to intrapartum hypoxia, in the absence of any other potential preconceptional or antepartum causes, is estimated to be approximately 1.6/10,000 [1]. Despite this, the practice of obstetrics is rapidly evolving as a reaction to both extrinsic and intrinsic factors. Today, cesarean section rates are at all-time highs, operative vaginal delivery rates are decreasing, and evidence-based obstetrics is threatened to be replaced by defensive, anecdotally based medicine.

In this chapter we shall review the available evidence regarding complications of labor and delivery and their potential effects on adverse neonatal injury in general and neurologic morbidity in particular. We hope that this information will enable physicians to make educated, informed, and rational obstetrical decisions, thereby improving overall patient care.

Cesarean Section

In the United States in 2013, 32.7% of live births were via cesarean section [2]. The overall cesarean delivery rate in the United States increased 60% from 1996 to 2009, from 20.7% to 32.9% [3]. In 2012, the primary cesarean section rate was 21.5%, compared with 14.6% in 1996 [2]. However, in 2013 the rate of vaginal delivery after previous cesarean (VBAC) was only 10.6%, whereas in 1996 the rate was 28.3% [2,4].

The current rise in cesarean section rates is driven by multiple factors, including increasing multiple gestations, obstetrical litigation, rising elective cesarean sections on maternal demand, advanced maternal age, increasing maternal comorbidities, decreasing operative vaginal deliveries and decreased VBAC rates. The old adage "Once a cesarean, always a cesarean" has made its way back into obstetrical practice after a 30-year hiatus.

Since 2009, the cesarean delivery rate has plateaued partly due to concerted efforts directed at providers and patients to reduce the occurrence of non–medically indicated cesarean delivery [5,6]. These efforts draw on data that have emerged in the last decade regarding the potential harmful effects of cesarean section on the mother, the fetus, and the neonate.

A large prospective cohort study of over 94,000 deliveries in South America compared vaginal delivery with elective and intrapartum cesarean section. In this multicenter cohort, cesarean delivery reduced the risk of intrapartum fetal death but increased the risk of severe neonatal morbidity and mortality. Also, lack of labor was a risk factor for prolonged stay in the neonatal intensive care unit (NICU), and neonatal mortality was higher for neonates delivered by elective cesarean when compared with vaginal delivery [7]. In the same study, maternal morbidity and mortality (including admission to the ICU), blood transfusion, hysterectomy, and prolonged hospital stay were higher in both the elective and intrapartum cesarean groups than in the vaginal delivery group [7]. Another study found that the risk of postpartum maternal death was 3.6 times higher following cesarean section [8].

Multiple studies have recently addressed maternal complications following one or more cesarean sections. Minor morbidities including difficult delivery, adhesions, and longer operative times, as well as significant morbidities including hysterectomy, blood transfusion, placenta accreta, and ICU admissions, have all been shown to increase with increasing cesarean deliveries [9–11]. Moreover a recently published large case-controlled Australian study of over 35,000 women linked adverse neonatal outcomes including preterm birth, low birth weight, small for gestational

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age, and unexplained stillbirth in subsequent pregnancies to primary cesarean delivery [12]. Cesarean delivery has also been associated with increased neonatal respiratory morbidity with higher rates of respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and subsequent NICU admissions [13]. There is also evidence suggesting that cesarean delivery is associated with long-term immune system effects with increased rates of asthma, food sensitivity, and atopy [13].

As we continue to analyze these drastic changes in practice in the years to come, we must ask ourselves whether neonatal morbidity and mortality are improving, whether maternal safety is compromised, and what effects, if any, these trends will have on future pregnancies.

Trial of Labor after Cesarean (TOLAC) and Uterine Rupture

The practice of trial of labor after cesarean (TOLAC) was introduced and rapidly endorsed by obstetricians in the 1980s and 1990s. It was initially intended to counteract what were then perceived as high cesarean section rates resulting largely from the discontinued practice of midforceps and vaginal breech deliveries. As the practice grew, reports of maternal and neonatal morbidity and mortality were published, leading to a rapid decline in TOLAC and successful vaginal birth after cesarean (VBAC) rates. Most labor units instituted policies requiring 24-hour in-hospital obstetric and anesthesia staff if TOLAC were to be attempted. Though the risk of rupture is less than 1% for most cases of spontaneously laboring patients, the potential for severe neonatal and maternal morbidity caused many hospitals and physician groups to avoid the practice altogether. In 2010, a National Institutes of Health panel examined the safety of TOLAC, concluded that it was a reasonable option for many women with a prior cesarean delivery, and sought to eliminate barriers to access to TOLAC [14]. In 2010, the American College of Obstetricians and Gynecologists (ACOG) also updated its guidelines for appropriate TOLAC candidates to clearly include women with two previous low transverse cesarean incisions, women carrying twins, and women with an unknown type of uterine scar. Further, while recommending that TOLAC be undertaken in facilities with staff immediately available to provide emergency care, the 2010 bulletin encouraged respect for patient autonomy and antenatal transfer of care to centers supporting TOLAC for women desiring to attempt TOLAC [15].

Studies over the last 10 years have focused on identifying the optimal TOLAC candidate based on prior cesarean section scar, as well as other fetal and maternal characteristics, such as fetal size and number of prior cesarean deliveries [16–19]. In the 2010 ACOG Bulletin, good candidates for TOLAC were deemed to be women with low risk of rupture balanced by a high chance of successful VBAC, such as women with one previous cesarean delivery with a low transverse incision, who have a greater than 60% chance of success [15]. Other studies have attempted to stratify the risk of rupture based on primary surgical technique (mainly single- versus double-layer uterine closure, suture type, locked versus unlocked stitches), as well as cervical favorability on presentation and labor management of the TOLAC, including the use of cervical induction methods and labor augmentation [20–24]. Multiple studies have investigated whether the risk of rupture may be determined by ultrasound measurements of lower uterine segment thickness prior to labor. A meta-analysis of 2,700 patients found a strong negative correlation between lower uterine segment thickness and risk of uterine defect during TOLAC [25].

In a recent review comparing elective cesarean section and TOLAC in over 400,000 patients, the maternal and neonatal risks were opposed. Compared with elective repeat cesarean delivery, the overall risk of maternal death associated with trial of labor was significantly lower (0.013% versus 0.004%) with a risk ratio of 0.33. However, the overall neonatal mortality rate was significantly lower in women with elective cesarean delivery than in women undergoing trial of labor (0.06% versus 0.11%) [26]. There was no significant difference in rates of maternal hysterectomy, transfusion, and infection between the two groups. There was also no significant difference in neonatal hypoxic-ischemic encephalopathy and Apgar scores. Five of six studies reviewed showed no difference in frequency of NICU admissions. Only one study found that trial of labor carried a significantly higher rate of NICU admission than elective repeat cesarean delivery (26.2% versus 17.6%, $p < 0.001$) [27]. In a large cohort study from the United States of over 39,000 patients at term with a history of prior cesarean section reported a 0.27% risk of adverse perinatal outcomes, including stillbirth, hypoxic-ischemic encephalopathy (HIE),

and neonatal death [28]. The overall rate of uterine rupture was 0.32%, whereas the rate among those attempting a vaginal delivery was 0.74%.

Because the majority of morbidity related to TOLAC trials is associated with failure to delivery vaginally, identifying the proportion of patients who are more likely to successfully deliver vaginally is important [29,30]. A large cohort study of 144,000 British women reported a VBAC success rate of 63.4%, with younger age and white ethnicity associated with higher rates of success and prior emergency cesarean and failed induction of labor correlated with lower success [31]. In the United States, the proportion of patients successfully delivering vaginally with attempted TOLAC has been declining from 69.8% in 2000 to 38.5% in 2008 [32]. Concerns about uterine rupture and neonatal morbidity not only may be deterring patients and providers from attempting trial of labor after cesarean but also may be leading to a lower threshold for conversion to cesarean delivery during a trial of labor. Strong predictors of who will achieve VBAC are prior successful vaginal delivery and spontaneous labor [33,34]. Decreased probability of success has been associated with a recurrent indication for cesarean delivery, increased maternal age, gestational age greater than 40 weeks, maternal obesity, preeclampsia, nonwhite ethnicity, short interpregnancy interval, and increased neonatal birth weight. Also, multiple studies have shown that the cost-effectiveness of TOLAC depends on the a priori chance of success versus risk of uterine rupture [10,35]. To aid in counseling women contemplating TOLAC, a normogram was developed to predict the patient-specific chance for successful VBAC [16]. This calculator has been validated and may help individual women to reach a more informed decision [36].

Counseling a woman with a prior cesarean is complex and requires consideration not only of her likely success, risk factors for uterine rupture, and risk of maternal and neonatal morbidity but also of the long-term consequences of delivery mode should she desire a large family. Though most studies on TOLAC safety have focused on short-term maternal and neonatal outcomes, multiple cesarean deliveries may have longer reproductive consequences for women. In a recent meta-analysis of 21 observational studies that included over 2 million cesarean deliveries, the risks of placenta accreta, placenta previa, surgical injury, the need for postoperative ventilation, intensive care unit admission, hysterectomy, and blood transfusion significantly increased with increasing number of cesarean deliveries in a dose-response fashion [37]. A decision analysis suggested that allowing women with a single prior cesarean delivery a TOLAC attempt will result in fewer cumulative hysterectomies compared with elective repeat cesareans if the woman desires two or more additional children [38]. Another cost-effectiveness analysis that incorporated long-term events found that trial of labor is less expensive and more effective than an elective repeat cesarean delivery when the likelihood of success is 47.2% or more and the probability of uterine rupture is 0.8% [39].

Once a TOLAC is attempted, close maternal and fetal monitoring is crucial. Certain clinical parameters including increased maternal abdominal pain, vaginal bleeding or hypotension, loss of fetal station, and nonreassuring fetal heart rates (FHRs) may be indicative of uterine rupture. In a retrospective study of 52 uterine ruptures, fetal heart rate abnormalities were the most common presenting sign, with bradycardia occurring in 77% of cases of complete uterine rupture [40]. Because changes in FHR are most common harbinger of uterine rupture, many prefer internalized monitoring of the fetal heart rate with application of a fetal scalp electrode after rupture of the membranes. Some practitioners have previously raised concerns of regional anesthesia masking the pain associated with uterine rupture. These concerns have not been confirmed in any observational studies, and ACOG also states that TOLAC is not a contraindication to epidural anesthesia [15]. However, frequent dosing of an epidural for uncontrolled pain should raise clinical suspicion for impending uterine rupture [41].

Spontaneous Uterine Rupture

Rupture of the unscarred uterus is a rare obstetric complication, with an estimated incidence of between 1/8,000 and 1/19,000 deliveries in the developed world [42]. In a recent case-control study, 20 cases of uterine rupture of an unscarred uterus were compared with 126 controls of women who had rupture of a scarred uterus [43]. Cases of primary rupture most commonly presented with nonreassuring FHR patterns (50%), vaginal bleeding (45%), or abdominal pain (30%). Primary uterine rupture of an unscarred uterus was found to be particularly morbid, with higher rates of

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blood transfusion, hysterectomy, and neonatal neurologic injury. In another review of 36 reported primigravid uterine rupture cases, only 20 cases presented with a live, viable infant, and among those, there was evidence of fetal compromise in 80% [44]. Risk factors for the cases included previous uterine surgery, adherent placenta, congenital uterine anomaly, adenomyosis, connective tissue disorders, oxytocin and prostaglandin induction, and labor. Twenty-six percent of the cases resulted in a hysterectomy, and maternal mortality was reported in one case.

Operative Vaginal Delivery

A significant reason for the rise in cesarean section rates is the decrease in operative vaginal delivery rates. Forceps deliveries are slowly becoming obsolete as negative public perception of these instruments increases and resident experience and training decrease. This is in sharp contrast to the practice of elective forceps use that permeated labor and delivery units only 30–40 years ago. Because of the experience necessary to acquire skill in performing forceps deliveries and the decrease in available cases in teaching institutions, vacuum deliveries have recently gained relative popularity, though still in smaller numbers than previously.

The indications for operative vaginal delivery, via forceps or vacuum, have not changed over the years. These include prolonged second stage, suspicion of immediate or potential fetal compromise, and shortening of the second stage for maternal benefit [45]. Peripartum considerations, namely, fetal position, presentation, lie, engagement, and clinical pelvimetry, are of vital importance when attempting an operative vaginal delivery. Mostly, the decision to proceed with either forceps or vacuum is based on operator experience and comfort.

Complications

A Cochrane review compared complications between vacuum- and forceps-assisted deliveries from 13 studies including 3,338 women [46]. While forceps lead to higher rates of successful vaginal delivery, they are also associated with increased maternal perineal trauma with an increased risk of third- and fourth-degree tears (relative risk [RR] = 2.48) and incontinence of flatus. Neonatal facial injury, including corneal abrasions and external ocular trauma, were more common with forceps in three of the studies (RR = 5.10), but in this review there was no significant difference in low Apgar score, umbilical pH, neonatal ICU admission, or death.

Multiple other studies comparing vacuum to forceps illustrated greater neonatal injury, including scalp lacerations, cephalohematomas, subgaleal hematomas, and intracranial hemorrhage with vacuum delivery [47,48]. In a study comparing 308 vacuum-assisted deliveries with 200 forceps-assisted deliveries, cephalohematomas were seen in 20.5% of vacuum versus 12.5% of forceps deliveries, and caput and molding were seen in 28.2% of vacuum versus 13.5% of forceps deliveries [47]. The rate of intracranial hemorrhage associated with vacuum delivery appears to be 0.1–0.8%, with 50% of children subsequently showing developmental impairment at 2 years of age in one small cohort study of 25 infants [49]. Despite these findings, the overall incidence of serious complications with vacuum extraction is approximately 5%.

The decision to proceed with operative delivery should also take into account the fetal size and position and the indication for operative delivery. Studies addressing the use of forceps in the setting of fetal macrosomia illustrated higher rates of significant injury, including neurologic abnormalities, than in spontaneous delivery or cesarean section [50]. Fetal malposition may often lead to a prolonged second stage, and trepidation exists as to the use of rotational operative delivery. A retrospective cohort study of 868 women found no difference between rotational instrumental delivery with either forceps or vacuum and cesarean section in rates of delayed neonatal respiration or low fetal arterial pH [51]. Another retrospective study of 1,291 births found comparable maternal and neonatal outcomes between rotational forceps, vacuum, and cesarean section for malposition [52]. However, for vacuum, there is a higher chance of failure with fetal malposition with increased morbidity associated with failed vaginal delivery [53]. When the indication for operative vaginal delivery is suspicion of fetal compromise, such as a terminal bradycardia, delivery may be accomplished faster with forceps than with vacuum, with one analysis showing the decision-to-delivery interval to be 8.6 versus 13.8 minutes, respectively [54].

When considering an operative vaginal delivery, maternal and neonatal risks should be considered and relayed to the patient prior to delivery. These risks should be weighed against the likelihood of

successful operative vaginal delivery. A large cohort study from a California database compared over 83,000 deliveries between 1992 and 1994 [55]. The lowest morbidity and mortality was seen with spontaneous vaginal delivery; an intermediate risk was seen with vacuum, forceps, or cesarean delivery during labor; and the highest risk was seen in those who delivered with combined forceps and vacuum extraction or who were delivered by cesarean section following failed operative vaginal delivery. Sequential use of vacuum and forceps has repeatedly been shown to be associated with increased rates of neonatal intracranial hemorrhage, facial nerve injury, and seizures compared with use of one instrument alone [56]. Thus operative vaginal delivery should be recommended only when it is likely to be successful, and only one method, either forceps or vacuum, should be used for each delivery.

Long-Term Infant Consequences

A few randomized studies have addressed the long-term consequences of operative vaginal delivery. One randomized study comparing vacuum to forceps failed to show a statistical difference in head circumference, weight, hearing, or vision at 9 months of age [57]. A separate randomized study comparing vacuum to forceps showed no difference in child development at 5 years after delivery [58]. A large cohort study of 3,413 children failed to show cognitive differences between those delivered by forceps and those delivered spontaneously [59]. Finally, a 10-year follow-up of 295 children delivered by vacuum and 302 controls delivered spontaneously revealed no difference in scholastic performance, speech, self-care ability, or neurologic abnormality between the groups [60].

Shoulder Dystocia

Shoulder dystocia is most often defined as a delivery that requires additional obstetric maneuvers following failure of gentle downward traction on the fetal head to effect delivery of the shoulders [61]. The most common mechanism is impaction of the anterior fetal shoulder behind the maternal pubic symphysis and rarely impaction of the posterior fetal shoulder on the sacral promontory. It is thought to complicate less than 1% of vaginal deliveries and is a significant contributor of maternal and neonatal injury, including brachial plexus injuries. Of note, approximately 4% of brachial plexus injuries are as a result of cesarean delivery.

Despite aggressive treatment of gestational diabetes, decreased operative vaginal delivery rates, and strict management guidelines for elective cesarean section to prevent shoulder dystocia published by ACOG, the incidence of shoulder dystocia has not decreased. A recent large US cohort study of over 94,000 deliveries reported a constant rate of shoulder dystocia and brachial plexus injury between 1998 and 2009 [62].

Risk factors for shoulder dystocia include gestational diabetes, macrosomia (fetal weight > 5,000 g in nondiabetics and 4,500 g in diabetics), operative vaginal delivery, prior history of shoulder dystocia, protracted labor, pitocin use, and prolonged second stage. Because macrosomia is a risk factor for shoulder dystocia, a recent randomized, controlled trial compared induction of labor at term for 407 women with expectant management for 411 women with large-for-gestational-age (LGA)fetuses [63]. They found a decrease in the rate of shoulder dystocia (4% versus 8%) and an increase in the rate of spontaneous vaginal delivery (59% versus 52%) with induction compared with expectant management. There was no difference in neonatal morbidity between the groups. Induction is thus an option for suspected macrosomia. For other known risk factors, the delivering clinician prepares for possible shoulder dystocia, but in only 10% of cases can a risk factor be identified; most cases are surprise presentations.

More than 95% of shoulder dystocias are uncomplicated, yet severe cases of shoulder dystocia may result in HIE and even death [61]. Of the 5% of shoulder dystocias associated with fetal injury, less than 10% lead to permanent neurologic morbidity, mostly brachial plexus injury. Other neonatal morbidity includes bone fractures, low Apgar scores, acidosis, NICU admissions, and hypoxic-ischemic brain injury, with risk especially increased when the head-to-body delivery duration is greater than 5 minutes [64]. None of the individual shoulder dystocia maneuvers are associated with more neonatal morbidity or injury than the others, and thus clinicians may use the maneuver most likely to result in successful delivery [65]. Maternal complications of shoulder dystocia include postpartum hemorrhage and perineal injury.

Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) is a rare but catastrophic event. It arises when small amounts of amniotic fluid, rich in thromboplastin and thrombin, enter the maternal circulation via the exposed uterine spiral arterioles at the placental bed. Suggested risk factors for AFE include advanced maternal age, medical induction of labor, polyhydramnios, amnioinfusion, multiple gestations, cesarean section, placenta previa or abruption, preeclampsia or eclampsia, maternal cardiac disease, cerebrovascular disease, uterine rupture, and postdelivery curettage [66]. Maternal morbidity includes emergency delivery, cardiopulmonary arrest, pulmonary embolus, disseminated intravascular coagulopathy (DIC), and death. Fetal morbidity includes neonatal hypoxia, low Apgar scores, NICU admissions, and death.

A large population-based retrospective study identified 182 cases of AFE out of over 3.5 million deliveries in California between 2001 and 2007 for a population incidence of 5.1/100,000 [66]. An older review of 46 suspected cases of AFE revealed that approximately 70% occurred during labor, 11% following vaginal delivery, and 19% during cesarean section following delivery of the infant. Maternal mortality was 61%, with neurologically intact survival seen in only 15% of women. Of the fetuses in utero at the time of the event, only 39% survived [67]. A more recent review of 120 cases of AFE reported a maternal mortality rate of 27% with a stillbirth rate of 4.2% [68]. Other large cohort studies have described maternal mortality rates as low as 13% [66].

Attempts to uncover the pathophysiology of AFE have suggested two etiologies. With the first, amniotic fluid carrying fetal materials causes physical obstructions in the maternal microvessels in various organs, such as the lung, leading to cardiopulmonary collapse. Clark et al. postulated that a biphasic hemodynamic response exists in the setting of an embolism [69]. Initially, a transient period of intense pulmonary vasospasm leads to acute right ventricular failure and hypoxemia. This may explain the high occurrence of maternal deaths during the acute episode. Subsequently, however, the predominant feature is one of left ventricular heart failure. With the second postulated etiology, the amniotic fluid causes an anaphylactoid reaction leading to pulmonary vasospasm and activation of platelets, white blood cells, and complement [70]. Events caused by this mechanism have been called *atypical amniotic fluid embolisms*, with hemorrhage and coagulopathy as the initial presentation rather than the classical pattern of cardiopulmonary collapse [71]. Low serum levels of C3 and C4 complement have been proposed as a sensitive (88–100%) and specific (100%) marker of both kinds of AFE [72].

Early diagnosis of AFE is an integral step in the delivery of timely and appropriate care [73]. Despite efforts to identify a "gold standard" diagnostic test, AFE remains a clinical diagnosis that depends on bedside judgment and exclusion of other diseases in the broad differential diagnosis, which includes pulmonary embolism, myocardial infarction, peripartum cardiomyopathy, postpartum hemorrhage, sepsis, and anesthetic complications. Patients with AFE are best managed using a multidisciplinary approach. There are no definitive pharmacologic or other therapies that prevent or treat AFE, and supportive care typically involves aggressive treatment of multiple types of shock simultaneously [74]. Invasive monitoring and aggressive treatment of hypoxia, hypotension, coagulopathy, hemorrhage, and left ventricular dysfunction are paramount. Some less common strategies that have been described include recombinant activated factor VIIa to manage severe DIC, cardiopulmonary bypass, thrombolysis, pulmonary artery thromboembolectomy, pulmonary vasodilators, continuous hemodialfiltration, and extracorporeal membrane oxygenation [73]. The difficulty in managing AFE is the rapidity with which progression of signs and symptoms occurs, most often including considerations for the health of both mother and fetus. In the cases in which AFE occurs during labor, immediate delivery of the fetus is mandated to prevent further hypoxic damage to the fetus and to facilitate cardiopulmonary resuscitative efforts [74].

Intra-Amniotic Infection

Intra-amniotic infection refers to infection of any fetal compartment, including the fetal membranes. It includes infection of the chorion (*chorioamnionitis* or *villitis*), amniotic fluid (*amnionitis*), umbilical cord (*funisitis*), and fetal circulation [75]. Clinically evident intra-amniotic infection occurs in approximately 2–4% of term pregnancies and 40–70% of women who delivery prematurely [76].

Intra-amniotic infection is a major risk factor for preterm labor and delivery [76]. Risk factors for intrapartum chorioamnionitis at term include preterm rupture of the membranes (rupture of membranes

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prior to uterine contractions), prolonged labor, performing multiple vaginal examinations, intrauterine fetal surveillance monitors such as intrauterine pressure catheters and scalp electrodes, and maternal infections. The most common pathway for development of chorioamnionitis is via the ascent of lower genital tract organisms into the amniotic cavity. Less frequently, hematogenous or transplacental passage of bacteria may be the culprit.

Clinical chorioamnionitis at term is the leading risk factor for neonatal sepsis. Multiple studies have linked chorioamnionitis with NICU admissions, pneumonia, cerebral palsy (CP), respiratory distress syndrome (RDS), and periventricular leukomalacia (PVL) [77,78]. In preterm infants, clinical (as opposed to histologic) chorioamnionitis is associated with developmental delay despite adequate treatment [79]. Despite these findings, among term infants born after intra-amniotic infection, perinatal mortality is less than 1% [80].

However, many infants born to mothers with chorioamnionitis have features of neonatal encephalopathy, such as low Apgar scores, metabolic acidosis, and FHR abnormalities. These infants are at increased risk of developing CP, and studies have documented a four- to ninefold increase in the incidence of CP in term and near-term infants of mothers with chorioamnionitis [77,78]. As noted by Wu et al., maternal infection leads to an elevation of fetal cytokines that can damage the fetal CNS and impair placental blood flow and gas exchange [78]. Maternal fever may also raise the core temperature of the fetus, which may be harmful to the developing fetus.

The pathophysiology involved in chorioamnionitis is clearly delineated in preterm infants in Chapter 4, and similar processes can be seen in the term infant as well. Chorioamnionitis is usually a polymicrobial disorder arising from *Bacteroides* species, *Gardnerella vaginalis*, group B *Streptococcus, Escherichia coli, Mycoplasma*, and other aerobic streptococci as well as aerobic gram-negative rods [81]. Diagnosis is typically made clinically by the presence of maternal fever, fetal tachycardia, uterine tenderness, maternal leukocytosis, and/or foul-smelling odor of the amniotic fluid. Several treatment regimens have been studied in the setting of chorioamnionitis, including combinations of ampicillin, gentamicin, clindamycin, vancomycin, cephalosporins, macrolides, and others with little consensus on the best regimen [82]. Ampicillin and gentamicin are the most commonly used regimen, and a randomized, controlled trial supports once-daily as opposed to three-times-daily dosing of gentamicin for improved efficacy and decreased toxicity [83]. Additional anerobic coverage for patients with intra-amniotic infection undergoing cesarean section with, for example, clindamycin or metronidazole is recommended. Despite the lack of a definitive standard, the goal of treatment regardless of regimen is to provide broad-spectrum antibiotic coverage in order to reduce neonatal morbidity and mortality.

Post-Term Pregnancy and Meconium Staining

Post-term pregnancy is defined as any pregnancy extending beyond 42 weeks' gestation. The reported incidence of post-term pregnancy is approximately 5.5% [84]. An important task when confronting a post-term pregnancy is to adequately assess the gestational age because poor dating is the most common cause of apparently prolonged gestation. Data now indicate that any pregnancy lasting beyond term is associated with increased neonatal morbidity and mortality, and these risks should be discussed with patients in order to develop a delivery plan based on individual obstetrical history, cervical Bishop score, and the likelihood of spontaneous labor.

Pregnancy beyond term is associated with increased neonatal demise. The nadir of neonatal mortality is at 39–40 weeks for singletons and rises exponentially following 42 weeks. Moreover, meconium staining, labor induction, cesarean section, macrosomia, shoulder dystocia, and operative vaginal delivery all increase in pregnancies beyond term. Low umbilical artery pH, low 5-minute Apgar scores, and NICU admissions have also been linked to post-term pregnancies.

Ten to twenty percent of post-term fetuses have *dysmaturity syndrome*, which refers to infants with characteristics similar to intrauterine growth restriction and placental insufficiency [84]. The syndrome is also associated with cord compression, oligohydramnios, meconium aspiration, and short-term neonatal complications such as hypoglycemia, seizures, and respiratory insufficiency [84].

Meconium-stained amniotic fluid results from the passing of fetal stool prior to delivery and occurs in approximately 5–20% of women in labor [85]. Meconium-stained fluid at term was associated with increased microbial invasion of the amniotic fluid in

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108 women who underwent amniocentesis in one study [85]. Though often linked to fetal stress, meconium at term, without other signs of fetal compromise, does not result in adverse neonatal outcomes. Meconium aspiration syndrome comprises a combination of airway obstruction, inflammation, atelectasis, lung overexpansion, inhibition of surfactant, and secondary surfactant deficiency, hypoxia, and pulmonary hypertension. The syndrome occurs in up to 5% of infants exposed to meconium-stained amniotic fluid and is associated with significant morbidity and mortality [85]. In one cohort study of 29 infants, 21% had neurodevelopment delays at 3 years after delivery despite having received conventional treatment [86]. Initial small cohort studies have suggested amnioinfusion as a treatment for meconium-stained fluid. Larger follow-up studies in facilities with standard permpartum surveillance, including a large multicenter trial, showed no benefit to amnioinfusion in terms of meconium aspiration syndrome, perinatal mortality, or cesarean delivery, but umbilical artery pH greater than 7.20, meconium below the vocal cords, and neonatal ventilation or NICU admission were reduced with amnioinfusion [87].

Malpresentation and Malposition

Determining fetal presentation is an important step in the evaluation of a laboring patient. Most fetuses at term will align along the longitudinal axis of the uterus. Transverse and oblique lies are less common at term, seen most often in the setting of multiple gestations and grand multiparity. The most common fetal presentation is vertex (sometimes referred to as *occiput*), occurring in 96% of fetuses at term. Less common nonvertex presentations include breech (further defined as frank, footling, complete), face, brow, and compound. Compound presentations (incidence 0.26–0.8%) with an upper extremity accompanying the head are managed expectantly because 75% will deliver safely vaginally [88]. A compound presentation with a lower extremity is less likely to retract spontaneously and is associated with a higher likelihood of cord prolapse and thus more often require cesarean delivery. Nonvertex presentations may complicate the labor process by compromising the ability of the fetus to either enter the pelvic inlet (engagement) or flex its neck as it traverses the maternal pelvis. Flexion and fetal descent occur most often in the midpelvis, the narrowest portion of the pelvis bordered by the ischial spines. Inability to enter or maneuver through the pelvis leads to protracted labor and may even lead to severe maternal and neonatal morbidity. Though mostly a clinical diagnosis, ultrasound confirmation of fetal presentation and position may assist with the diagnosis of malpresentation and malposition in labor [89,90].

Face Presentation

Fetal face presentation is caused by sharp extension of the fetal neck during the process of labor. Face presentation is often associated with fetal factors such as anencephaly, anterior neck masses, hydrocephalus, or hypertoncity. Maternal factors including cephalopelvic disproportion, macrosomia, abnormal pelvic structures, uterine anomalies, and factors leading to laxity of the anterior abdominal tone such as multiparity and connective tissue disorders may lead to abnormal presentation. The incidence of face presentation is between 0.1% and 0.3% [88].

Face presentation is often diagnosed in the second stage of labor on digital examination. The position of the face relative to the pelvis will determine the likelihood of a successful vaginal delivery. Sixty percent of face presentations occur in the mentum anterior position, 15% in the mentum transverse position, and 26% in the mentum posterior position [91]. Up to 50% of fetuses in the mentum transverse and mentum posterior positions will spontaneously convert to mentum anterior during the course of labor. Knowing the fetal position is crucial because most mentum anterior positions are likely to deliver vaginally. FHR abnormalities and low 5-minute Apgar scores are also associated with face presentation.

In the mentum anterior presentation, as the face descends onto the perineum, the fetal chin passes under the maternal pubic symphysis. Flexion of the head follows as the baby is delivered. However, in the mentum posterior position, the fetal neck must extend the length of the maternal sacrum in order to reach the perineum, a difficult task given its short length. Vaginal delivery is therefore usually not possible unless spontaneous rotation occurs or the fetus is very small. Manual rotation of the mentum posterior to the vertex or mentum anterior position should be attempted only with extreme caution. Case reports of uterine rupture, neonatal asphyxia due to cord prolapse, and neonatal neurologic injury from spine trauma have been described.

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Breech Presentation

Breech presentation occurs in 3–4% of term pregnancies [92]. Delivery of a breech presentation was described as early as the first century AD. For over 1,000 years, obstructed labor was treated by converting the presentation to a footling breech and delivering the baby by traction. Different techniques have been described to deliver a breech singleton, including assisted vaginal delivery, spontaneous vaginal delivery, and total breech extraction. The assisted vaginal breech delivery includes spontaneous delivery of the fetus to the umbilicus followed by the Pinard (flexion of the leg at the knee in order to facilitate its delivery out of the vagina), Loveset (rotation of the body and sweeping of the fetal arms), and Mauriceau (delivery of the after-coming head) maneuvers. In the eighteenth century, William Smellie applied forceps to the after-coming head, and in 1924, Edmund Piper designed a forceps specifically for the after-coming head.

In the 1900s, concerns over vaginal breech delivery grew as reports of birth trauma, including intraventricular hemorrhage, spinal cord and brachial plexus injury, fractures, genital injury, birth asphyxia, and perinatal mortality, surfaced. In 2000, Hannah et al. published their results from a multicenter randomized trial of planned cesarean section versus planned vaginal birth [93]. The study had planned to enroll 2,800 participants in 26 countries, with a primary outcome of perinatal or neonatal mortality. The study was halted early when an interim analysis showed 5% perinatal mortality or serious neonatal morbidity in the planned vaginal group versus 1.6% in the planned cesarean group. Moreover, the authors concluded that "for every additional 14 cesarean sections done, one baby will avoid death or serious morbidity." Following the study, the ACOG released a committee opinion stating that a "planned vaginal delivery of a singleton term breech may no longer be appropriate" and that "patients with persistent breech presentation at term in singleton gestation should undergo a planned cesarean section" [94]. Over the last 15 years, criticisms of the Term Breech Trial have surfaced, including a study failing to show a significant difference in long-term neurologic sequelae between neonates delivered by cesarean and those delivered by breech delivery, which resulted in the ACOG rescinding its original statement and replacing it with the following in 2006: "In light of recent studies that further clarify the long-term risks of vaginal breech delivery, ACOG recommends that the decision regarding mode of delivery should depend on the experience of the health care provider . . . Cesarean delivery will be the preferred mode for most physicians because of the diminishing expertise in vaginal breech delivery" [95,96]. Controversy in the literature continues over whether to perform breech deliveries, but most patients and providers prefer to avoid the risk of vaginal breech deliveries. A recent meta-analysis of showed low absolute risks in vaginal breeech delivery, with perinatal mortality 0.3%, fetal neurologic morbidity 0.7%, birth trauma 0.7%, 5-minute Apgar score less than seven 2.45%, and neonatal asphyxia 3.3% but two- to fivefold higher perinatal mortality and morbidity relative to planned cesarean delivery [97].

Fetal Malposition

Fetal position describes the relation of the fetal occiput relative to the maternal pelvis, with the most common and advantageous position being occiput anterior (OA). Most fetuses that enter labor in either the occiput posterior (OP) or occiput transverse (OT) position will rotate during labor to OA, with only 2–13% of fetuses remaining OP at delivery [98]. Malposition represents a failure of rotation in labor such that fetuses remain OP or OT. Fetal malposition is a significant risk factor for a prolonged second stage of labor as well as increased rates of third- or fourth-degree perineal lacerations, postpartum hemorrhage, chorioamnionitis, operative vaginal delivery, and cesarean delivery [98]. Epidural analgesia has been associated with a higher rate of OP position at delivery, which may contribute to the lower rate of vaginal delivery observed with epidural [99]. Neonates delivered in the OP position have higher risks for adverse neonatal outcomes, including acidemia with pH less than 7.0 or base deficit less than 12, birth trauma, NICU admission, and longer neonatal stay in the hospital [100]. Manual rotation from the OP or OT position to OA at the beginning of the second stage has been described as a safe and effective intervention to shorten the second stage of labor and decrease the rate of operative delivery [101].

External Cephalic Version

External cephalic version (ECV), or manual rotation of a fetus by the application of external pressure to the maternal abdomen, was described as early as 400 BC by Hippocrates. In 2000, the ACOG published revised

guidelines for ECV, including gestational age greater than 36 completed weeks [92]. Success rates for ECV have ranged from approximately 30% to 80%, with greater success reported in multiparous patients and those with oblique or transverse lie. Greater success has also been reported with the use of uterine relaxants, including terbutaline and ritodrine [102]. Data are limited and conflicting regarding the use of spinal or epidural anesthesia [102]. Reported complications of ECV include intrauterine fetal demise, antepartum hemorrhage, premature labor, and preterm premature rupture of the membranes (PPROM). However, in a recent Cochrane review when ECV was attempted, there was no significant difference in neonatal complications such 1- and 5-minute Apgar scores, low umbilical vein pH levels, NICU admission, or perinatal death compared with when ECV was not attempted [103]. Controversy regarding ECV still exists for patients with prior cesarean section, decreased amniotic fluid volume, or uterine malformations. Contraindications to ECV include PPROM, placenta previa, suspected placental abruption, and nonreassuring FHR.

Cord Prolapse

Umbilical cord prolapsed is seen when the umbilical cord prolapses out of the cervix ahead of the presenting fetal part, causing cord compression and fetal ischemia. The prevalence of cord prolapse has been reported as 0.1–0.6% [104]. Cord prolapse is an obstetric emergency and requires immediate cesarean section because studies have shown that the longer the interval between diagnosis and delivery, the worse are neonatal outcomes [104]. In one study of 307 cases of cord prolapse, the fetal death rate was 6.8% [105]. Risk factors for cord prolapse include multiparity, preterm delivery, nonvertex presentation, presence of polyhydramnios, and spontaneous membrane rupture. Cord prolapse is estimated to result in neonatal encephalopathy in 2% of cases and in CP in 0.43% of cases [106]. The overall incidence of cord prolapse has decreased over time according to a recent review, and although it is a rare, it is important to be aware of because of the importance of rapid intervention.

Prolonged Second Stage

ACOG defines labor as the presence of uterine contractions of sufficient intensity, frequency, and duration to bring about demonstrable effacement and dilation of the cervix [107]. Normal labor is divided into three stages based on the landmark work of Emmanuel Friedman looking at 500 primigravid women at term with a 55% rate of low or middle forceps [108]. The first stage, including both the latent and active phases, begins with cervical change and concludes with full cervical dilation. The second stage is the time from full cervical dilation to delivery of the neonate, and the third stage is the time interval from delivery of the neonate to delivery of the placenta.

The term *cephalopelvic disproportion* has been used to describe a disparity between the size of the maternal pelvis and the size of the fetal head that precludes vaginal delivery [107]. Protracted and arrested disorders can occur throughout the course of labor, and their management depends on evaluation of maternal uterine contractions; the size, presentation, and position of the fetus; and maternal pelvic characteristics, assessed most commonly using clinical pelvimetry. Labor dystocia accounts for the majority of cesarean deliveries performed.

Kilpatrick et al. characterized the stages of labor in 6,991 women in 1989 and found that the mean duration for the second stage of labor was 20 minutes for multiparous women and 50 minutes for nulliparous women without regional anesthesia [109]. The 95th percentile length for the second stage of labor for nulliparous women was 2.2 hours with and 3.1 hours without regional anesthesia, respectively, and 1 and 2.2 hours, respectively, for multiparous women with and without regional anesthesia [109]. From these data, the ACOG determined its guidelines for prolonged second stage, which should be considered in nulliparous women if the second stage lasts beyond 2 hours or, when regional anesthesia is used, 3 hours [107]. The second stage is considered prolonged in multiparous women if it lasts longer than 1 hour or, with regional anesthesia, 2 hours [107].

In a recent large retrospective cohort study of 42,200 patients at one institution from 1976 to 2014, the 95th percentile length of the second stage was 5.6 hours for nulliparous women and 4.25 hours for multiparious women with an epidural, suggesting that the range of the second stage may be longer than previously suspected with regional anesthesia [110]. This raises the question of whether women should be allowed to labor longer in the second stage to improve vaginal delivery rates or whether longer lengths of the second stage place fetuses at increased risk of asphyxia. In this cohort, there was no significant

difference in 5-minute Apgar score less than 7, umbilical cord pH less than 7, meconium aspiration syndrome, sepsis, or NICU admission between women with no prolonged second stage and women with a prolonged second stage as defined by either the ACOG guidelines or by the 95th percentile thresholds from the cohort. There was, however, a significant increase in birth trauma with prolonged second stage with an increasing odds ratio found for longer thresholds.

Because the maximum duration of a normal second stage of labor remains unclear, the ACOG states that the decision to perform an operative delivery in the second stage versus continued observation should be made on the basis of clinical assessment of the woman and the fetus and the skill and training of the obstetrician, and "if progress is being made, duration of the second stage alone does not mandate intervention by operative delivery" [107]. Management of prolonged second stage therefore will vary depending on reassessment of the woman, fetus, and expulsive forces. Once a second-stage arrest disorder is diagnosed, the obstetrician has three options: (1) continued observation, (2) operative vaginal delivery, or (3) cesarean delivery.

Risk factors for prolonged labor include nulliparity, diabetes, macrosomia, epidural anesthesia, oxytocin usage, and chorioamnionitis [111]. Although some studies have shown reassuring findings, arrested and prolonged labor, particularly in the second stage, may lead to severe neonatal and maternal morbidity. Chorioamnionitis, particularly in the setting of prolonged ruptured membranes, has been linked to protracted labor. Fetal infection and bacteremia, including pneumonia caused by aspiration of infected amniotic fluid, has also been linked to prolonged labor [107]. From a maternal perspective, increased cesarean operative times, greater extensions at the time of cesarean section, increased operative vaginal delivery rates, and increased third- and fourth-degree lacerations have all been linked to prolonged second stage [112,113]. Prolonged second stage may also result in injuries of the pelvic floor, and in developing nations, very prolonged second stages of labor have resulted in severe necrosis and development of vesico- and rectovaginal fistulas [114].

Fetal Heart Rate Monitoring

FHR monitors are ubiquitous on labor and delivery units across the United States and other developed countries. In 2004, approximately 89% of all live births were assessed with electronic fetal heart rate monitoring (EFM) [115]. Despite widespread use, major limitations to EFM remain, including poor inter- and intraobserver reliability, uncertain efficacy, and a high false-positive rate [116].

A Cochrane review comparing EFM with intermittent auscultation showed higher rates of cesarean section and operative vaginal deliveries in the EFM group [117]. Also, despite a lower rate of perinatal mortality caused by fetal hypoxia in the EFM group, the overall perinatal mortality was equal [117]. Most studies comparing the two modalities exclude high-risk pregnancies such as those with suspected fetal growth restriction, preeclampsia, and type 1 diabetes mellitus; the ACOG still recommends continuous monitoring of such pregnancies [116].

Marked inter- and intraobserver variability in EFM has been described in multiple studies [118–120]. For example, when nine experienced obstetricians examined 634 intrapartum tracings, agreement was reached in only 48% of cases [119]. In another study, agreement was reached in only 22% of cases of four obstetricians evaluating 50 tracings. Moreover, 2 months later, the same clinicians interpreted 21% of the tracings differently than they did during the first evaluation [118]. In an effort to improve subjective variability in the diagnosis and management of EFM, the National Institute of Child Health and Human Development (NICHD) along with ACOG and the Society for Maternal-Fetal Medicine published guidelines in 2008 for the definitions and interpretation of EFM [121]. In these guidelines, a three-tier system was developed based on the FHR, the variability of the heart rate, the presence and type of FHR decelerations, and the presence of FHR accelerations. Category I FHR tracings are considered normal, category II FHR tracings are considered indeterminate, and category III FHR tracings are considered abnormal, requiring immediate evaluation. Individual parameters are discouraged from being interpreted individually and in the absence of clinical context.

Since introduction of the FHR categories, several studies have attempted to correlate specific FHR categories with adverse outcomes. In a study of 4,736 term singleton vertex nonanomalous gestations, 96% with intrapartum category II FHR tracings, baseline tachycardia, marked FHR variability, and prolonged decelerations were significantly associated with an

increased likelihood of neonatal respiratory morbidity, defined as oxygen requirement at >6 hours of life or mechanical ventilation in the first 24 hours [122]. Of note, despite the fact that 96% of FHR tracings were category II, only 3.4% of neonates experienced respiratory morbidity.

The greatest limitation of EFM remains its high false-positive rate, particularly with adverse neurologic injury in the neonatal period. For example, in a study of 5,388 women with term singleton nonanomalous gestations, the incidence of acidemia among 951 women with a terminal deceleration prior to delivery was only 1.3% [123]. Moreover, the positive predictive value of a nonreassuring FHR pattern in predicting CP among singletons with a birth weight of 2,500 g or more is only 0.14% [124]. Thus, for 1,000 fetuses with a nonreassuring FHR pattern, only one or two will develop CP [116]. Attempts have been made to improve the predictive value of EFM by monitoring changes in the ST segment of the fetal electrocardiogram (ECG), but after six randomized, controlled trials it remains unclear whether ST-segment analysis decreases metabolic acidosis at birth [125].

Despite increasing prevalence, the widespread use of EFM has not led to a reduction in CP over time [126]. FHR tracing categories did not differ significantly between neonates with encephalopathy who required hypothermia treatment after birth and controls [127,128]. This is also consistent with the fact that only 4–14% of encephalopathies can be attributed solely to intrapartum events [1,128].

References

1. American College of Obstetricians and Gynecologists (ACOG). Executive summary: Neonatal encephalopathy and neurologic outcome (2nd edn.) Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol* 2014; **123**(4): 896–901.
2. Births: Final data for 2013. *National Vital Statistics Reports*. Hyattsville, MD: National Center for Health Statistics, 2014. Available at www.cdc.gov/nchs/data (accessed July 2015).
3. Martin JA, Hamilton BE, Osterman MJK, et al. Births: Final data for 2012. In *National Vital Statistics Reports*; vol **62**, no 9. Hyattsville, MD: National Center for Health Statistics, 2013. Available from www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_09.pdf (accessed July 2015).
4. March of Dimes. Peri stats: births by method of delivery, 1994–2004. 2006. Available at www.marchofdimes.com/peristats/ (accessed January 2008).
5. American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine, Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2014; **210**(3): 179–93.
6. American College of Obstetricians and Gynecologists (ACOG). Cesarean delivery on maternal request (Committee Opinion No. 559). *Obstet Gynecol* 2013; **121**(4): 904–7.
7. Villar J, Carroli G, Zavaleta N, et al. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. *BMJ* 2007; **335**: 1025–35.
8. Deneux-Tharaux C, Carmona E, Bouvier-Colle MH, Breart G. Postpartum maternal mortality and cesarean delivery. *Obstet Gynecol* 2006; **108**: 541–8.
9. Nisenblat V, Barak S, Griness OB, et al. Maternal complications associated with multiple cesarean deliveries. *Obstet Gynecol* 2006; **108**: 21–6.
10. Gilbert SA, Grobman WA, Landon MB. Cost-effectiveness of trial of labor after previous cesarean in a minimally biased cohort. *Am J Perinatol* 2013; **30**(1): 11–20.
11. Liu S, Liston RM, Joseph KS, et al. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. Maternal Health Study Group of the Canadian Perinatal Surveillance System. *CMAJ* 2007; **176**: 455–60.
12. Kennare R, Tucker G, Heard A, et al. Risks of adverse outcomes in the next birth after a first cesarean delivery. *Obstet Gynecol* 2007; **109**: 270–6.
13. Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? Whose benefits? *Am J Perinatol* 2012; **29**:7–18.
14. Cunningham FG, Bangdiwala SI, Brown SS, et al. NIH consensus development conference draft statement on vaginal birth after cesarean: new insights. *NIH Consens State Sci Statements* 2010; **27**(3): 1–42.
15. American College of Obstetricians and Gynecologists. Vaginal birth after previous cesarean delivery (Practice Bulletin No. 115). *Obstet Gynecol* 2010; **116**(2 Pt 1): 450–63.
16. Grobman WA, Lai Y, Landon MB, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. *Obstet Gynecol* 2007; **109**: 806–12.
17. Peaceman AM, Gersnoviez R, Landon MB, et al. The MFMU Cesarean Registry: impact of fetal size on trial of labor success for patients with previous cesarean for dystocia. *Am J Obstet Gynecol* 2006; **195**: 1127–31.
18. Landon MB, Spong CY, Thom E, et al. Risk of uterine rupture with a trial of labor in women with multiple and single prior cesarean delivery. *Obstet Gynecol* 2006; **108**: 12–20.

16:20:27

.013

19. Miller ES, Grobman WA. Obstetric outcomes associated with induction of labor after two prior cesarean deliveries. *Am J Obstet Gynecol* 2015; **213**(1): 89.
20. Gyamfi C, Juhasz G, Gyamfi P, et al. Single- versus double-layer uterine incision closure and uterine rupture. *J Matern Fetal Neonatal Med* 2006; **19**: 639–43.
21. Bujold E, Goyet M, Marcoux S, Brassard N, et al. The role of uterine closure in the risk of uterine rupture. *Obstet Gynecol* 2010; **116**(1): 43–50.
22. Roberge S, Chaillet N, Boutin A, et al. Single- versus double-layer closure of the hysterotomy incision during cesarean delivery and risk of uterine rupture. *Int J Gynaecol Obstet* 2011; **115**(1): 5–10.
23. Cahill AG, Stamilio DM, Odibo AO, et al. Does a maximum dose of oxytocin affect risk for uterine rupture in candidates for vaginal birth after cesarean delivery? *Am J Obstet Gynecol* 2007; **197**: 495.e1–5.
24. Harper LM, Cahill AG, Boslaugh S, et al. Association of induction of labor and uterine rupture in women attempting vaginal birth after cesarean: a survival analysis. *Am J Obstet Gynecol* 2012; **206**(1): 51.e1–5.
25. Kok N, Wiersma IC, Opmeer BC, et al. Sonographic measurement of lower uterine segment thickness to predict uterine rupture during a trial of labor in women with previous Cesarean section: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **42**(2): 132–9.
26. Guise JM, Denman MA, Emeis C, et al. Vaginal birth after cesarean: new insights on maternal and neonatal outcomes. *Obstet Gynecol* 2010; **115**(6): 1267–78.
27. Fisler RE, Cohen A, Ringer SA, Lieberman E. Neonatal outcome after trial of labor compared with elective repeat cesarean section. *Birth* 2003; **30**: 83–8.
28. Spong CY, Landon MB, Gilbert S, et al. Risk of uterine rupture and adverse perinatal outcome at term after cesarean delivery. *Obstet Gynecol* 2007; **110**: 801–7.
29. Chen HY, Chauhan SP, Grobman WA, et al. Association of labor induction or stimulation with infant mortality in women with failed versus successful trial of labor after prior cesarean. *J Matern Fetal Neonatal Med*. 2013; **26**(12): 1162–5.
30. Rossi AC, D'Addario V. Maternal morbidity following a trial of labor after cesarean section vs elective repeat cesarean delivery: a systematic review with metaanalysis. *Am J Obstet Gynecol*. 2008; **199**(3): 224–31.
31. Knight HE, Gurol-Urganci I, van der Meulen JH, et al. Vaginal birth after caesarean section: a cohort study investigating factors associated with its uptake and success. *BJOG*. 2014; **121**(2): 183–92.
32. Uddin SF, Simon AE. Rates and success rates of trial of labor after cesarean delivery in the United States, 1990–2009. *Matern Child Health J*. 2013; **17**(7): 1309–14.
33. Landon MB, Leindecker S, Spong CY, et al. The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery. *Am J Obstet Gynecol* 2005; **193**: 1016–23.
34. Cahill AG, Stamilio DM, Odibo AO, et al. Is vaginal birth after cesarean (VBAC) or elective repeat cesarean safer in women with a prior vaginal delivery? *Am J Obstet Gynecol* 2006; **195**: 1143–7.
35. Macario A, El-Sayed YY, Druzin ML. Cost-effectiveness of a trial of labor after previous cesarean delivery depends on the a priori chance of success. *Clin Obstet Gynecol* 2004; **47**: 378–85.
36. Costantine MM, Fox K, Byers BD, et al. Validation of the prediction model for success of vaginal birth after cesarean delivery. *Obstet Gynecol*. 2009; **114**(5): 1029–33.
37. Marshall NE, Fu R, Guise J-M. Impact of multiple cesarean deliveries on maternal morbidity: a systematic review. *Am J Obstet Gynecol* 2011; **205**: 262.e1-8.
38. Pare E, Quinones JN, Macones GA. Vaginal birth after caesarean section versus elective repeat caesarean section: assessment of maternal downstream health outcomes. *BJOG* 2006; **113**: 75–85.
39. Gilbert SA, Grobman WA, Landon MB, et al. Lifetime cost-effectiveness of trial of labor after cesarean in the United States. *Value Health* 2013; **16**(6): 953–64.
40. Guiliano M, Closset E, Therby D, et al. Signs, symptoms and complications of complete and partial uterine ruptures during pregnancy and delivery. *Eur J Obstet Gynecol Reprod Biol*. 2014; **179**: 130–4.
41. Cahill AG, Odibo AO, Allsworth JE, et al. Frequent epidural dosing as a marker for impending uterine rupture in patients who attempt vaginal birth after cesarean delivery. *Am J Obstet Gynecol* 2010; **202**(4): 355.e1–5.
42. Catanzarite V, Cousins L, Dowling D, et al. Oxytocin-associated rupture of an unscarred uterus in a primigravida. *Obstet Gynecol* 2006; **108** (3 Pt 2): 723–5.
43. Gibbins KJ, Weber T, Holmgren CM, et al. Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. *Am J Obstet Gynecol* 2015; **213** (3): 382.e1–6.
44. Walsh CA, Baxi LV. Rupture of the primigravid uterus: a review of the literature. *Obstet Gynecol Surv* 2007; **62**: 327–34.
45. American College of Obstetricians and Gynecologists. Operative vaginal delivery: clinical management guidelines for obstetrician–gynecologists. *Int J Gynaecol Obstet* 2001; **74**: 69–76 (reaffirmed 2012).
46. O'Mahony F, Hofmeyr GJ, Menon V. Choice of instruments for assisted vaginal delivery. *Cochrane Database Syst Rev* 2010; **10(11)**: CD005455.

.013

47. Johnson JH, Figueroa R, Garry D, et al. Immediate maternal and neonatal effects of forceps and vacuum-assisted deliveries. *Obstet Gynecol* 2004; **103**: 513–18.
48. Caughey AB, Sandberg PL, Zlatnik MG, et al. Forceps compared with vacuum: rates of neonatal and maternal morbidity. *Obstet Gynecol* 2005; **106**: 908–12.
49. Schot MJ, Halbertsma FJ, Katgert T, et al. Development of children with symptomatic intracranial hemorrhage born after vacuum extraction. *J Child Neurol* 2013; **28**(4): 520–3.
50. Kolderup LB, Laros RK, Musci TJ. Incidence of persistent birth injury in macrosomic infants: association with mode of delivery. *Am J Obstet Gynecol* 1997; **177**: 37–41.
51. Aiken AR, Aiken CE, Alberry MS. Management of fetal malposition in the second stage of labor: a propensity score analysis. *Am J Obstet Gynecol* 2015; **212**(3): 355.e1–7.
52. Tempest N, Hart A, Walkinshaw S, et al. A re-evaluation of the role of rotational forceps: retrospective comparison of maternal and perinatal outcomes following different methods of birth for malposition in the second stage of labour. *BJOG* 2013; **120**(10): 1277–84.
53. Bhide A, Guven M, Prefumo F, et al. Maternal and neonatal outcome after failed ventouse delivery: comparison of forceps versus cesarean section. *J Matern Fetal Neonatal Med* 2007; **20**(7): 541–5.
54. Lurie S, Glezerman M, Baider C, et al. Decision-to-delivery interval for instrumental vaginal deliveries: vacuum extraction versus forceps. *Arch Gynecol Obstet* 2006; **274**(1): 34–6.
55. Towner D, Castro MA, Eby-Wilkens E, et al. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999; **341**: 1709–14.
56. Gardella C, Taylor M, Benedetti T, et al. The effect of sequential use of vacuum and forceps for assisted vaginal delivery on neonatal and maternal outcomes. *Am J Obstet Gynecol* 2001; **185**(4):896–902.
57. Carmody F, Grant A, Mutch L, et al. Follow up of babies delivered in a randomized controlled comparison of vacuum extraction and forceps delivery. *Acta Obstet Gynecol Scand* 1986; **65**: 763–6.
58. Johanson RB, Heycock E, Carter J, et al. Maternal and child health after assisted vaginal delivery: five-year follow up of a randomized, controlled study comparing forceps and ventouse. *Br J Obstet Gynaecol* 1999; **106**(6): 544–9.
59. Wesley BD, van den Berg BJ, Reece EA. The effect of forceps delivery on cognitive development. *Am J Obstet Gynecol* 1993; **169**: 1091–5.
60. Ngan HY, Miu P, Ko L, et al. Long-term neurological sequelae following vacuum extractor delivery. *Aust NZ J Obstet Gynaecol* 1990; **30**: 111–14.
61. Sokol RJ, Blackwell SC. Shoulder dystocia (ACOG Practice Bulletin No. 40). *Int J Gynaecol Obstet* 2003; **80**: 87–92 (reaffirmed 2015).
62. Paris AE, Greenberg JA, Ecker JL, McElrath TF. Is an episiotomy necessary with a shoulder dystocia? *Am J Obstet Gynecol* 2011; **205**(217): e1–3.
63. Boulvain M, Senat MV, Perrotin F, et al. Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet* 2015; **385**(9987): 2600–5.
64. Dajani NK, Magann EF. Complications of shoulder dystocia. *Semin Perinatol* 2014; **38**(4): 201–4.
65. Spain JE, Frey HA, Tuuli MG, et al. Neonatal morbidity associated with shoulder dystocia maneuvers. *Am J Obstet Gynecol* 2015; **212**(3): 353.e1–5.
66. Fong A, Chau CT, Pan D, et al. Amniotic fluid embolism: antepartum, intrapartum and demographic factors. *J Matern Fetal Neonatal Med* 2015; **28**(7): 793–8.
67. Clark SL, Hankins GD, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. *Am J Obstet Gynecol* 1995; **172**: 1158–67.
68. Kramer MS, Rouleau J, Liu S, et al. Amniotic fluid embolism: incidence, risk factors, and impact on perinatal outcome. *BJOG* 2012; **119**(7): 874–9.
69. Clark SL, Montz FJ, Phelan JP. Hemodynamic alterations associated with amniotic fluid embolism: a reappraisal. *Am J Obstet Gynecol* 1985; **151**: 617–21.
70. Kanayama N, Tamura N. Amniotic fluid embolism: pathophysiology and new strategies for management. *J Obstet Gynaecol Res* 2014; **40**(6): 1507–17.
71. Shen F, Wang L, Yang W, et al. From appearance to essence: 10 years review of atypical amniotic fluid embolism. *Arch Gynecol Obstet* 2015; **292**(2): 329–34.
72. Benson MD, Kobayashi H, Silver RK, et al. Immunologic studies in presumed amniotic fluid embolism. *Obstet Gynecol* 2001; **97**: 510–14.
73. Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. *Am J Obstet Gynecol* 2009; **201**(5): 445.e1–13.
74. O'Shea A, Eappen S. Amniotic fluid embolism. *Int Anesthesiol Clin* 2007; **45**(1): 17–28.
75. Cunningham FG, Williams JW. *Williams Obstetrics*, 21st edn. New York: McGraw-Hill, 2001.
76. Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: from pathogenesis to treatment. *Clin Microbiol Infect* 2011; **17**(9): 1304–11.

77. Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA* 1997; **278**: 207–11.

78. Wu YW, Escobar GJ, Grether JK, et al. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA* 2003; **290**(20): 2677–84.

79. Nasef N, Shabaan AE, Schurr P, et al. Effect of clinical and histological chorioamnionitis on the outcome of preterm infants. *Am J Perinatol* 2013; **30**(1): 59–68.

80. Malloy MH. Chorioamnionitis: epidemiology of newborn management and outcome United States 2008. *J Perinatol* 2014; **34**(8): 611–5.

81. Fishman SG, Gelber SE. Evidence for the clinical management of chorioamnionitis. *Semin Fetal Neonatal Med* 2012; **17**(1): 46–50.

82. Chapman E, Reveiz L, Illanes E, et al. Antibiotic regimens for management of intra-amniotic infection. *Cochrane Database Syst Rev* 2014 **19**(12): CD010976.

83. Lyell DJ, Pullen K, Fuh K, et al. Daily compared with 8-hour gentamicin for the treatment of intrapartum chorioamnionitis: a randomized controlled trial. *Obstet Gynecol*. 2010; **115**(2 Pt 1): 344–9.

84. American College of Obstetricians and Gynecologists. Management of late-term and postterm pregnancies (Practice Bulletin No. 146). *Obstet Gynecol* 2014; **124**(2 Pt 1): 390–6.

85. Romero R, Yoon BH, Chaemsaithong P, et al. Bacteria and endotoxin in meconium-stained amniotic fluid at term: could intra-amniotic infection cause meconium passage? *J Matern Fetal Neonatal Med* 2014; **27**: 775–88.

86. Beligere N, Rao R. Neurodevelopmental outcome of infants with meconium aspiration syndrome: report of a study and literature review. *J Perinatol* 2008; **28**(Suppl. 3):S93–101.

87. Hofmeyr GJ, Xu H, Eke AC. Amnioinfusion for meconium-stained liquor in labour. *Cochrane Database Syst Rev* 2014; **1**: CD000014.

88. Katz VL, Seeds JW. Malpresentations other than breech. *Clin Obstet Gynecol* 1986; **29**(2): 329–38.

89. Chou MR, Kreiser D, Taslimi MM, et al. Vaginal versus ultrasound examination of fetal occiput position during the second stage of labor. *Am J Obstet Gynecol* 2004; **191**: 521–4.

90. Zahalka N, Sadan O, Malinger G, et al. Comparison of transvaginal sonography with digital examination and transabdominal sonography for the determination of fetal head position in the second stage of labor. *Am J Obstet Gynecol* 2005; **193**(2): 381–6.

91. Cruikshank DP, White CA. Obstetric malpresentations: twenty years' experience. *Am J Obstet Gynecol* 1973; **116**: 1097–104.

92. American College of Obstetricians and Gynecologists. Committee on Practice Bulletins: Obstetrics (Practice Bulletin No. 161: External Cephalic Version). *Obstet Gynecol* 2016; **127**(2): e54–61.

93. Hannah ME, Hannah WJ, Hewson SA, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet* 2000; **356**: 1375–83.

94. American College of Obstetricians and Gynecologists. Mode of term single breech delivery (Committee Opinion No. 265). *Obstet Gynecol* 2001; **98**: 1189–90.

95. American College of Obstetricians and Gynecologists. Mode of term singleton breech delivery (Committee Opinion No. 340). *Obstet Gynecol* 2006; **108**: 235–7.

96. Whyte H, Hannah ME, Saigal S, et al. Outcomes of children at 2 years after planned cesarean birth versus planned vaginal birth for breech presentation at term: the International Randomized Term Breech Trial. *Am J Obstet Gynecol* 2004; **191**: 864–71.

97. Berhan Y, Haileamlak A. The risks of planned vaginal breech delivery versus planned caesarean section for term breech birth: a meta-analysis including observational studies. *BJOG* 2016; **123**(1): 49–57.

98. Caughey AB, Sharshiner R, Cheng YW. Fetal malposition: impact and management. *Clin Obstet Gynecol* 2015; **58**(2): 241–5.

99. Lieberman E, Davidson K, Lee-Parritz A, et al. Changes in fetal position during labor and their association with epidural analgesia. *Obstet Gynecol* 2005; **105**(5 Pt 1): 974–82.

100. Cheng YW, Shaffer BL, Caughey AB. The association between persistent occiput posterior position and neonatal outcomes. *Obstet Gynecol* 2006; **107**(4): 837–44.

101. Reichman O, Gdansky E, Latinsky B, et al. Digital rotation from occipito-posterior to occipito-anterior decreases the need for cesarean section. *Eur J Obstet Gynecol Reprod Biol* 2008; **136** (1): 25–8.

102. Cluver C, Hofmeyr GJ, Gyte GM, et al. Interventions for helping to turn term breech babies to head first presentation when using external cephalic version. *Cochrane Database Syst Rev* 2012; **1**: CD000184.

103. Hofmeyr GJ, Kulier R, West HM. External cephalic version for breech presentation at term. *Cochrane Database Syst Rev* 2015; **4**: CD000083.

104. Kaymak O, Iskender C, Ibanoglu M, et al. Retrospective evaluation of risk factors and perinatal outcome of umbilical cord prolapse during labor. *Eur Rev Med Pharmacol Sci* 2015; **19**(13): 2336–9.

105. Hartigan L, Hehir M, McHugh A, et al. Analysis of incidence and outcomes of umbilical cord prolapse over 20 years at a large tertiary referral center (abstract no. 431). *Am J Obstet Gynecol* 2013; **208** (Suppl. 1): S188.

106. Gibbons C, O'Herlihy C, Murphy JF. Umbilical cord prolapsed – changing patterns and improved outcomes: a retrospective cohort study. *BJOG* 2014; **121**(13): 1705–8.

107. American College of Obstetricians and Gynecologists. Dystocia and augmentation of labor (Practice Bulletin No. 49). *Obstet Gynecol* 2003; **102**: 1445–54.

108. Friedman EA. Primigravid labor: a graphicostatistical analyis. *Obstet Gynecol* 1955; **6**(6): 567–89.

109. Kilpatrick SJ, Laros RK. Characteristics of normal labor. *Obstet Gynecol* 1989; **74**: 85–7.

110. Cheng YW, Shaffer BL, Nicholson JM, et al. Second stage of labor and epidural use: a larger effect than previously suggested. *Obstet Gynecol* 2014; **123**(3): 527–35.

111. Myles TD, Santolaya J. Maternal and neonatal outcomes in patients with a prolonged second stage of labor. *Obstet Gynecol* 2003; **102**: 52–8.

112. Rouse DJ, Weiner SJ, Bloom SL, et al. Second-stage labor duration in nulliparous women: relationship to maternal and perinatal outcomes. *Am J Obstet Gynecol* 2009; **201**(4): 357.e1–7.

113. Sung JF, Daniels KI, Brodzinsky L, et al. Cesarean delivery outcomes after a prolonged second stage of labor. *Am J Obstet Gynecol* 2007; **197**: 306.e1–5.

114. Benfield N, Young-Lin N, Kimona C, et al. Fistula after attended delivery and the challenge of obstetric care capacity in the eastern Democratic Republic of Congo. *Int J Gynaecol Obstet* 2015; **130**(2): 157–60.

115. Chen HY, Chauhan SP, Ananth CV, et al. Electronic fetal heart rate monitoring and its relationship to neonatal and infant mortality in the United States. *Am J Obstet Gynecol* 2011; **204**(6): 491.e1–10.

116. American College of Obstetricians and Gynecologists. Management of intrapartum fetal heart rate tracings (Practice Bulletin No. 116). *Obstet Gynecol* 2010; **116**(5): 1232–40.

117. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. *Cochrane Database Syst Rev*. 2013; **5**: CD006066.

118. Nielsen PV, Stigsby B, Nickelsen C, et al. Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms. *Acta Obstet Gynecol Scand* 1987; **66**: 421–4.

119. Hruban L, Spilka J, Chudáček V, et al. Agreement on intrapartum cardiotocogram recordings between expert obstetricians. *J Eval Clin Pract* 2015; **21**(4): 694–702.

120. Chauhan SP, Klauser CK, Woodring TC, et al. Intrapartum nonreassuring fetal heart rate tracing and prediction of adverse outcomes: interobserver variability. *Am J Obstet Gynecol* 2008; **199**(6): 623.e1–5.

121. Macones GA, Hankins GD, Spong CY, et al. The 2008 National Institute of Child Health and Human Development Workshop Report on Electronic Fetal Monitoring: update on definitions, interpretation, and research guidelines. *J Obstet Gynecol Neonatal Nurs* 2008; **37**(5): 510–5.

122. Liu L, Tuuli MG, Roehl KA, et al. Electronic fetal monitoring patterns associated with respiratory morbidity in term neonates. *Am J Obstet Gynecol* 2015; **213**(5): 681.e1–6.

123. Cahill AG, Caughey AB, Roehl KA, et al. Terminal fetal heart decelerations and neonatal outcomes. *Obstet Gynecol* 2013; **122**(5): 1070–6.

124. Nelson KB, Dambrosia JM, Ting TY, et al. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. *N Engl J Med* 1996; **334**: 613–18.

125. Amer-Wahlin I, Kwee A. Combined cardiotocographic and ST event analysis: a review. *Best Pract Res Clin Obstet Gynaecol* 2016; **30**: 48–61.

126. Clark SL, Hankins GD. Temporal and demographic trends in cerebral palsy: fact and fiction. *Am J Obstet Gynecol* 2003; **188**: 628–33.

127. Graham EM, Adami RR, McKenney SL, et al. Diagnostic accuracy of fetal heart rate monitoring in the identification of neonatal encephalopathy. *Obstet Gynecol* 2014; **124**(3): 507–13.

128. Graham EM, Ruis KA, Hartman AL, et al. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008; **199**(6): 587–95.

Chapter 13

Fetal Responses to Asphyxia

Laura Bennet, Guido Wassink, and Alistair J. Gunn

Introduction

For most of the twentieth century the concept of perinatal brain damage centered around cerebral palsy (CP) and intrapartum asphyxia. It is only in the last 20 years that this view has been seriously challenged by clinical and epidemiologic studies that have demonstrated that ~10–30% of CP in infants born at term is related to intrapartum events [1,2]. Many term infants who subsequently develop CP are believed to have sustained asphyxial events in mid-gestation. In some cases, prenatal injury may lead to chronically abnormal heart rate tracings and impaired ability to adapt to labor that may be confounded with an acute event [3].

Furthermore, it has become clear that the various abnormal fetal heart rate (FHR) patterns that have been proposed to be markers for potentially injurious asphyxia are consistently only very weakly predictive for CP [4]. Although metabolic acidosis is more strongly associated with outcome, more than half of babies born with severe acidosis (base deficit [BD] >16 mmol/L and pH < 7.0) do not develop encephalopathy, whereas conversely encephalopathy can still occur, although at low frequency, in association with relatively modest acidosis (BD = 12–16 mmol/L) [5]. These data contrast with the presence of very abnormal FHR tracings, severe metabolic acidosis [6], and acute cerebral lesions [7] in the great majority of infants who *do* develop acute neonatal encephalopathy.

The key factor underlying these observations is the effectiveness of fetal adaptation to asphyxia. The fetus is spectacularly good at defending itself against asphyxia, and injury occurs only in a very narrow window between intact survival and death. These adaptations work sufficiently well in the majority of cases that even the concept of "birth asphyxia" itself has been controversial. For example, recent studies where cerebral function has been monitored from birth in infants with clinical evidence of compromise during labor have shown that many such children did have a precipitating episode in the immediate peripartum period, with evidence of acute evolving clinical encephalopathy [6], abnormal electroencephalograph (EEG) recordings [8], evolving loss of mitochondrial oxidative activity [9], acute cerebral lesions on magnetic resonance imaging (MRI) [7], and an increased rate of long-term cognitive or functional sequelae [10].

In infants with evidence for acute perinatal asphyxial event(s), the link between asphyxia and long-term problems is the severity of early-onset encephalopathy. Newborns with mild encephalopathy show normal development during follow-up, whereas at least 90% of those with severe (stage III) encephalopathy die or have severe handicap by 18 months of age. In contrast, only half of those with moderate (stage II) hypoxic-ischemic encephalopathy (HIE) show moderate to severe neurodevelopmental disability, but even those who do not develop neurologic impairment are at risk of future academic failure [11].

Causes of Pathologic Asphyxia

A number of events, some peculiar to labor, may result in asphyxia before birth. Broadly, these may be grouped as chronic, acute catastrophic, and repeated hypoxia [6]. Chronic hypoxia may be caused by decreased fetal hemoglobin (e.g., fetomaternal or fetofetal hemorrhage), placental insufficiency, and maternal causes such as preeclampsia. Immediate catastrophic events include cord prolapse and to some extent cord entanglements, true knots in the cord, vasa previa, placental abruption, uterine rupture, and fetal entrapment such as shoulder dystocia. The impact of asphyxia during placental abruption may be potentiated by fetal blood loss with fetal volume contraction. Finally, the fetus

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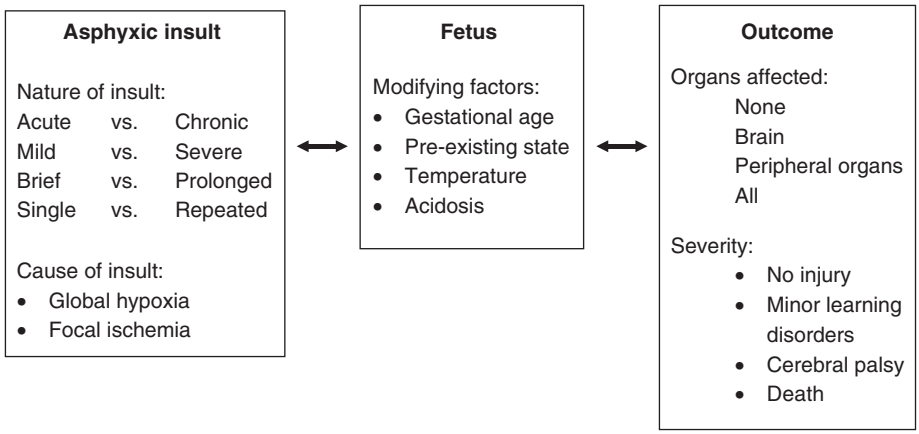


Figure 13.1 Schema of the factors influencing the development of cerebral injury after perinatal asphyxia.

may be exposed to shorter but frequent episodes during labor that may lead to a progressive decompensation over time [3]. Naturally, there is potential for antenatal and intrapartum insults to be combined. For example, approximately 23–36% of cases of moderate to severe neonatal encephalopathy have been reported to be associated with abnormal FHR recordings before the start of labor and so potentially may have been associated with preceding neural injury [6,12].

Characteristics of Perinatal Asphyxial Encephalopathy

The fetal response to asphyxia is not stereotypical. Both the fetal responses and the ability of the fetus to avoid or attenuate injury depend on the type of the insult, the precise environmental conditions, and the maturity and condition of the fetus (Figure 13.1). This chapter focuses on recent developments in our understanding of the factors that determine whether the brain develops damage after an asphyxial insult. We will briefly review the fundamental cellular mechanisms of cerebral damage and discuss in detail the systemic adaptations of the fetus to asphyxia in relation to the factors that can modulate the evolution of cerebral injury.

Pathogenesis of Cell Death

What Initiates Neuronal Injury?

At the most fundamental level, injury requires a period of insufficient delivery of oxygen and substrates including glucose and other substrates in the fetus such that neurons and glia cannot maintain homeostasis. Once the neurons' supply of high-energy metabolites such as ATP can no longer be maintained during hypoxia-ischemia, there is failure of the energy-dependent mechanisms of intracellular homeostasis, such as the Na^+/K^+-ATP-dependent pump. Neuronal depolarization then occurs, leading to sodium and calcium entry into cells. This creates an osmotic and electrochemical gradient that in turn favors further cation and water entry, leading to cell swelling (cytotoxic edema). If sufficiently severe, this may lead to immediate lysis [13]. The swollen neurons may still recover, at least temporarily, if the hypoxic insult is reversed or the environment is manipulated. Evidence suggests that several additional factors act to increase cell injury during and following depolarization. These include the extracellular accumulation of excitatory amino acid neurotransmitters due to impairment of energy-dependent reuptake, which promote further receptor-mediated cell swelling and intracellular calcium entry, and the generation of oxygen free radicals and inflammatory cytokines [14].

Nevertheless, it is critical to appreciate that these factors appear to be injurious almost entirely in the presence of hypoxic cell depolarization. For example, glutamate is far more toxic during hypoxia (or mitochondrial dysfunction) than during normoxia [15]. Conversely, in vitro, hypoxia can still trigger cell death despite glutamate receptor blockade, through apoptotic mechanisms [16].

Neural Adaptation to Hypoxia

If blood oxygen content is reduced, but blood flow and substrate concentrations are not impaired (i.e., moderate, pure, or nearly pure hypoxia), neural

adaptations complement the cardiovascular adaptations discussed later to delay and often completely avoid cell depolarization. First, the brain can reduce nonobligatory energy consumption, with a transient switch to a high-voltage, low-frequency EEG state that requires less oxygen consumption [17,18]. Next, as hypoxia-ischemia becomes more severe, neuronal activity ceases completely at a threshold above that which causes neuronal depolarization [19]. This regulated suppression of metabolic rate before energy stores are depleted during hypoxia or ischemia, termed *adaptive hypometabolism*, is actively mediated through inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) and adenosine [19] and protects the brain by delaying the onset of cell depolarization. The duration of neuronal depolarization, in turn, determines the severity of injury [20].

Brain cells can also use anaerobic metabolism to support production of high-energy metabolites for a limited time. This is extremely inefficient because whereas aerobic glycolysis produces 38 ATP molecules with complete oxidation of glucose, anaerobic glycolysis produces lactate and only 2 ATP, so glucose reserves are rapidly consumed, with a concomitant metabolic acidosis. In some circumstances, the fetus may be able to benefit from increased circulating lactate. Many fetal tissues, such as the heart, get a high proportion of their substrate from sources other than glucose, particularly lactate [21], and the brain can oxidize lactate when its concentration is elevated in fetal sheep [22] and very likely in human newborn infants [23]. However, because lactate requires oxygen to be metabolized, this strategy is only possible during mild or intermittent hypoxia and not during sustained, severe asphyxia.

Neural Responses to Severe Hypoxia-Ischemia

In contrast, under conditions where both oxygen and substrate delivery are reduced, the options for the neuron are much more limited because there is both less oxygen and less glucose available to support anaerobic metabolism. This may occur during pure ischemia (reduced tissue blood flow, such as occurs in stroke) and during conditions of hypoxia-ischemia (i.e., a combination of reduced oxygen content with reduced tissue blood flow). In the fetus, hypoxia-ischemia commonly occurs due to hypoxic cardiac compromise, which leads to secondary hypotension and hypoperfusion. Under these conditions, depletion of cerebral high-energy metabolites will occur much more rapidly and profoundly, while at the same time there may actually be *less* acidosis both because there is much less glucose available to be metabolized to lactate and because the insult evolves more quickly.

These concepts help to explain the consistent observation, discussed later in this chapter, that most cerebral injury after acute perinatal insults occurs in association with hypotension and consequent tissue hypoperfusion or ischemia. In contrast, although asphyxial brain injury by definition requires exposure to an anaerobic environment, there is only a broad correlation between the severity of systemic acidosis and the severity of injury in any paradigm [24]. *Asphyxia* is defined as the combination of impaired respiratory gas exchange (i.e., hypoxia and hypercapnia) and the development of metabolic acidosis. When we think about the impact on the brain of clinical asphyxia, it will be critical to keep in mind that this definition tells us much about things that are relatively easily measured (fetal blood gases and systemic acidosis) and nothing about the fetal blood pressure and perfusion of the brain, the key factors that most directly trigger brain injury.

Systemic and Cardiovascular Adaptations to Asphyxia

The systemic adaptations of the fetus to whole-body asphyxia are critical to outcome. Although the focus of most of the classic studies in this area was to delineate the cardiovascular and cerebrovascular responses, more recently, the relationship between particular patterns of asphyxia and neural outcome has been examined. The majority of experimental studies of the pathophysiology of fetal asphyxia have been performed in chronically instrumented fetal sheep in utero. The sheep is a highly precocial species whose neural development broadly approximates that of term human infants around 0.8 to 0.85 of gestation and that of 27- to 30-week preterm infants at 0.7 of gestation [25]. The reader should note that the baseline heart rate of the fetal sheep is approximately 20 beats per minute higher than that of the human fetus.

Fetal Adaptations and Defense Mechanisms

The fetus is highly adapted to intrauterine conditions, which include low partial pressures of oxygen and relatively limited supply of substrates compared with

postnatal life. Although tissue myoglobin could in theory act as an oxygen store, in practice, the fetus does not have appreciable tissue myoglobin levels except in the heart [26]. Myocardial myoglobin concentrations do increase in hypoxic fetuses, consistent with previous observations in postnatal animals. This appears to represent an intracellular compensatory mechanism for sustaining short-term mitochondrial oxygen delivery in a critical organ with high oxygen consumption [27].

Thus the fetus is largely dependent on a steady supply of oxygen, and consequently, it has many adaptive features, some unique to the fetus, that help it to maximize oxygen availability to its tissues even during moderate hypoxia. Thanks to these adaptations, the fetus normally exists with a surplus of oxygen relative to its needs, which provides a significant margin of safety when oxygen delivery is impaired. These adaptive features include: higher basal blood flow to organs, the higher affinity of fetal hemoglobin for oxygen, greater sensitivity of hemoglobin to acid-promoting release of oxygen to tissues, the amount of oxygen that can be extracted at typical fetal oxygen tensions, the capacity to significantly reduce energy-consuming processes, greater anaerobic capacity in many tissues, and the capacity to redistribute blood flow toward essential organs and away from the periphery.

Additional structural features of the fetal circulation further support these adaptive features, including the systems of shunts, such as the ductus arteriosus, and preferential blood flow streaming in the inferior vena cava to avoid intermixing of oxygenated blood from the placenta and deoxygenated blood in the fetal venous system. These features ensure maximal oxygen delivery to essential organs such as the brain and heart [28]. During mild to moderate placental restriction, fetal oxygen consumption can be maintained at normal levels until uteroplacental blood flow falls below 50% [29] with normal removal of waste products of metabolism, mainly carbon dioxide and water [30].

Cerebral oxygen consumption is even more protected and is little changed even if arterial oxygen content falls as low as 1.5 mM (compared with ~4 mM in the normal fetus) thanks to compensating increases in both cerebral blood flow (CBF) and oxygen extraction [31]. Nitric oxide (NO) and adenosine have been shown to play a role in mediating the local increase in CBF during hypoxia [18,32].

Fetal Responses to Mild or Moderate Hypoxia

The response of the fetal sheep to moderate, stable hypoxia has been evaluated extensively [33]. Fetal isocapnic hypoxia is typically induced by reduction of maternal inspired oxygen fraction to 10–12%, with CO_2 added to the inspirate to maintain fetal and maternal normocapnia. This model permits the fetal responses to changes in oxygenation to be studied separately from the effects of hypercapnia and acidosis. In the late-gestation fetus, the response to this degree of hypoxia is characterized by an initial transient moderate bradycardia followed by a return of heart rate to baseline or tachycardia. Arterial blood pressure increases due to intense peripheral vasoconstriction (Figure 13.2), despite a net reduction in combined ventricular output (CVO, the sum of right and left ventricular outputs). CVO is redistributed in favor of the cerebral, myocardial, and adrenal vascular beds (central or vital organs; see Figure 13.2) at the expense of the gastrointestinal tract, renal, pulmonary, cutaneous, and skeletal beds (i.e., the periphery) [34]. The magnitude of the hemodynamic changes largely depends on the magnitude of changes in arterial pH and blood gases [35]. There is greater and more sustained bradycardia and vasoconstriction during hypoxia as the fetus approaches full term [36]. These changes may due to maturation of the autonomic nervous system but more likely reflect the greater metabolic demand of the fetus as it gets older such that the same insult poses a more severe homeostatic challenge.

The fetal cardiovascular response to hypoxia is initially mediated via reflex responses, which are rapid in onset, and via endocrine and endothelial responses, which augment these reflexes but which take somewhat longer to become fully active. The afferent component of the reflex arc triggering the initial bradycardia and increase in peripheral vasoconstriction during hypoxia is mediated by carotid chemoreceptors (*chemoreflex*). Hypoxia stimulates the carotid chemoreceptors, which are known to be functional in utero [37,38]. During mild to moderate hypoxia, the aortic chemoreceptors do not appear to play a role in these responses [39], although they may have a role during asphyxia [40]. The efferent limb of the fall in FHR is mediated by the parasympathetic nervous system via muscarinic receptors, as demonstrated by abolition of hypoxic bradycardia by

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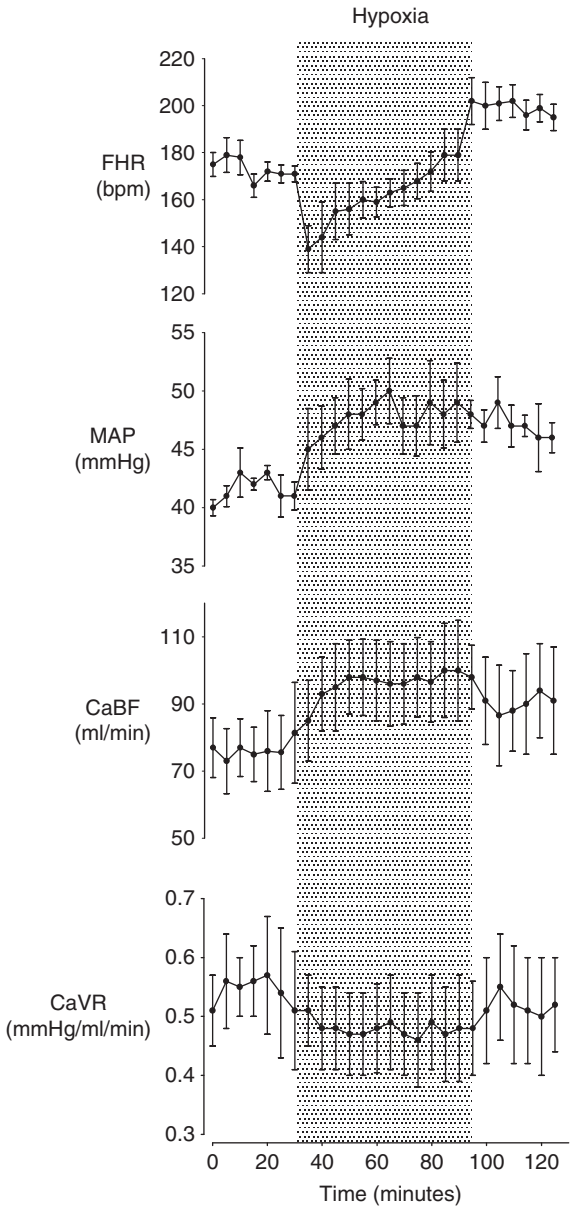


Figure 13.2 The responses in the near-term fetal sheep to moderate isocapnic hypoxia for 60 minutes induced by altering the maternal inspired gas mixture, showing changes in fetal heart rate (FHR), mean arterial blood pressure (MAP), carotid blood flow (CaBF), and carotid vascular resistance (CaVR). Moderate hypoxia is associated with a sustained redistribution of blood flow away from peripheral organs to essential organs such as the brain. Data derived from Bennet *et al* [67].

vagotomy [41] or blockade with atropine [42]. The initial fall in FHR is then followed by a progressively increase in heart rate, which is mediated by the increase in circulating catecholamines [43]. These temporal changes in FHR likely reflect changes in metabolism. The initial bradycardia acts to conserve cardiac energy by reducing work. However, as hypoxia progresses, the fetus reduces the metabolic demand in several ways. The fetus expends considerable energy making fetal breathing movements (FBMs), particularly in late gestation. In contrast to the neonate and adult, where hypoxia initially stimulates breathing, in the fetus, hypoxia strongly inhibits FBMs [44]. This inhibition is mediated through activation of neural networks that either arise from or pass through the upper pons [45] and thalamus [46]. Similarly, the fetus suspends other energy-consuming activities such as body and limb movements [47] and reduces cerebral oxygen requirements, as discussed earlier [48].

The reflex vasoconstriction is mediated in part by the sympathetic nervous system and partly by circulating catecholamines because it is reduced by sympathectomy [49] and abolished by alpha-adrenergic blockade [30,50]. The increase in peripheral vasoconstriction is the primary mediator of the rise in blood pressure observed during hypoxia and is augmented by release of other vasopressors such as arginine vasopressin [51] and angiotensin II [52]. There is also a large adrenocorticotrophic and cortisol response to hypoxia [53]. Their role in the cardiovascular response to hypoxia is unclear, but cortisol has been shown to augment the actions of other vasopressors [54]. The fetal adrenals secrete epinephrine during hypoxia by both neural mechanisms and direct stimulation by hypoxia [55,56]. This secretory response depends on the activation of voltage-sensitive Ca^{2+} channels in the chromaffin cell membrane, which declines toward term [56].

Protracted Hypoxia

The effect of prolonged hypoxemia on cerebral metabolism in near-term fetal sheep has been studied during stepwise reductions of the maternal inspired oxygen concentration from 18% to 10–12% over 4 successive days [57]. Until the fetal arterial oxygen saturation was reduced to less than 30% of baseline, cerebral oxidative metabolism remained stable. At the lowest inspired oxygen concentration (with 3% CO_2) a progressive metabolic acidemia was induced. Initially, CBF increased, thus maintaining cerebral oxygen delivery and consumption at control values, consistent with the effect of acute hypoxia.

However, once the fetal pH fell below 7.00, cerebral oxygen consumption fell to less than 50% of control values.

If mild to moderate hypoxia is sustained, the fetus may be able to fully adapt, as shown by normalization of FHR and blood pressure and the return of FBMs and body movements, but redistribution of blood flow is maintained indefinitely [58]. This is consistent with the clinical situation of "brain sparing" in growth retardation. In this situation, the fetus can secondarily improve tissue oxygen delivery to near baseline levels by increasing hemoglobin synthesis, mediated by greater erythropoietin release [59].

Maturational Changes in Responses to Hypoxia

Some aspects of the cardiovascular response to fetal hypoxia appear to be age related. In the premature fetal sheep before 0.7 of gestation, isocapnic hypoxia and hemorrhagic hypotension were not associated with hypertension, bradycardia, or peripheral vasoconstriction [17,60–62]. Even from late gestation to full term there is a further developmental increase in the magnitude and persistence of fetal bradycardia and the magnitude of the femoral constrictor response to moderate hypoxia in fetal sheep [63]. Thus it has been suggested that peripheral vasomotor control starts to develop at 0.7 of gestation, coincident with maturation of neurohormonal regulators and chemoreceptor function [43,64]. However, as noted earlier, when interpreting these results, it is also important to consider that the homeostatic requirement of the fetus for oxygen increases with maturation. The preterm fetus has much greater anaerobic reserves and correspondingly lower obligate aerobic requirements than at term [65,66]. This suggests that relatively mild hypoxic insults simply may not represent a sufficient homeostatic challenge to elicit the responses seen later in gestation. As discussed later, in the section on premature fetal asphyxia, it is likely that the degree of hypoxia attained in these studies did not reduce tissue oxygen availability below the critical homeostatic threshold for this developmental stage.

The preterm fetus does show increased blood flow to cerebral hemispheres, the cerebellum, and the pons-medulla during moderate hypoxia [60]. However, in contrast to near-term fetuses, the increase in blood flow to the cerebral hemispheres was not sufficient to fully maintain oxygen delivery such that cerebral oxygen consumption was sustained in part by increased fractional extraction [60].

Fetal Responses to Asphyxia

Studies of asphyxia by definition involve both hypoxia and hypercapnia with metabolic acidosis. It is important to appreciate that these studies of asphyxia also involve a greater depth of hypoxia than is possible using maternal inhalational hypoxia. Further, asphyxia can be induced relatively abruptly, limiting the time available for adaptation. Complete clamping of the uterine artery or umbilical cord leads to a rapid reduction in fetal oxygenation over the first minute [67]. In contrast, gradual partial occlusion induces a slow fetal metabolic deterioration without the initial fetal cardiovascular responses of bradycardia and hypertension, reflecting the greater time available for fetal adaptation and lesser degree of hypoxia [68]. During profound asphyxia, corresponding with a severe reduction of uterine blood flow to 25% or less and a fetal arterial oxygen content of less than 1 mmol/L, the fetal cardiovascular responses are substantially different from those during moderate hypoxia or asphyxia [69].

Three broad phases of the cardiovascular responses of the fetus to such severe events can be distinguished: the initial, rapid chemoreflex-mediated adaptations [30,37,39,41], sustained adaptation that is supported by circulating humoral factors, and the final period of progressive hypoxic decompensation ultimately terminated by profound systemic hypotension (Figure 13.3) and cerebral hypoperfusion (Figure 13.4).

Initial, Reflex Responses to Asphyxia

The initial responses include rapid, sustained bradycardia and generalized vasoconstriction involving essentially all organs [43]. In marked contrast to the increase in CBF during moderate hypoxia, during asphyxia, CBF does not increase or may even fall despite a marked initial increase in fetal blood pressure due to significant cerebral vasoconstriction [67,70] (Figure 13.4). The factors mediating this increase in cerebral vascular resistance are not clearly understood. However, while the failure of CBF to increase may seem counterintuitive, it should be remembered that it occurs in conjunction with profound suppression of brain activity. This suppression is mediated by activation of the adenosine A1 receptor, and if it is blocked, neural injury is exacerbated [19]. Further, blood flow within the brain is preferentially redirected during asphyxia to protect structures important for survival, such as the brainstem, at the expense of the cerebrum. Speculatively, this redirection may help to maintain

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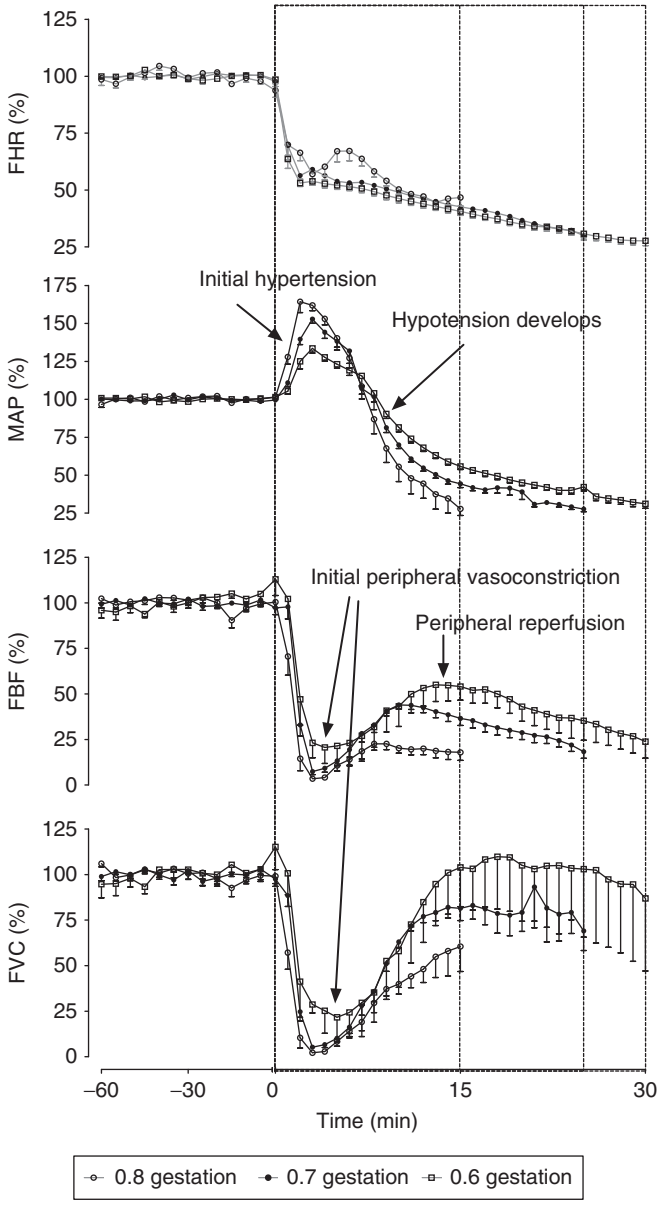


Figure 13.3 The responses of fetal sheep to severe asphyxia induced by complete umbilical cord occlusion. Fetal heart rate (FHR, % baseline), mean arterial pressure (MAP, % baseline), femoral blood flow (FBF, % baseline), and femoral vascular conductance (FVC, % baseline) at 0.6 of gestation (0.6 ga; open squares), 0.7 of gestation (0.7 ga; closed circles), and 0.85 of gestation (0.85 ga; open circles) fetuses. Conductance is the reciprocal of resistance; i.e., a reduction in conductance indicates increased vascular resistance to flow. FHR and MAP data represent 5-minute averages before occlusion and 1-minute averages during occlusion and are expressed as a percentage of baseline. Umbilical cord occlusion begins at 0 minute and ends for each group as indicated by the dotted rectangles. Data are mean ± SEM. Between-group comparisons by oneway ANOVA and least significance difference test: $^{a}P < 0.05$, 0.6 versus 0.7 ga. $^{b}p < 0.05$, 0.6 versus 0.85ga. $^{c}p < 0.05$, 0.7 versus 0.85 ga. (Data derived from Wassink et al. [79].)

autonomic function [64]. Furthermore, reduced oxygen content physically limits oxygen extraction from the blood. The combination of these two factors, restricted CBF and reduced oxygen extraction, in turn, profoundly reduces cerebral oxygen consumption below even minimum cerebral requirements [43].

The initial bradycardia and intense peripheral vasoconstriction in the late-gestation fetus during asphyxia

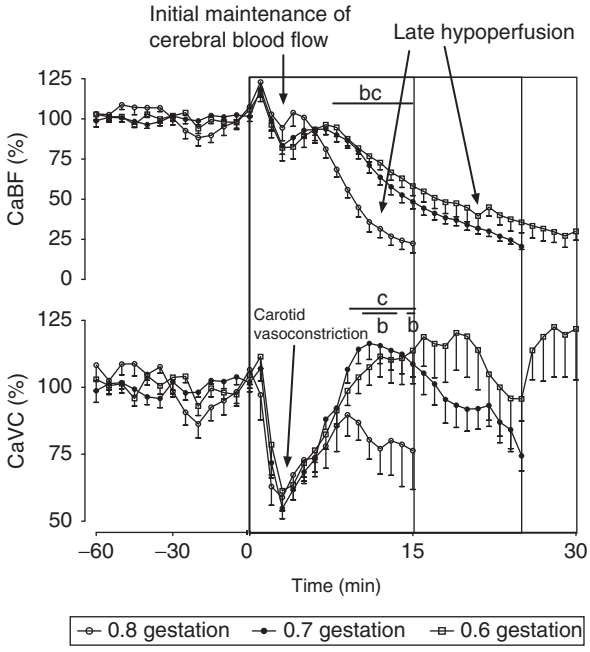


Figure 13.4 The effect of umbilical cord occlusion on carotid blood flow (CaBF, % baseline, top panel) and carotid vascular conductance (CaVC, % baseline, bottom panel) in 0.6 of gestation (0.6 ga; open squares), 0.7 of gestation (0.7 ga; closed circles), and 0.85 of gestation (0.85 ga; open circles) fetuses. CaBF and CaVC data represent 5-minute averages before occlusion and 1-minute averages during occlusion and are expressed as a percentage of baseline. Umbilical cord occlusion for each group begins at 0 minute and ends as indicated by the rectangles. Data are mean ± SEM. Between-group comparisons by one-way ANOVA and LSD test: $^{a}p < 0.05$, 0.6 versus 0.7 ga; $^{b}p < 0.05$, 0.6 versus 0.85 ga; $^{c}p < 0.05$, 0.7 versus 0.85 ga. (Data derived from Wassink et al. [116].)

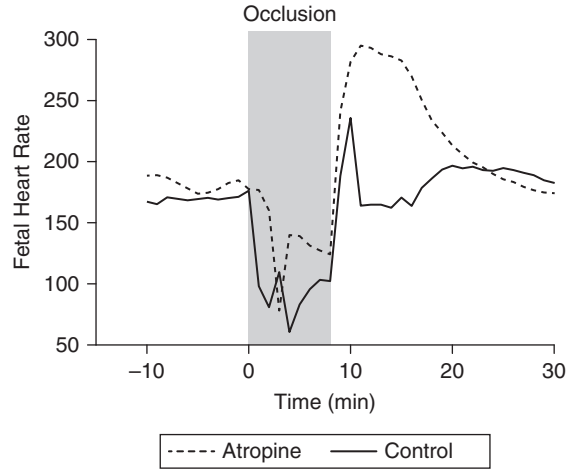


Figure 13.5 An example showing the contribution of the parasympathetic system to bradycardia during 8 minutes of severe asphyxia in near-term sheep fetuses. Pretreatment with atropine delayed the fall in heart rate until the third minute after the start of umbilical cord occlusion, in contrast with the immediate bradycardia seen in the control fetus. This abrupt, delayed fall in FHR in the atropine-treated fetus was due to transient atrioventricular (A-V) blockade. This was followed by partial recovery due to resolution of the A-V block but a progressive fall from the fourth minute onward. Thus the typical variable deceleration that lasts for approximately 1 minute is entirely chemoreflex mediated, whereas prolonged decelerations involve an increasing proportion of true hypoxic myocardial depression.

are mediated by afferent input from the carotid chemoreceptors leading to activation of the efferent parasympathetic and sympathetic systems, respectively. Selective carotid chemodenervation slows but does not prevent the initial fall in heart rate during asphyxia and has little effect on blood pressure [40]. Nevertheless, vagal blockade delays the onset of bradycardia during complete umbilical cord occlusion for several minutes [41], as shown in Figure 13.5. These data suggest that there are substantial additional afferent inputs that are not well understood at present. Speculatively, one factor might be greater recruitment of aortic chemoreceptors during severe asphyxia [43].

Fetal Adaptations to Continuing Asphyxia

The initial large increase in sympathetic neural activity is attenuated over ~2 minutes during profound asphyxia, as shown by continuous renal sympathetic nerve recordings [71]. Peripheral vasoconstriction and cardiac contractility are then maintained by release of key humoral factors, including cortisol, catecholamines, angiotensin, vasopressin, and others [72,73].

Similarly, despite parasympathetic blockade or vagotomy, fetal bradycardia will develop during sustained severe hypoxia after several minutes [41]. Bradycardia is then maintained, in contrast with moderate hypoxia, where there is a progressive later rise in FHR during the insult. These experimental data are consistent with the clinical observation by Caldeyro-Barcia et al. that late decelerations during labor are not abolished by atropine [74]. This indicates that in contrast with the initial reflex-mediated bradycardia in the first few minutes of profound asphyxia, continuing bradycardia must be related in some way to severe myocardial hypoxia [42].

Clinical Implications

These data indicate that the chemoreflexes that mediate the early FHR deceleration are highly sensitive indicators of hypoxemia but are poor indicators of fetal well-being. Decelerations due to true myocardial hypoxia do not occur unless hypoxia is continued for a pathologically long time or, we may speculate,

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unless the fetus is chronically hypoxic with low reserves of myocardial glycogen. In fetal sheep, the depth to which FHR falls is broadly related to the severity of the hypoxia [75,76]. Thus shallow decelerations indicate a modest reduction in uteroplacental flow, whereas a deep deceleration indicates near-total or total abolition of uteroplacental flow [75]. Unfortunately, once deep decelerations are established, there is relatively little further change in the shape of the deceleration despite repeated decelerations and the consequent development of hypotension [77]. Detailed analysis suggests that developing fetal acidosis during repeated brief occlusion of the umbilical cord is associated with relatively subtle changes, including an increase in FHR between occlusions, leading to a greater depth and rate of fall in FHR during each deceleration [78]. In contrast, major changes in the shape of the deceleration tend to be near-terminal events [77]. Thus all we can say from inspecting the typical variable deceleration is that the fetus has been exposed to a brief period of deep hypoxia [3].

The Decompensation Phase

The initial phase with peripheral vasoconstriction and hypertension is sustained only for the first 5–6 minutes of occlusion and is followed not by vasodilatation but rather by a progressive return of peripheral perfusion to control values [70,79]. In engineering terms, the fetal adaptations may be said to fail gracefully. In preterm fetal sheep, the initial attenuation of renal vasoconstriction is associated in time with loss of renal sympathetic activity in the first 2 minutes [71], consistent with a partial role of suppression of CNS control. However, loss of peripheral vasoconstriction continues after CNS activity is lost, so there must be additional peripheral mechanisms. This is unlikely to be due to local accumulation of metabolites because a similar biphasic pattern occurs even during a more moderate insult such as partial umbilical cord occlusion [80]. Speculatively, in part, it may reflect feedback within the peripheral organs to support local metabolic needs.

The loss of initial vasoconstriction is associated with a rapid fall in fetal blood pressure, leading to overt hypotension [79]. There is no evidence for continuing reflex mechanisms during this period of decompensation [41]. Fetal hypotension is in part a direct function of loss of peripheral vasoconstriction and of a further progressive fall in FHR that will reduce CVO and also a function of impaired contractility due to the profound acidosis itself, depletion of myocardial glycogen, and evolving injury of the cardiomyocytes [81]. Cardiac glycogen is critical for anaerobic cardiac function, and once it is depleted, there is rapid loss of high-energy metabolites such as ATP in mitochondria [65]. During a shorter episode (e.g., 5 minutes) of asphyxia, the fetus may not become hypotensive. If the insult is repeated before myocardial glycogen can be replenished, successive periods of asphyxia are associated with increasing duration of hypotension [77].

Further, myocardial injury is commonly found at postmortem after severe birth asphyxia [82]. In addition to frank myocardial necrosis, exposure to repeated brief umbilical cord occlusions in the term-equivalent fetal lamb is associated with reversible myocardial injury, increased circulating cardiac troponin-T levels, and delayed postreperfusion hypotension [81].

Slow-Onset Asphyxia

During gradually induced asphyxia, even to arterial oxygen contents of less than 1 mmol/L, fetal adaptation may be closer to that seen with hypoxia associated with acidosis, with umbilical blood flow maintained but blood flow to the fetal body reduced by 40% [35,83]. Progressive reductions of uterine perfusion over a 3- to 4-hour period in near-term fetal sheep led to a mean pH of less than 7.00, serum lactate levels greater than 14 mM, with a fetal mortality of 53%. Surviving animals remained normotensive and normoglycemic, and CBF was more than doubled. Interestingly, in surviving fetuses, neuronal damage was limited to selective loss of the very large, metabolically active cerebellar Purkinje cells [68].

Uterine Contractions and Brief, Repeated Asphyxia

Although the fetus can be exposed to a wide range of insults during labor, the key, distinctive characteristic of labor is the development of brief, intermittent, repetitive episodes of asphyxia that are almost entirely related to uterine contractions [3]. In turn, the effects of repeated asphyxia may be amplified by fetal vulnerability, for example, due to intrauterine growth retardation and/or chronic hypoxia [84], or by greater severity of contractions [85]. Even a normal fetus with normal placental function may not be able to fully adapt to hyperstimulation causing brief but severe asphyxia repeated at an excessive frequency.

Uterine contractions have such a significant impact on fetal gas exchange during labor that it is worth examining their effect in detail. FHR decelerations are not seen in most antenatal recordings. When they occur more than sporadically, they indicate that further assessment of fetal condition is urgently required [3]. However, during labor, decelerations are common, particularly in second stage. Doppler studies have shown that uterine contractions are associated with increased intrauterine pressure and a nearly linear fall in maternal uterine artery blood flow and so reduced fetal oxygenation [86]. The impact of contractions on umbilical blood flow in humans is not fully described and is likely to be more complex than changes in uterine artery blood flow. However, umbilical resistance increased significantly during contractions in human fetuses with a positive oxytocin challenge test, that is, at-risk fetuses that developed FHR decelerations [87], suggesting that uterine contractions sufficient to cause a FHR deceleration are likely to be associated with reduced umbilical as well as uterine artery blood flow.

Even during normal labor, there is intermittent reduction in placental gas exchange. This reduction is associated with a consistent fall in pH and oxygen tension and a rise in carbon dioxide and BD in normal, uncomplicated labor [88]. Typically, the second stage of normal labor will be the time of greatest asphyxic stress for the fetus and is accompanied by a more rapid decline in pH [89] and transcutaneous oxygen tension [90] and a rise in transcutaneous carbon dioxide tension [91]. Thus, in a technical sense, essentially all fetuses may be said to be exposed to "asphyxia" during labor. Fortunately, it is usually mild and well tolerated by the fetus. Unfortunately, both the lay public and many clinicians associate the term *asphyxia* with the development of severe metabolic acidosis, postasphyxial encephalopathy, and other end-organ damage or death. In our haste to avoid using the term, the normal nature of labor and its effects on the fetus are often not fully appreciated.

Most fetuses enter labor with a large reserve of placental capacity that helps to accommodate the repeated brief reductions in oxygen supply during contractions. Contraction strength, frequency, and duration are the key factors that determine the rate at which fetal asphyxia develops during labor. Critically, the proportion of time the uterus spends at resting tone compared with contracting tone will determine the extent to which fetal gas exchange can be restored between contractions [92]. Thus any intervention that increases the frequency and/or duration of uterine contractions clearly places the fetus at increased risk of compromise. For example, studies using near-infrared spectroscopy showed a progressive fall in cerebral oxygen saturation when contractions occurred more frequently than every 2.3 minutes [90]. The effects of repeated hypoxia may be amplified in vulnerable fetuses, for example, in those with preexisting placental insufficiency [84]. Conversely, even a normal fetus with normal placental function may be unable to fully adapt to tonic contractions or uterine hyperstimulation related to oxytocin infusion used for induction or augmentation or prostaglandin preparations for induction of labor [93].

Experimental Studies of Brief, Repeated Asphyxia

Brief, repeated asphyxia has been produced in the fetal sheep by repeated complete occlusion of the umbilical cord at frequencies chosen to represent different stages of labor. This allows us to examine not only FHR and blood gas changes but also the accompanying changes in blood pressure and cerebral perfusion, which are not available clinically. Studies have compared the effect of 1-minute umbilical cord occlusions repeated every 5 minutes (1:5 group), consistent with early labor, with that of 1-minute occlusions repeated every 2.5 minutes (1:2.5 group), consistent with late first- and second-stage labor [85,94–96]. Occlusions were continued for 4 hours or until the development of fetal hypotension (MAP < 20 mmHg) for two successive occlusions.

1:5 Occlusion Series (Figure 13.6A). The onset of each occlusion was accompanied by a variable FHR deceleration with rapid return to baseline levels between occlusions [78,84]. Fetal MAP rose at the onset of each occlusion and never fell below baseline levels during the occlusions. There was a sustained elevation in baseline MAP between occlusions. A small fall in pH and rise in BD and lactate occurred in the first 30 minutes of occlusions (pH = 7.34 ± 0.07, BD = 1.3 ± 3.9 mmol/L, and lactate = 4.5 ± 1.3 mmol/L). Subsequently, these values remained stable despite a further 3.5 hours of repeated occlusions. This experiment demonstrated the remarkable

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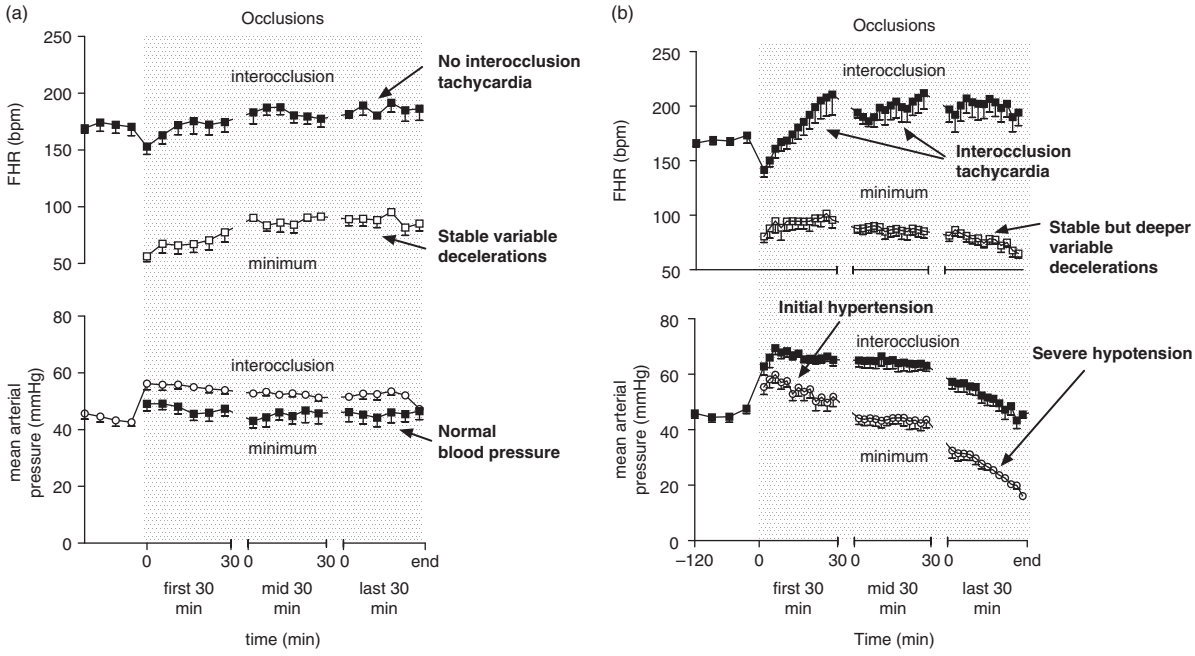


Figure 13.6 Fetal heart rate (FHR) and mean arterial pressure (MAP) changes occurring in near-term fetal sheep exposed to (A) 1 minute of umbilical cord occlusion repeated every 5 minutes for 4 hours (1:5 group) and (B) 1 minute of occlusion repeated every 2.5 minutes (1:2.5 group) until fetal MAP fell to less than 20 mmHg for two successive occlusions. The minimum FHR and MAP during each occlusion and the interocclusion FHR and MAP are shown. Because the individual experiments in the 1:2.5 group were of unequal duration, the data in both groups are presented for three time intervals: the first 30 minutes, the middle 30 minutes (defined as the median ± 15 minutes) and the final 30 minutes of occlusions. In the 1:5 group, there was no significant change in interocclusion baseline FHR and minimum MAP during occlusions, and they never fell below preocclusion levels. A small fall in pH and rise in BD and lactate occurred in the first 30 minutes of occlusions (pH = 7.34 ± 0.07, BD = 1.3 ± 3.9 mmol/L, and lactate = 4.5 ± 1.3 mmol/L), but no subsequent change occurred despite a further 3.5 hours of occlusions. In the 1:2.5 group, interocclusion FHR rose in the first and middle 30 minutes. Minimum MAP fell steadily in the first 30 minutes, stabilized in the middle 30 minutes, and fell progressively in the last 30 minutes. All animals developed a severe metabolic acidosis with a pH of 6.92 ± 0.03, a BD of 19.2 ± 1.46 mmol/L, and a lactate of 14.6 ± 0.8 mmol/L after the last occlusion. (Data derived from [96,153,154].)

capacity of the healthy fetus to fully adapt to a low frequency of repeated episodes of severe hypoxia.

1:2.5 Occlusion Series (Figure 13.6B). Although this paradigm was also associated with variable decelerations, the outcome in this group was substantially different [85]. The rapid occlusion frequency provided only a brief period of recovery between occlusions, which was insufficient to allow full recovery of fetal cellular metabolism and replenishment of glycogen stores [97]. Three distinctive phases of the fetal response to occlusions were observed in this 1:2.5 occlusion series as follows:

First 30-Minute Period. During the first three occlusions, there was a sustained rise in MAP during occlusions followed by recovery to baseline once the occlusion ended. After the third occlusion, all fetuses developed a biphasic blood pressure response to successive occlusions, with initial hypertension followed by a fall in MAP, reaching a nadir a few seconds after release of the occluder. However, minimum MAP did not fall below baseline values. Over this initial 30 minutes, pH fell from 7.40 ± 0.01 to 7.25 ± 0.02, BD rose from −2.6 ± 0.6 to 3.3 ± 1.1 mmol/L, and lactate rose from 0.9 ± 0.1 to 3.9 ± 0.6 mmol/L.

Middle 30-Minute Period. In the middle 30 minutes, minimum FHR during occlusions fell and interocclusion baseline rose compared with the first 30 minutes. Although the minimum MAP did fall over the course of this phase, it never fell below baseline levels. Despite a stable blood pressure response, without hypotension, the metabolic acidosis slowly worsened: pH fell

to 7.09 ± 0.03, BD rose to 13.6 ± 1.2 mmol/L, and lactate rose to 9.9 ± 0.7 mmol/L.

Final 30-Minute Period. Finally, in the last 30 minutes, minimum FHR during decelerations continued to fall compared with the middle 30 minutes, but there was no further rise in interocclusion (baseline) FHR. Minimum MAP fell below baseline levels and the degree of hypotension became greater with successive occlusions. All animals developed a severe metabolic acidosis, with pH = 6.92 ± 0.03, BD = 19.2 ± 1.5 mmol/L, and lactate = 14.6 ± 0.8 mmol/L by the end of occlusions. Studies were stopped after a mean of 183 ± 43 minutes (range 140–235 minutes).

The key difference in outcome between these protocols was that frequent 1-minute occlusions (every 2.5 minutes) were associated with focal neuronal damage in the parasagittal cortex, the thalamus, and the cerebellum, whereas no damage was seen after less frequent occlusions (1-minute occlusions every 5 minutes) [94]. These findings are highly consistent with clinical evidence that fetal intracerebral oxygenation is impaired during short contraction intervals (<2.3 minutes) in labor [90]. Thus a prolonged series of brief, variable decelerations can ultimately lead to severe, repeated hypotension and profound metabolic acidosis even in healthy singleton fetuses, if they are repeated sufficiently frequently.

The progressive hypotension in this paradigm is not due to impaired autonomic function. Chemical sympathectomy attenuated the initial rise in fetal blood pressure during umbilical cord occlusion and, after the onset of hypotension during occlusions, was associated with markedly more rapid fall of MAP to the nadir, with a correspondingly slower fall in femoral blood flow [73]. These data show that sympathetic nervous system (SNS) activity provides ongoing support for fetal MAP during repeated episodes of brief asphyxia. In contrast, sympathectomy did not affect the increase in interocclusion FHR, suggesting that FHR is maintained by the marked increase in circulating catecholamines [73]. Further, sympathectomy also did not affect the marked increase in FHR variability between repeated brief occlusions, suggesting that SNS activity is suppressed between occlusions and that increased variability is instead mediated by the parasympathetic nervous system [98].

Maturational Changes in Fetal Responses to Asphyxia

The preterm sheep fetus at 90 days' gestation (term is ~147 days), before the onset of cortical myelination, can tolerate extended periods of up to 20 minutes of umbilical cord occlusion without neuronal loss [99,100]. The very prolonged cardiac survival during profound asphyxia (up to 30 minutes; see Figure 13.3) [101] corresponds to the maximal levels of cardiac glycogen that are seen near midgestation in sheep and other precocial species such as humans [65]. Interestingly, while the response of preterm fetal sheep to hypoxia appears to be different from that seen at term, the overall cardiovascular and cerebrovascular response during asphyxia was very similar to that seen in more mature fetuses, with sustained bradycardia accompanied by circulatory centralization, initial hypertension, and then a progressive fall in pressure [79]. As also reported in the term fetus, there was no increase in blood flow to the brain during this initial phase, and again, this was due to a significant increase in vascular resistance rather than to hypotension (see Figure 13.4). Indeed, blood pressure is initially markedly increased as a function of peripheral vasoconstriction, and thus at this stage, the preterm fetus has not lost cerebral autoregulation.

In contrast to the term fetus, at 0.6 and 0.7 of gestation there was a very small delay in the suppression of neural activity [79,101]. Speculatively, the delay is indicative of the relative anaerobic tolerance of the preterm brain (discussed further in Chapter 5). As shown in Figures 13.3 and 13.4, as in the term fetus, once blood pressure begins to fall, blood flow to the brain falls in parallel, although the fall in blood pressure and blood flow is relatively slower in less mature fetuses [79]. The fall in blood pressure is partly a function of the loss of peripheral vasoconstriction, as seen in Figure 13.3, with a rise in femoral blood flow (FBF). Similar responses are also seen in the kidney and gut [71,102,103].

The progressive failure of CVO, with a fall in both central and peripheral perfusion, is associated with falling blood pressure. This phase is much shorter in term than in preterm fetuses because cardiac glycogen stores are much less at term [65]. Thus the majority of fetuses at 0.6 of gestation survived for up to 30 minutes [101]. In contrast, term fetuses are unable to survive such prolonged periods of sustained hypotension and typically will recover spontaneously from a

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maximum of 10–12 minutes of cord occlusion, whereas after a 15-minute period of complete umbilical artery occlusion, the majority of fetuses either died or required active resuscitation with epinephrine after release of occlusion [67,79,104]. As a consequence of this extended survival during severe asphyxia, the premature fetus is exposed to profound and prolonged hypotension and hypoperfusion. It may be speculated that during this final phase of asphyxia, there is a catastrophic failure of redistribution of blood flow within the fetal brain that places previously protected areas of the brain such as the brainstem at risk of injury [105], consistent with clinical reports [106].

After the end of asphyxia, a brief period of "overshoot" arterial hypertension and hyperperfusion occurs and is followed by delayed hypoperfusion despite normalization of blood pressure [103,107]. Although the significance of this consistent finding remains controversial, in the fetal sheep it was associated with suppression of cerebral metabolism and increased cerebral oxygen tension, suggesting that postasphyxial hypoperfusion is actively mediated and reflects suppressed cerebral metabolism [108] (also see Chapter 43). The brain is not the only organ to be affected. Experimental evidence shows that profound hypoperfusion also occurs in renal, gut, and femoral beds [103,107]. Hypoperfusion does not appear to be mediated by endothelial factors [109]. In the gut, alpha-adrenergic blockade with phentolamine prevented the fall in superior mesenteric artery blood flow [107] if the blocker was given early enough [109]. Further, the data suggest that peripheral vasoconstriction may be acting in part to support the heart during recovery [107]. This may be advantageous in the fetus, where the gut and kidney are not vital to survival. However, poor perfusion of the kidneys and gut and associated functional impairment are considered major problems in the first days of life in very preterm infants. These complications can be associated with substantial mortality and further problems such as reduced kidney growth and chronic renal problems in later childhood [110].

Acute-on-Chronic Hypoxia/Asphyxia

In addition to its potential impact on neurodevelopment (as outlined later), chronic hypoxia may also adversely affect the ability of the fetus to adapt to acute insults. Clinically, antenatal hypoxia, for example, due to growth retardation and multiple pregnancy, is associated with an increased incidence of stillbirth, metabolic acidosis during labor, and subsequent abnormal neurodevelopment [111], including CP [112]. Although this clinical experience suggests that such infants are likely to be compromised by otherwise well-tolerated labor, intriguingly, older experimental studies seem to suggest improved or greater cardiovascular adaptation to moderate induced hypoxemia. When chronically hypoxic fetal sheep were exposed to a further episode of acute hypoxia, they exhibited more pronounced centralization of circulation with enhanced femoral vasoconstriction [113]. This was associated with greater increases in plasma norepinephrine and vasopressin [114]. It is important to note, however, that these studies tested the response to mild to moderate hypoxia only rather than to labor-like or profound hypoxic insults. Thus it may be speculated that these greater reflex responses reflect reduced fetal reserve that would be exposed during a more severe insult [113].

As discussed earlier (Figure 13.6A), normoxic fetal sheep are easily able to adapt to 1-minute occlusions of the umbilical cord repeated every 5 minutes for 4 hours, with only minimal acidosis and without hypotension. In contrast, during the same insult, chronically hypoxic fetuses from multiple pregnancies developed severe, progressive metabolic acidosis (pH = 7.07 ± 0.14 versus 7.34 ± 0.07 compared with previously normoxic fetuses) and hypotension (a nadir of 24 ± 2 versus 45.5 ± 3 mm Hg after 4 hours of occlusion) [84]. The fetuses with preexisting hypoxia were smaller on average and had lower blood glucose values and higher $PaCO_2$ values. These data support the clinical concept that fetuses with chronic placental insufficiency are vulnerable even to normally well-tolerated periods of intermittent hypoxia in early labor, as shown by the development of hypotension, cephalic hypoperfusion, greater EEG suppression, interocclusion seizures, and more sustained cytotoxic brain swelling than healthy normoxic fetuses, consistent with early onset of neural injury [115,116].

Less obvious adverse intrauterine events may also modify fetal responses to hypoxia. There is considerable interest in the effects of stimuli such as maternal undernutrition and steroid exposure, particularly at critical times in pregnancy, not only on the fetal responses to challenges to its environment such as hypoxia but also on risks for adverse health outcomes in adult life [117]. For example, mild maternal undernutrition that does not alter fetal growth may still

affect development of the fetal hypothalamic-pituitary-adrenal function, with reduced pituitary and adrenal responsiveness to moderate hypoxia [118].

In adult animals, pretreatment with steroids before cerebral ischemia increases injury. In contrast, in newborn rats, treatment with glucocorticoids is reported to be neuroprotective when given between 48 and 1 hour before, but not after, an hypoxic-ischemic insult [119]. More recently, studies in preterm fetal sheep have shown that dexamethasone increased fetal asphyxial brain injury when given intramuscularly to pregnant ewes shortly after the insult [120]. Increased injury was associated with both greater hypoperfusion in the critical latent phase, leading to impaired intracerebral oxygenation that may exacerbate neural injury after asphyxia, and marked hyperglycemia [121].

In preterm infants, hyperglycemia is associated with greater risk of death and morbidity; however, it is not known whether controlling glucose improves outcomes [122]. In newborn piglets, hyperglycemia during, but not after, hypoxia-ischemia (HI) exacerbated neural injury [123]. Thus, further studies are essential to better understand whether hyperglycemia should be aggressively treated to reduce neural injury.

Does Gender Modify Fetal Responses to Asphyxia?

Numerous studies have shown that there is an increased risk of perinatal mortality and morbidity in boys compared with girls at all stages of gestation [124]. The mechanisms mediating the influence of gender on perinatal death and disability are poorly understood but are likely to be multifactorial, affecting the intrinsic responses of cells to hypoxia-ischemia and fetal physiologic adaptation. Sexual dimorphism exists in the normal developing mammalian brain, and increasingly, studies show that there are sex-related differences in the neuronal and glial responses to hypoxia-ischemia, the induction of cell death pathways, and neuroprotective treatments [125,126]. In the adult, estrogen is believed to play a key role in protecting females from injury, and there is increasing evidence that estradiol also plays a significant neuroprotective role in the developing brain [127]. In addition, there may be differential effects of other endogenous neuroprotective factors [128].

There are some data that male fetuses may be less able to physiologically adapt to hypoxia. Male fetuses have higher rates of abnormal FHR recordings, metabolic acidosis, low Apgar scores, and the need for operative intervention or resuscitation in labor [129,130]. Male fetuses are, on average, bigger, grow faster, and have a higher metabolic rate than females [131], suggesting that when oxygen is limited, they might deplete available resources more rapidly. Further, there is evidence that preterm boys have lower plasma catecholamine levels after exposure to asphyxia at birth than girls [132].

In healthy singleton preterm fetal sheep, most fetuses, regardless of sex, can survive a prolonged, near-terminal episode of acute asphyxia of a defined duration (25 minutes) induced by umbilical cord occlusion [133]. Neither the average responses nor the incidence of failure to complete the full period of umbilical cord occlusion were significantly different between male and female fetuses. However, significantly more male fetuses developed profound hypotension (<8 mmHg) before the end of the occlusion period, and intriguingly, male but not female fetuses showed a significant correlation between postmortem weight and severity of the fall in arterial blood pressure after 15 minutes of occlusion. This is consistent with the clinical observation that relatively small reductions in birth weight are associated with a significantly greater mortality and rates of perinatal complications in boys compared with girls [134,135]. Interestingly, in the study of fetal sheep, male fetuses that did not tolerate prolonged umbilical cord occlusion had significantly lower $PaCO_2$ and lactate levels near the end of occlusion than males that did tolerate the full period of occlusion [133], consistent with a previous report from near-term fetuses [70]. Thus these fetuses may have had reduced glycogen stores and thus reduced anaerobic metabolism leading to reduced CO_2 and lactate production [133].

Further, male and female fetuses that failed to tolerate prolonged occlusion showed different patterns of early and late adaptation that suggested altered chemoreflex and cardiac responses between the genders [133]. The males demonstrated slower and reduced initial peripheral vasoconstriction compared with fetuses that tolerated the full insult and then developed earlier and significantly greater hypotension associated with greater falls in heart rate and carotid and femoral artery blood flow. In contrast, females that did not tolerate the full insult showed a markedly more rapid onset of initial femoral vasoconstriction, and their subsequent falls in blood pressure and heart rate were intermediate between the

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full-occlusion fetuses and short-occlusion males. Collectively, these data suggest that for some fetuses, mainly male, previously restricted growth trajectory or nutrition may have altered both metabolic reserves and autonomic function. For example, moderate maternal undernutrition in pregnant rats that had only a transient effect on growth of the pups has been associated with increased SNS activity in female but not male rats [136]. Further, there may be sexual dimorphism in the sensitivity of cardiac cells to ischemia, as suggested by the observation that in pregnancies complicated by placental insufficiency before 34 weeks' gestation, boys show greater rise in cardiac troponin-T levels at birth [137].

Pathophysiologic Determinants of Asphyxial Injury

Recent studies using well-defined experimental paradigms of asphyxia in near-term fetal sheep have explored the relationship between the distribution of neuronal damage and the type of insult. These studies suggest that while local cerebral hypoperfusion due to hypotension is required to cause injury, a number of factors including the pattern of repetition of insults as well as fetal factors such as maturity, preexisting metabolic state, and cerebral temperature (see Figure 13.1) markedly alter the impact of the insult on the brain.

Hypotension and the "Watershed" Distribution of Neuronal Loss

The development of hypotension is highly associated with neural injury during acute asphyxia (Figure 13.7). This is readily understood because reduced perfusion will reduce the supply of glucose for anaerobic metabolism, compounding the reduction in oxygen delivery and concentration. The real-life importance of hypotension is supported by both the correlation of injury with arterial blood pressure across multiple paradigms and the common patterns of neural damage.

The close relationship between changes in carotid blood flow (CaBF) and blood pressure during asphyxia is shown in Figures 13.3, 13.4, and 13.6. In these fetuses, MAP initially rose with intense peripheral vasoconstriction. At this time, CaBF was maintained. As cord occlusion was continued, MAP eventually fell, probably as a function of impaired cardiac contractility and failure of peripheral redistribution. Once MAP fell below baseline, carotid blood flow fell in parallel, consistent with the known relatively narrow cerebral autoregulatory range in the fetus [69].

In the near-term fetus, neural injury has been commonly reported in areas such as the parasagittal cortex, the dorsal horn of the hippocampus, and the cerebellar neocortex after a range of insults including pure ischemia, prolonged single complete umbilical cord occlusion, and prolonged partial asphyxia and repeated brief cord occlusion (e.g., as illustrated in the left panel of Figure 13.8) [68,94,104,138,139]. These areas are "watershed" zones between the borders of major cerebral arteries, where perfusion pressure is least, and in both adults and children lesions in these areas are typically seen after systemic hypotension [140].

There are some data suggesting that limited or localized white or gray matter injury may occur even in the absence of significant hypotension [68,141], particularly when hypoxia is very prolonged [142]. There may have been some relative hypoperfusion in these studies, even if overall perfusion was maintained. Nevertheless, there is a strong correlation between either the depth or duration of hypotension and the amount of neuronal loss within individual studies of acute asphyxia [77,94,139,141] (see, e.g., Figure 13.7). This is also seen between similar asphyxial paradigms causing severe fetal acidosis that have been manipulated to either cause fetal hypotension [139] or not [68]. In fetal lambs exposed to prolonged severe partial asphyxia, as judged by the degree of metabolic compromise, neuronal loss occurred only in those fetuses

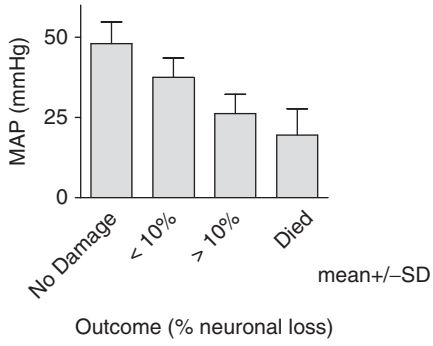


Figure 13.7 The relationship between hypotension and neuronal damage. The severity of fetal systemic hypotension during asphyxia, induced by partial common uterine artery occlusion, is closely related to the degree of neuronal loss in the near-term fetal sheep (mean arterial pressure, MAP). (Data derived from Gunn et al. [139].)

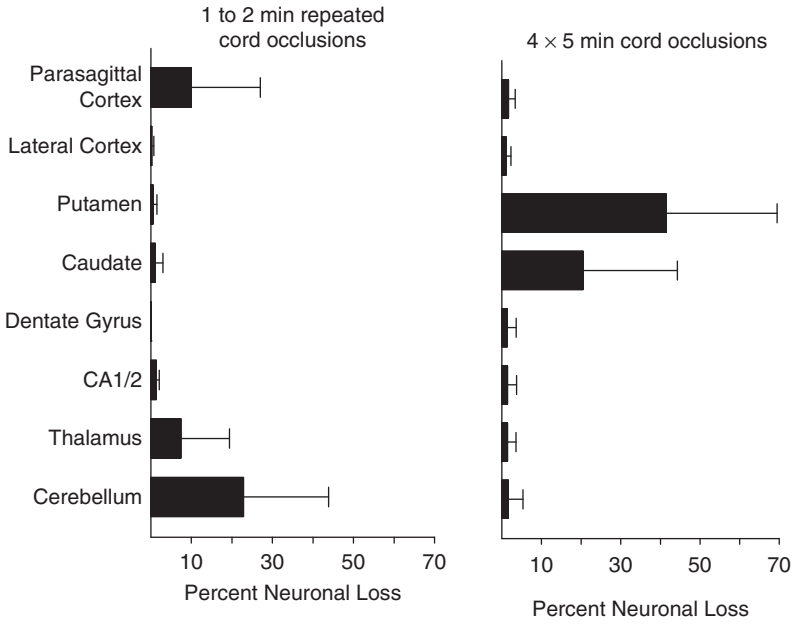


Figure 13.8 The distribution of neuronal loss assessed after 3 days of recovery from two different patterns of prenatal asphyxia in near-term fetal sheep. The left panel shows the effects of brief (1 or 2 minutes) cord occlusions repeated at frequencies consistent with established labor. Occlusions were terminated when the fetal blood pressure fell below 20 mmHg for two successive occlusions. This insult led to damage in the watershed regions of the parasagittal cortex and cerebellum [94]. The right hand panel shows the effect of 5-minute episodes of cord occlusion repeated four times at intervals of 30 minutes. This paradigm is associated with selective neuronal loss in the putamen and caudate nucleus, which are nuclei of the striatum [77]. CA 1/2 and the dentate gyrus are regions of the hippocampus. Mean ± SD.

in which one or more episodes of acute hypotension occurred [139]. In a study in which an equally "severe" insult was induced gradually but titrated to maintain normal or elevated blood pressure throughout the insult, no neuronal loss was seen except in the cerebellum [68].

The Pattern of Injury: Repeated Insults

One apparent exception to a general tendency to a "watershed" distribution after global asphyxial insults in the near-term fetus is the selective neuronal loss in striatal nuclei (putamen and caudate nucleus; see Figure 13.8, right panel) that develops when relatively prolonged periods of asphyxia or ischemia are repeated [94,143]. Whereas 30 minutes of continuous cerebral ischemia was associated with predominantly parasagittal cortical neuronal loss, with only moderate striatal injury, 3 × 10-minute periods of ischemia lead to a greater proportion of striatal injury relative to cortical neuronal loss (Figure 13.9) [143]. Intriguingly, significant striatal involvement was also seen after prolonged partial asphyxia in which distinct episodes of bradycardia and hypotension occurred [139]. Given that both parasagittal and basal ganglia predominant patterns of injury are seen on early MRI scans in term infants with encephalopathy [144], intermittent severe insults are likely to be clinically important.

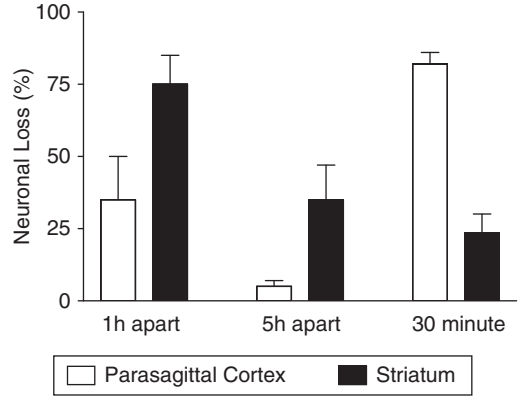


Figure 13.9 The effects of different intervals between insults on the distribution of cerebral damage after ischemia in the near-term fetal sheep. Cerebral ischemia was induced by carotid occlusion for 10 minutes repeated three times at intervals of either 1 or 5 hours compared with a single continuous episode of 30 minutes of occlusion. The divided insults were associated with a preponderance of striatal injury, whereas the single 30-minute episode of carotid occlusion was associated with severe cortical neuronal loss. Increasing the interval to 5 hours nearly completely abolished cortical injury but was still associated with significant neuronal loss in the striatum. (Data derived from Mallard et al. [155].)

The striatum is not in a watershed zone but rather within the territory of the middle cerebral artery. Thus it is likely that the pathogenesis of striatal involvement in the near-term fetus is related to the precise

timing of the relatively prolonged episodes of asphyxia and not to more severe local hypoperfusion. Speculatively, the apparent vulnerability of striatal medium-sized neurons to this type of insult may be related to a greater release of glutamate into the extracellular space after repeated insults compared with a single insult of the same cumulative duration. Consistent with this, immunohistochemical techniques have shown that inhibitory striatal neurons were primarily affected [143].

Preexisting Metabolic Status and Chronic Hypoxia

While the original studies of factors influencing the degree and distribution of brain injury, primarily by Myers [105], focused on metabolic status, the issue remains controversial. The most common metabolic disturbance to the fetus is intrauterine growth retardation (IUGR) associated with placental dysfunction. Neural maturation is markedly altered in IUGR with some aspects delayed and others advanced [145,146]. This is likely to influence the response to asphyxia but also introduces a confounding independent effect on neural development. Severe growth retardation has been associated with altered neurotransmitter expression, reduced cerebral myelination, altered synaptogenesis, and smaller brain size [147]. The effect of the timing and severity of placental restriction has been examined in a range of studies in fetal sheep [142]. Chronic mild growth retardation due to periconceptual placental restriction was associated with delayed formation of neuronal connections in the hippocampus, cerebellum, and visual cortex but did not alter neuronal migration or numbers. In near-midgestation fetuses, chronic hypoxia induced by a variety of methods was associated with a reduction in numbers of Purkinje cells in the cerebellum and delayed development of neural processes. With more severe hypoxia, the cortex and hippocampus were also affected, and there was reduced subcortical myelination [142].

Temperature and Hypoxia-Ischemia

Hypothermia during and after experimental cerebral ischemia is consistently associated with potent dose-related long-lasting neuroprotection, whereas, conversely, hyperthermia of even 1 to 2°C extends and markedly worsens neural damage [148]. The impact of cerebral cooling or warming of the brain by only a few degrees is disproportionate to the known changes in brain metabolism (approximately a 5% change in oxidative metabolism per °C), suggesting that changes in temperature modulate the downstream factors that mediate ischemic injury [14]. Mechanisms that are likely to be involved in the worsening of ischemic injury by hyperthermia include greater release of oxygen free radicals and excitatory neurotransmitters such as glutamate, enhanced toxicity of glutamate on neurons, increased dysfunction of the blood-brain barrier, and accelerated cytoskeletal proteolysis [14]. The efficacy of postasphyxial hypothermia is discussed in Chapter 43.

Pyrexia in Labor: Chorioamnionitis and Hyperthermia

These data logically lead to the concept that although mild pyrexia during labor might not necessarily be harmful in most cases, in those fetuses also exposed to an acute hypoxic-ischemic event, it would be expected to accelerate and worsen the development of encephalopathy. Case-control studies strongly suggest that maternal pyrexia is indeed associated with an approximately fourfold increase in the risk for unexplained CP or newborn encephalopathy [149].

Clearly, this association could potentially be mediated by maternal infection or by the fetal inflammatory reaction. However, maternal pyrexia was a major component of the operational definition of chorioamnionitis in all these studies, and in several studies pyrexia was either considered sufficient for diagnosis even in isolation or was the only criterion [149]. Consistent with the hypothesis that pyrexia can have a direct adverse effect, in a case-control study of 38 term infants with early-onset neonatal seizures, in whom sepsis or meningitis were excluded, and 152 controls, intrapartum fever was associated with a comparable 3.4-fold increase in the risk of unexplained neonatal seizures in a multifactorial analysis [150]. Finally, it is very interesting to note that although exposure to lipopolysaccharide (LPS) at the time of hypoxia-ischemia in adult rats worsened injury, this effect was not seen when LPS-induced hyperthermia was prevented [151]. Thus part of the adverse effects of chorioamnionitis may be mediated by hyperthermia.

Concluding Thoughts

One of the most important issues in perinatology is to identify the fetus at risk of decompensation at an early enough stage that we may intervene and

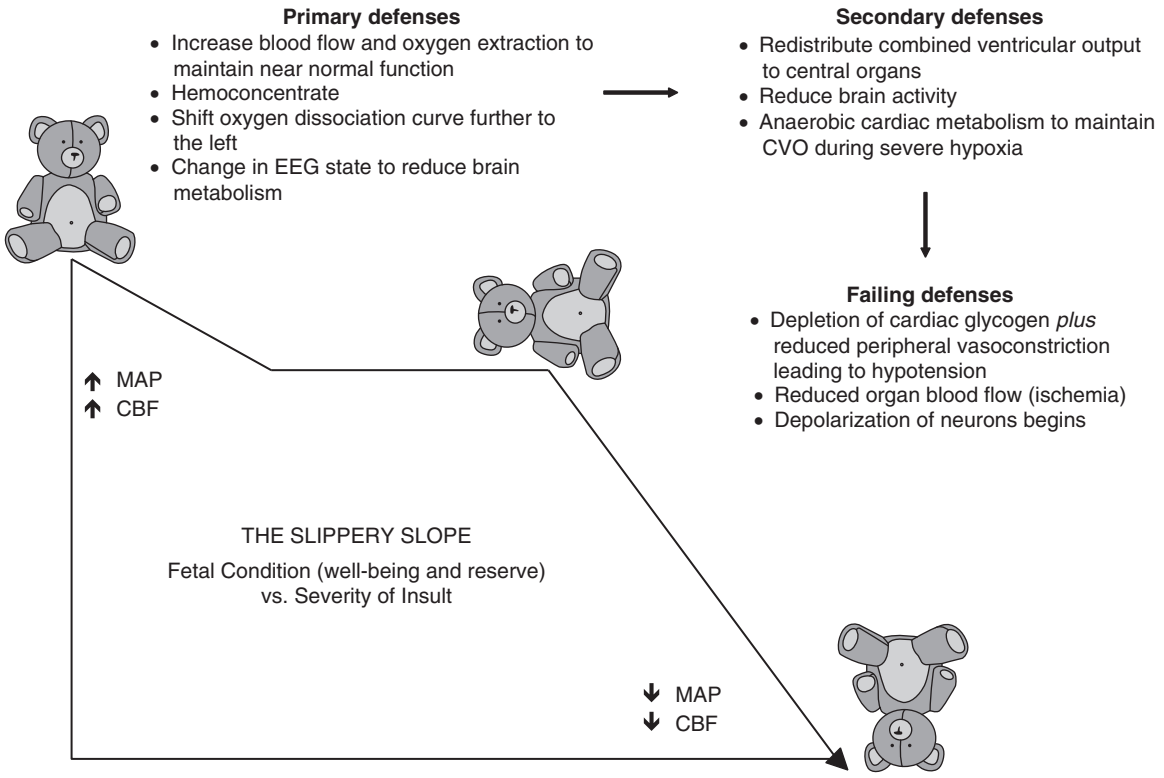


Figure 13.10 The slippery slope. A conceptual outline of fetal adaptations to episodes of asphyxia. The impact of asphyxia on the fetus depends greatly on the quality of fetal adaptation, which certainly depends partly on the severity of the insult and how long it has continued, but also where the fetus starts on the slope, that is, its preexisting reserves. With a sufficiently severe insult, for example, very frequent, more prolonged contractions, even a very healthy fetus will ultimately become profoundly acidotic and develop intermittent hypotension, but only after a prolonged period where cerebral and cardiac perfusions are maintained. In contrast, a chronically hypoxic fetus or one that has had recent exposure to hypoxia and so has depleted its cardiac glycogen may develop hypotension from very shortly after the start of the insult.

prevent actual injury or death. The ability to measure fetal pH or oxygenation at any single point in time generally provides little information about how well maintained fetal cardiac or brain function is at that point. Impaired gas exchange and mild asphyxia are a normal part of labor, and the normal fetus has a remarkable ability to respond to the consequent intervals of hypoxia/asphyxia while maintaining the function of essential organs such as the brain and the heart.

What sort of fetal problem are we trying to detect? If the fetus is being monitored in any way, there is no difficulty in detecting the prolonged bradycardia that accompanies an acute, catastrophic event of whatever cause, such as abruption or prolapse of the umbilical cord. Such events account for approximately 25% of cases of moderate to severe postasphyxial encephalopathy and are seldom predictable or even potentially preventable [6].

Thus the major clinical problem is to identify the fetuses whose adaptation to repeated asphyxia is beginning to fail. Conceptually, the fetus can be thought of as being on a "slippery slope" (Figure 13.10). The fetal condition or reserve determines the fetus' position on the slope, whereas the effectiveness of the primary defenses and the severity of the insult determine how quickly the fetus moves down the slope (decompensation). Healthy fetuses are at the very top of the slope with considerable reserves for initial adaptation before significant hypoperfusion develops, whereas others start further down, closer to the final catastrophic, failure of adaptation that leads to death or injury. When compensation begins to fail, the pattern of the insult, modified by fetal maturity, aerobic reserve, and environmental temperature, determines the severity and localization of cerebral damage. With sufficient spacing between short (1-minute) periods of profound asphyxia, a healthy fetus may be able to

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defend its central organs almost indefinitely. In contrast, and not surprisingly, a growth-retarded or previously hypoxic fetus may have very limited reserves and begin to decompensate very early and yet show a similar pattern of variable decelerations to the healthy fetus [115].

How can we identify the fetus whose adaptations are failing? The options are limited because access to the fetus is limited. Traditionally, we try to assess fetal condition by assessing changes in FHR and occasional fetal scalp pH measurements. Although FHR changes have an excellent negative predictive value, the positive predictive value of heart rate changes in isolation is very low. As we discussed earlier, the development of severe variable decelerations simply indicates transient exposure to hypoxia regardless of whether the fetus is still in the initial stage of adaptation or is beginning to decompensate. Delayed recovery from the decelerations with continued occlusions occurs only in a minority of fetuses at a time that is very close to terminal hypoxic cardiac arrest [3]. Nevertheless, more subtle features of decelerations may be useful [3].

Similarly, both the experimental studies reviewed earlier and clinical experience [152] demonstrate that there is, and can be, no close, intrinsic pathophysiologic relationship between the severity of metabolic acidosis and fetal compromise. Peripheral acidosis is primarily a consequence of peripheral vasoconstriction and reflects peripheral oxygen debt that occurs during redistribution of combined ventricular output. Thus severe acidosis may accompany both successful protection of the brain and catastrophic failure [94]. Conversely, brief but intense insults such as complete umbilical cord occlusion may cause brain injury in association with comparatively modest acidosis [19].

In contrast, there are very strong relationships, both within and between paradigms, between the development and severity of fetal hypotension and impairment of cerebral perfusion and the development of subsequent cerebral injury. The impact of hypotension is directly related to both its depth and cumulative duration in relationship to the brains' metabolic requirements given its developmental stage. Thus, ideally, we would like to measure fetal blood pressure, but this is not feasible at present. Newer methods for fetal surveillance include fetal pulse oximetry, near-infrared spectroscopy, more detailed analysis of the fetal ECG, and assessment of Doppler velocity waveforms. At present, these techniques still provide only indirect measurements of the key variables, fetal blood pressure and cerebral perfusion, and it remains unclear whether they are superior to systematic monitoring of FHR [3]. As the critical events that lead to clinically significant perinatal hypoxic-ischemic encephalopathy are clarified by innovative experimental approaches, our ability to recognize significant prenatal events and to intervene appropriately will also improve.

References

1. Stoknes M, Andersen GL, Dahlseng MO, et al. Cerebral palsy and neonatal death in term singletons born small for gestational age. *Pediatrics* 2012; **130**: e1629–35.
2. Garfinkle J, Wintermark P, Shevell MI, et al. Cerebral palsy after neonatal encephalopathy: how much is preventable? *J Pediatr* 2015; **167**: 58–63.
3. Westgate JA, Wibbens B, Bennet L, et al. The intrapartum deceleration in center stage: a physiological approach to interpretation of fetal heart rate changes in labor. *Am J Obstet Gynecol* 2007; **197**: e1–e11.236.
4. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. *N Engl J Med* 1996; **334**: 613–8.
5. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol* 1997; **177**: 1391–4.
6. Westgate JA, Gunn AJ, Gunn TR. Antecedents of neonatal encephalopathy with fetal acidaemia at term. *Br J Obstet Gynaecol* 1999; **106**: 774–82.
7. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.
8. Hellstrom-Westas L, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **72**: F34–8.
9. Roth SC, Baudin J, Cady E, et al. Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. *Dev Med Child Neurol* 1997; **39**: 718–25.
10. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 2010; **340**: c363.
11. Robertson CM, Finer NN. Long-term follow-up of term neonates with perinatal asphyxia. *Clin Perinatol* 1993; **20**: 483–500.

12. Jonsson M, Agren J, Norden-Lindeberg S, et al. Neonatal encephalopathy and the association to asphyxia in labor. *Am J Obstet Gynecol* 2014; **211**(667): e1–8.
13. Johnston MV. Excitotoxicity in perinatal brain injury. *Brain Pathol* 2005; **15**: 234–40.
14. Wassink G, Gunn ER, Drury PP, et al. The mechanisms and treatment of asphyxial encephalopathy. *Front Neurosci* 2014; **8**: 40.
15. Deng W, Yue Q, Rosenberg PA, et al. Oligodendrocyte excitotoxicity determined by local glutamate accumulation and mitochondrial function. *J Neurochem* 2006; **98**: 213–22.
16. Niquet J, Seo DW, Allen SG, Wasterlain CG. Hypoxia in presence of blockers of excitotoxicity induces a caspase-dependent neuronal necrosis. *Neuroscience* 2006; **141**: 77–86.
17. Boddy K, Dawes GS, Fisher R, et al. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. *J Physiol* 1974; **243**: 599–618.
18. Blood AB, Hunter CJ, Power GG. Adenosine mediates decreased cerebral metabolic rate and increased cerebral blood flow during acute moderate hypoxia in the near-term fetal sheep. *J Physiol* 2003; **553**: 935–45.
19. Hunter CJ, Bennet L, Power GG, et al. Key neuroprotective role for endogenous adenosine A1 receptor activation during asphyxia in the fetal sheep. *Stroke* 2003; **34**: 2240–5.
20. Li J, Takeda Y, Hirakawa M. Threshold of ischemic depolarization for neuronal injury following four-vessel occlusion in the rat cortex. *J Neurosurg Anesthesiol* 2000; **12**: 247–54.
21. Fisher DJ, Heymann MA, Rudolph AM. Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. *Am J Physiol* 1982; **242**: H657–61.
22. Turbow RM, Curran-Everett D, Hay WW Jr, Jones MD Jr. Cerebral lactate metabolism in near-term fetal sheep. *Am J Physiol* 1995; **269**: R938–42.
23. Harris DL, Weston PJ, Harding JE. Lactate, rather than ketones, may provide alternative cerebral fuel in hypoglycaemic newborns. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**: F161–4.
24. Gunn AJ, Bennet L. Fetal hypoxia insults and patterns of brain injury: insights from animal models. *Clin Perinatol* 2009; **36**: 579–93.
25. McIntosh GH, Baghurst KI, Potter BJ, Hetzel BS. Foetal brain development in the sheep. *Neuropathol Appl Neurobiol* 1979; **5**: 103–14.
26. Longo LD, Koos BJ, Power GG. Fetal myoglobin: quantitative determination and importance for oxygenation. *Am J Physiol* 1973; **224**: 1032–6.
27. Guiang SF, 3rd, Widness JA, Flanagan KB, et al. The relationship between fetal arterial oxygen saturation and heart and skeletal muscle myoglobin concentrations in the ovine fetus. *J Dev Physiol* 1993; **19**: 99–104.
28. Reuss ML, Rudolph AM, Heymann MA. Selective distribution of microspheres injected into the umbilical veins and inferior venae cavae of fetal sheep. *Am J Obstet Gynecol* 1981; **141**: 427–32.
29. Wilkening RB, Meschia G. Fetal oxygen uptake, oxygenation, and acid-base balance as a function of uterine blood flow. *Am J Physiol* 1983; **244**: H749–55.
30. Giussani DA, Spencer JA, Moore PJ, et al. Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep. *J Physiol* 1993; **461**: 431–49.
31. Peeters LL, Sheldon RE, Jones MD Jr, et al. Blood flow to fetal organs as a function of arterial oxygen content. *Am J Obstet Gynecol* 1979; **135**: 637–46.
32. Green LR, Bennet L, Hanson MA. The role of nitric oxide synthesis in cardiovascular responses to acute hypoxia in the late gestation sheep fetus. *J Physiol* 1996; **497**: 271–7.
33. Giussani DA, Spencer JAD, Hanson MA. Fetal and cardiovascular reflex responses to hypoxaemia. *Fetal Maternal Med Rev* 1994; **6**: 17–37.
34. Jensen A, Garnier Y, Berger R. Dynamics of fetal circulatory responses to hypoxia and asphyxia. *Eur J Obstet Gynecol Reprod Biol* 1999; **84**: 155–72.
35. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* 1974; **120**: 817–24.
36. Fletcher AJ, Gardner DS, Edwards CM, et al. Development of the ovine fetal cardiovascular defense to hypoxemia towards full term. *Am J Physiol Heart Circ Physiol* 2006; **291**: H3023–34.
37. Itskovitz J, Rudolph AM. Denervation of arterial chemoreceptors and baroreceptors in fetal lambs in utero. *Am J Physiol* 1982; **242**: H916–20.
38. Giussani DA, McGarrigle HH, Spencer JA, et al. Effect of carotid denervation on plasma vasopressin levels during acute hypoxia in the late-gestation sheep fetus. *J Physiol* 1994; **477**: 81–7.
39. Bartelds B, van Bel F, Teitel DF, Rudolph AM. Carotid, not aortic, chemoreceptors mediate the fetal cardiovascular response to acute hypoxemia in lambs. *Pediatr Res* 1993; **34**: 51–5.
40. Jensen A, Hanson MA. Circulatory responses to acute asphyxia in intact and chemodenervated fetal sheep near term. *Reprod Fertil Dev* 1995; **7**: 1351–9.
41. Barcroft J. *Researches in Prenatal Life*. London: Blackwell Scientific Publications, 1946.

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42. Caldeyro-Barcia R, Medez-Bauer C, Poseiro J, et al. Control of the human fetal heart rate during labour. In Cassels D, ed., *The Heart and Circulation in the Newborn and Infant*. New York: Grune & Stratton, 1966: 7–36.
43. Hanson MA. Do we now understand the control of the fetal circulation? *Eur J Obstet Gynecol Reprod Biol* 1997; **75**: 55–61.
44. Dawes GS. The central control of fetal breathing and skeletal muscle movements. *J Physiol* 1984; **346**: 1–18.
45. Gluckman PD, Johnston BM. Lesions in the upper lateral pons abolish the hypoxic depression of breathing in unanaesthetized fetal lambs in utero. *J Physiol* 1987; **382**: 373–83.
46. Koos BJ, Chau A, Matsuura M, et al. Thalamic locus mediates hypoxic inhibition of breathing in fetal sheep. *J Neurophysiol* 1998; **79**: 2383–93.
47. Natale R, Clewlow F, Dawes GS. Measurement of fetal forelimb movements in the lamb in utero. *Am J Obstet Gynecol* 1981; **140**: 545–51.
48. Richardson BS. The effect of behavioral state on fetal metabolism and blood flow circulation. *Semin Perinatol* 1992; **16**: 227–33.
49. Iwamoto HS, Rudolph AM, Mirkin BL, Keil LC. Circulatory and humoral responses of sympathectomized fetal sheep to hypoxemia. *Am J Physiol* 1983; **245**: H767–72.
50. Reuss ML, Parer JT, Harris JL, Krueger TR. Hemodynamic effects of alpha-adrenergic blockade during hypoxia in fetal sheep. *Am J Obstet Gynecol* 1982; **142**: 410–5.
51. Giussani DA, Riquelme RA, Sanhueza EM, et al. Adrenergic and vasopressinergic contributions to the cardiovascular response to acute hypoxemia in the llama fetus. *J Physiol* 1999; **515**: 233–41.
52. Green LR, McGarrigle HH, Bennet L, Hanson MA. Angiotensin II and cardiovascular chemoreflex responses to acute hypoxia in late gestation fetal sheep. *J Physiol* 1998; **507**: 857–67.
53. Jensen EC, Bennet L, Fraser M, et al. Adenosine A1 receptor mediated suppression of adrenal activity in near-term fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**: R700–6.
54. Tangalakis K, Lumbers ER, Moritz KM, et al. Effect of cortisol on blood pressure and vascular reactivity in the ovine fetus. *Exp Physiol* 1992; **77**: 709–17.
55. Comline RS, Silver IA, Silver M. Factors responsible for the stimulation of the adrenal medulla during asphyxia in the foetal lamb. *J Physiol* 1965; **178**: 211–38.
56. Cheung CY. Direct adrenal medullary catecholamine response to hypoxia in fetal sheep. *J Neurochem* 1989; **52**: 148–53.
57. Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. *Comp Biochem Physiol A Mol Integr Physiol* 1998; **119**: 717–23.
58. Danielson L, McMillen IC, Dyer JL, Morrison JL. Restriction of placental growth results in greater hypotensive response to alpha-adrenergic blockade in fetal sheep during late gestation. *J Physiol* 2005; **563**: 611–20.
59. Kitanaka T, Alonso JG, Gilbert RD, et al. Fetal responses to long-term hypoxemia in sheep. *Am J Physiol* 1989; **256**: R1348–54.
60. Gleason CA, Hamm C, Jones MD Jr. Effect of acute hypoxemia on brain blood flow and oxygen metabolism in immature fetal sheep. *Am J Physiol* 1990; **258**: H1064–9.
61. Iwamoto HS, Kaufman T, Keil LC, Rudolph AM. Responses to acute hypoxemia in fetal sheep at 0.6–0.7 gestation. *Am J Physiol* 1989; **256**: H613–20.
62. Matsuda Y, Patrick J, Carmichael L, et al. Effects of sustained hypoxemia on the sheep fetus at midgestation: endocrine, cardiovascular, and biophysical responses. *Am J Obstet Gynecol* 1992; **167**: 531–40.
63. Fletcher AJ, Gardner DS, Edwards M, et al. Development of the ovine fetal cardiovascular defense to hypoxemia towards term. *Am J Physiol Heart Circ Physiol* 2006; **291**: H3023–34.
64. Jensen A. The brain of the asphyxiated fetus–basic research. *Eur J Obstet Gynecol Reprod Biol* 1996; **65**: 19–24.
65. Shelley HJ. Glycogen reserves and their changes at birth and in anoxia. *Br Med Bull* 1961; **17**: 137–43.
66. Drury PP, Bennet L, Booth LC, et al. Maturation of the mitochondrial redox response to profound asphyxia in fetal sheep. *PLoS One* 2012; **7**: e39273.
67. Bennet L, Peebles DM, Edwards AD, et al. The cerebral hemodynamic response to asphyxia and hypoxia in the near-term fetal sheep as measured by near infrared spectroscopy. *Pediatr Res* 1998; **44**: 951–7.
68. de Haan HH, van Reempts JL, Vles JS, et al. Effects of asphyxia on the fetal lamb brain. *Am J Obstet Gynecol* 1993; **169**: 1493–501.
69. Parer JT. Effects of fetal asphyxia on brain cell structure and function: limits of tolerance. *Comp Biochem Physiol A Mol Integr Physiol* 1998; **119**: 711–6.
70. Jensen A, Hohmann M, Kunzel W. Dynamic changes in organ blood flow and oxygen consumption during acute asphyxia in fetal sheep. *J Dev Physiol* 1987; **9**: 543–59.
71. Booth LC, Malpas SC, Barrett CJ, et al. Renal sympathetic nerve activity during asphyxia in fetal

sheep. *Am J Physiol, Regul Integr Comp Physiol* 2012; **303**: R30–8.

72. Jensen A, Hohmann M, Kunzel W. Redistribution of fetal circulation during repeated asphyxia in sheep: effects on skin blood flow, transcutaneous PO_2, and plasma catecholamines. *J Dev Physiol* 1987; **9**: 41–55.
73. Galinsky R, Jensen EC, Bennet L, et al. Sustained sympathetic nervous system support of arterial blood pressure during repeated brief umbilical cord occlusions in near-term fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2014; **306**: R787–95.
74. Mendez-Bauer C, Poseiro JJ, Arellano-Hernandez G, et al. Effects of atropine of the heart rate of the human fetus during labor. *Am J Obstet Gynecol* 1963; **85**: 1033–53.
75. Itskovitz J, LaGamma EF, Rudolph AM. Heart rate and blood pressure responses to umbilical cord compression in fetal lambs with special reference to the mechanism of variable deceleration. *Am J Obstet Gynecol* 1983; **147**: 451–7.
76. Baan J Jr, Boekkooi PF, Teitel DF, Rudolph AM. Heart rate fall during acute hypoxemia: a measure of chemoreceptor response in fetal sheep. *J Dev Physiol* 1993; **19**: 105–11.
77. de Haan HH, Gunn AJ, Williams CE, et al. Magnesium sulfate therapy during asphyxia in near-term fetal lambs does not compromise the fetus but does not reduce cerebral injury. *Am J Obstet Gynecol* 1997; **176**: 18–27.
78. Bennet L, Westgate JA, Lui YC, et al. Fetal acidosis and hypotension during repeated umbilical cord occlusions are associated with enhanced chemoreflex responses in near-term fetal sheep. *J Appl Physiol* 2005; **99**: 1477–82.
79. Wassink G, Bennet L, Booth LC, et al. The ontogeny of hemodynamic responses to prolonged umbilical cord occlusion in fetal sheep. *J Appl Physiol* 2007; **103**: 1311–7.
80. Giussani DA, Unno N, Jenkins SL, et al. Dynamics of cardiovascular responses to repeated partial umbilical cord compression in late-gestation sheep fetus. *Am J Physiol* 1997; **273**: H2351–60.
81. Gunn AJ, Maxwell L, de Haan HH, et al. Delayed hypotension and subendocardial injury after repeated umbilical cord occlusion in near-term fetal lambs. *Am J Obstet Gynecol* 2000; **183**: 1564–72.
82. Costa S, Zecca E, De Rosa G, et al. Is serum troponin T a useful marker of myocardial damage in newborn infants with perinatal asphyxia? *Acta Paediatr* 2007; **96**: 181–4.
83. Parer JT. The effect of acute maternal hypoxia on fetal oxygenation and the umbilical circulation in the sheep. *Eur J Obstet Gynecol Reprod Biol* 1980; **10**: 125–36.
84. Westgate J, Wassink G, Bennet L, Gunn AJ. Spontaneous hypoxia in multiple pregnancy is associated with early fetal decompensation and greater T wave elevation during brief repeated cord occlusion in near-term fetal sheep. *Am J Obstet Gynecol* 2005; **193**: 1526–33.
85. de Haan HH, Gunn AJ, Gluckman PD. Fetal heart rate changes do not reflect cardiovascular deterioration during brief repeated umbilical cord occlusions in near-term fetal lambs. *Am J Obstet Gynecol* 1997; **176**: 8–17.
86. Janbu T, Nesheim BI. Uterine artery blood velocities during contractions in pregnancy and labour related to intrauterine pressure. *Br J Obstet Gynaecol* 1987; **94**: 1150–5.
87. Li H, Gudmundsson S, Olofsson P. Acute increase of umbilical artery vascular flow resistance in compromised fetuses provoked by uterine contractions. *Early Hum Dev* 2003; **74**: 47–56.
88. Wiberg N, Kallen K, Olofsson P. Physiological development of a mixed metabolic and respiratory umbilical cord blood acidemia with advancing gestational age. *Early Hum Dev* 2006; **82**: 583–9.
89. Modanlou H, Yeh SY, Hon EH. Fetal and neonatal acid-base balance in normal and high-risk pregnancies: during labor and the first hour of life. *Obstet Gynecol* 1974; **43**: 347–53.
90. Peebles DM, Spencer JA, Edwards AD, et al. Relation between frequency of uterine contractions and human fetal cerebral oxygen saturation studied during labour by near infrared spectroscopy. *Br J Obstet Gynaecol* 1994; **101**: 44–8.
91. Katz M, Lunenfeld E, Meizner I, et al. The effect of the duration of the second stage of labour on the acid-base state of the fetus. *Br J Obstet Gynaecol* 1987; **94**: 425–30.
92. Huch A, Huch R, Schneider H, Rooth G. Continuous transcutaneous monitoring of fetal oxygen tension during labour. *Br J Obstet Gynaecol* 1977; **84**: 1–39.
93. Winkler M, Rath W. A risk-benefit assessment of oxytocics in obstetric practice. *Drug Saf* 1999; **20**: 323–45.
94. de Haan HH, Gunn AJ, Williams CE, Gluckman PD. Brief repeated umbilical cord occlusions cause sustained cytotoxic cerebral edema and focal infarcts in near-term fetal lambs. *Pediatr Res* 1997; **41**: 96–104.
95. Westgate JA, Bennet L, de Haan HH, Gunn AJ. Fetal heart rate overshoot during repeated umbilical cord occlusion in sheep. *Obstet Gynecol* 2001; **97**: 454–9.
96. Westgate JA, Bennet L, Brabyn C, et al. ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. *Am J Obstet Gynecol* 2001; **184**: 743–51.
97. Hokegard KH, Eriksson BO, Kjellmer I, et al. Myocardial metabolism in relation to electrocardiographic changes and cardiac function

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during graded hypoxia in the fetal lamb. *Acta Physiol Scand* 1981; **113**: 1–7.

98. Lear CA, Galinsky R, Wassink G, et al. Sympathetic neural activation does not mediate heart rate variability during repeated brief umbilical cord occlusions in near-term fetal sheep. *J Physiol* 2016; **594**:1265–77.
99. Keunen H, Blanco CE, van Reempts JL, Hasaart TH. Absence of neuronal damage after umbilical cord occlusion of 10, 15, and 20 minutes in midgestation fetal sheep. *Am J Obstet Gynecol* 1997; **176**: 515–20.
100. George S, Gunn AJ, Westgate JA, et al. Fetal heart rate variability and brainstem injury after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R925–33.
101. Bennet L, Rossenrode S, Gunning MI, et al. The cardiovascular and cerebrovascular responses of the immature fetal sheep to acute umbilical cord occlusion. *J Physiol* 1999; **517**: 247–57.
102. Bennet L, Quaedackers JS, Gunn AJ, et al. The effect of asphyxia on superior mesenteric artery blood flow in the premature sheep fetus. *J Pediatr Surg* 2000; **35**: 34–40.
103. Quaedackers JS, Roelfsema V, Hunter CJ, et al. Polyuria and impaired renal blood flow after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2004; **286**: R576–83.
104. Mallard EC, Gunn AJ, Williams CE, et al. Transient umbilical cord occlusion causes hippocampal damage in the fetal sheep. *Am J Obstet Gynecol* 1992; **167**: 1423–30.
105. Myers RE. Experimental models of perinatal brain damage: relevance to human pathology. In *Intrauterine Asphyxia and the Developing Fetal Brain*. Chicago: Year Book Medical Publishers, 1977: 37–97.
106. Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. *AJNR Am J Neuroradiol* 1995; **16**: 1837–46.
107. Quaedackers JS, Roelfsema V, Heineman E, et al. The role of the sympathetic nervous system in post-asphyxial intestinal hypoperfusion in the preterm sheep fetus. *J Physiol* 2004; **557**: 1033–44.
108. Jensen EC, Bennet L, Hunter CJ, et al. Post-hypoxic hypoperfusion is associated with suppression of cerebral metabolism and increased tissue oxygenation in near-term fetal sheep. *J Physiol* 2006; **572**: 131–9.
109. Bennet L, Booth LC, Drury PP, et al. Preterm neonatal cardiovascular instability: does understanding the fetus help evaluate the newborn? *Clin Exp Pharmacol Physiol* 2012; **39**: 965–72.
110. Bennet L, Booth L, Malpas SC, et al. Acute systemic complications in the preterm fetus after asphyxia: the role of cardiovascular and blood flow responses. *Clin Exp Pharmacol Physiol* 2006; **33**: 291–9.
111. Soothill PW, Ajayi RA, Campbell S, et al. Fetal oxygenation at cordocentesis, maternal smoking and childhood neuro-development. *Eur J Obstet Gynecol Reprod Biol* 1995; **59**: 21–4.
112. Blair EM, Nelson KB. Fetal growth restriction and risk of cerebral palsy in singletons born after at least 35 weeks' gestation. *Am J Obstet Gynecol* 2015; **212**(520): e1–7.
113. Block BS, Llanos AJ, Creasy RK. Responses of the growth-retarded fetus to acute hypoxemia. *Am J Obstet Gynecol* 1984; **148**: 878–85.
114. Gardner DS, Fletcher AJ, Bloomfield MR, et al. Effects of prevailing hypoxaemia, acidaemia or hypoglycaemia upon the cardiovascular, endocrine and metabolic responses to acute hypoxaemia in the ovine fetus. *J Physiol* 2002; **540**: 351–66.
115. Wassink G, Bennet L, Davidson JO, et al. Pre-existing hypoxia is associated with greater EEG suppression and early onset of evolving seizure activity during brief repeated asphyxia in near-term fetal sheep. *PLoS One* 2013; **8**: e73895.
116. Wassink G, Galinsky R, Drury PP, et al. Does maturity affect cephalic perfusion and T/QRS ratio during prolonged umbilical cord occlusion in fetal sheep? *Obstet Gynecol Int* 2014; **2014**: 314159.
117. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 2005; **85**: 571–633.
118. Hawkins P, Steyn C, McGarrigle HH, et al. Effect of maternal nutrient restriction in early gestation on responses of the hypothalamic-pituitary-adrenal axis to acute isocapnic hypoxaemia in late gestation fetal sheep. *Exp Physiol* 2000; **85**: 85–96.
119. Bennet L, Davidson JO, Koome M, Gunn AJ. Glucocorticoids and preterm hypoxic-ischemic brain injury: the good and the bad. *J Pregnancy* 2012; **2012**: 751694.
120. Koome ME, Davidson JO, Drury PP, et al. Antenatal dexamethasone after asphyxia increases neural injury in preterm fetal sheep. *PLoS One* 2013; **8**: e77480.
121. Lear CA, Koome MM, Davidson JO, et al. The effects of dexamethasone on post-asphyxial cerebral oxygenation in the preterm fetal sheep. *J Physiol* 2014; **592**: 5493–505.
122. Heald A, Abdel-Latif ME, Kent AL. Insulin infusion for hyperglycaemia in very preterm infants appears safe with no effect on morbidity, mortality and long-term neurodevelopmental outcome. *J Matern Fetal Neonatal Med* 2012; **25**: 2415–8.
123. LeBlanc MH, Huang M, Vig V, et al. Glucose affects the severity of hypoxic-ischemic brain injury in newborn pigs. *Stroke* 1993; **24**: 1055–62.

124. Di Renzo GC, Rosati A, Sarti RD, et al. Does fetal sex affect pregnancy outcome? *Gend Med* 2007; **4**: 19–30.

125. Hurn PD, Vannucci SJ, Hagberg H. Adult or perinatal brain injury: does sex matter? *Stroke* 2005; **36**: 193–5.

126. Nijboer CH, Groenendaal F, Kavelaars A, et al. Gender-specific neuroprotection by 2-iminobiotin after hypoxia-ischemia in the neonatal rat via a nitric oxide independent pathway. *J Cereb Blood Flow Metab* 2007; **27**: 282–92.

127. McCarthy MM. Estradiol and the developing brain. *Physiol Rev* 2008; **88**: 91–134.

128. Hussein MH, Daoud GA, Kakita H, et al. The sex differences of cerebrospinal fluid levels of interleukin 8 and antioxidants in asphyxiated newborns. *Shock* 2007; **28**: 154–9.

129. Dawes NW, Dawes GS, Moulden M, Redman CWG. Fetal heart rate patterns in term labor vary with sex, gestational age, epidural analgesia, and fetal weight. *Am J Obstet Gynecol* 1999; **180**: 181–7.

130. Thorngren-Jerneck K, Herbst A. Low 5-Minute Apgar score: a population-based register study of 1 million term births. *Obstet Gynecol* 2001; **98**: 65–70.

131. Mittwoch U. The elusive action of sex-determining genes: mitochondria to the rescue? *J Theor Biol* 2004; **228**: 359–65.

132. Greenough A, Lagercrantz H, Pool J, Dahlin I. Plasma catecholamine levels in preterm infants: effect of birth asphyxia and Apgar score. *Acta Paediatr Scand* 1987; **76**: 54–9.

133. Bennet L, Booth LC, Ahmed-Nasef N, et al. Male disadvantage? Fetal sex and cardiovascular responses to asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2007; **293**: R1280–6.

134. Joseph KS, Wilkins R, Dodds L, et al. Customized birth weight for gestational age standards: perinatal mortality patterns are consistent with separate standards for males and females but not for blacks and whites. *BMC Pregnancy Childbirth* 2005; **5**: 3.

135. Simchen MJ, Weisz B, Zilberberg E, et al. Male disadvantage for neonatal complications of term infants, especially in small-for-gestational age neonates. *J Matern Fetal Neona* 2014; **27**: 839–43.

136. Jansson T, Lambert GW. Effect of intrauterine growth restriction on blood pressure, glucose tolerance and sympathetic nervous system activity in the rat at 3–4 months of age. *J Hypertens* 1999; **17**: 1239–48.

137. Nomura RM, Ortigosa C, Fiorelli LR, et al. Gender-specific differences in fetal cardiac troponin T in pregnancies complicated by placental insufficiency. *Gender Med* 2011; **8**: 202–8.

138. Gunn AJ, Gunn TR, de Haan HH, et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997; **99**: 248–56.

139. Gunn AJ, Parer JT, Mallard EC, et al. Cerebral histologic and electrocorticographic changes after asphyxia in fetal sheep. *Pediatr Res* 1992; **31**: 486–91.

140. Torvik A. The pathogenesis of watershed infarcts in the brain. *Stroke* 1984; **15**: 221–3.

141. Ikeda T, Murata Y, Quilligan EJ, et al. Physiologic and histologic changes in near-term fetal lambs exposed to asphyxia by partial umbilical cord occlusion. *Am J Obstet Gynecol* 1998; **178**: 24–32.

142. Rees S, Mallard C, Breen S, et al. Fetal brain injury following prolonged hypoxemia and placental insufficiency: a review. *Comp Biochem Physiol A Mol IntegrPhysiol* 1998; **119**: 653–60.

143. Mallard EC, Williams CE, Johnston BM, et al. Repeated episodes of umbilical cord occlusion in fetal sheep lead to preferential damage to the striatum and sensitize the heart to further insults. *Pediatr Res* 1995; **37**: 707–13.

144. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005; **146**: 453–60.

145. Cook CJ, Gluckman PD, Williams C, Bennet L. Precocial neural function in the growth-retarded fetal lamb. *Pediatr Res* 1988; **24**: 600–4.

146. Stanley OH, Fleming PJ, Morgan MH. Abnormal development of visual function following intrauterine growth retardation. *Early Hum Dev* 1989; **19**: 87–101.

147. Kramer MS, Olivier M, McLean FH, et al. Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. *Pediatrics* 1990; **86**: 707–13.

148. Gunn AJ, Gunn TR. The "pharmacology" of neuronal rescue with cerebral hypothermia. *Early Hum Dev* 1998; **53**: 19–35.

149. Gunn AJ, Bennet L. Is temperature important in delivery room resuscitation? *Semin Neonatol* 2001; **6**: 241–9.

150. Lieberman E, Eichenwald E, Mathur G, et al. Intrapartum fever and unexplained seizures in term infants. *Pediatrics* 2000; **106**: 983–8.

151. Thornhill J, Asselin J. Increased neural damage to global hemispheric hypoxic ischemia (GHHI) in febrile but not nonfebrile lipopolysaccharide *Escherichia coli* injected rats. *Can J Physiol Pharmacol* 1998; **76**: 1008–16.

152. Low JA. Intrapartum fetal asphyxia: definition, diagnosis, and classification. *Am J Obstet Gynecol* 1997; **176**: 957–9.

153. Westgate JA, Gunn AJ, Bennet L, et al. Do fetal electrocardiogram PR-RR changes reflect progressive asphyxia after repeated umbilical cord occlusion in fetal sheep? *Pediatr Res* 1998; **44**: 297–303.

154. Westgate JA, Bennet L, Gunn AJ. Fetal heart rate variability changes during brief repeated umbilical cord occlusion in near term fetal sheep. *Br J Obstet Gynaecol* 1999; **106**: 664–71.

155. Mallard EC, Williams CE, Gunn AJ, et al. Frequent episodes of brief ischemia sensitize the fetal sheep brain to neuronal loss and induce striatal injury. *Pediatr Res* 1993; **33**: 61–5.

Chapter 14

Antepartum Evaluation of Fetal Well-Being

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Introduction

In the United States, approximately 50% of all perinatal death occurs prior to birth [1]. While fetal death from acute events such as cord accidents cannot be predicted, identifying, testing, and intervening for the fetus at risk for chronic in utero compromise may prevent neonatal and infant morbidity. This chapter discusses the antenatal assessment of fetal well-being.

An antepartum fetal test should reduce perinatal morbidity and mortality and reassure parents and the healthcare team. The test of choice depends on gestational age. When a fetus at risk for acidosis and asphyxia has reached viability, one of several tests may be employed for screening, including the nonstress test (NST), the contraction stress test (CST), fetal movement monitoring, the biophysical profile (BPP), the modified biophysical profile (mBPP), and Doppler ultrasound. The sensitivity of these tests is generally high, while the specificity is highly variable.

These tests are commonly used in obstetric practice with the goal of reducing perinatal mortality. The assumption behind this strategy is that in a select group of at-risk pregnancies, an abnormal antenatal test or series of abnormal tests will predict fetal death with a certain false-negative and false-positive rate. Indeed, the predictive value of each test with regard to fetal death has been well documented, as detailed in Table 14.1. However, it is worth noting that to date, studies have failed to confirm that the use of any particular antenatal testing strategy, aside from Doppler ultrasound in the setting of fetal growth restriction, results in a decrease in perinatal mortality. This may be ascribed to numerous factors, including difficulty of choosing the correct at-risk pregnancies for testing and the timing of perceptible abnormal test results in relation to hypoxic injury.

The purpose of this chapter is to discuss common antepartum screening tests, including a description of each test, its indication, and its accuracy in predicting fetal death.

Perinatal Mortality

Since 1965, the perinatal mortality rate (PMR) in the United States has fallen steadily, and the pattern of perinatal death has changed considerably. Though the relationship between our understanding of fetal well-being and perinatal outcomes remains complex, it is worthwhile to consider how improved techniques of antepartum fetal evaluation may contribute to a decrease in PMR.

The PMR is defined in several ways. According to the National Center for Health Statistics (NCHS), the PMR is the number of late fetal deaths (28 weeks' gestation or more) plus early neonatal deaths per 1,000 live births [2]. The World Health Organization (WHO) defines the PMR as the number of deaths of fetuses and live births weighing at least 500 g per 1,000 live births. If the weight is unavailable, a fetus is counted if the gestational age is 22 weeks or greater or if the crown-to-heel length is 25 cm or more in a newborn that dies before day 7 of life per 1,000 live births. The American College of Obstetricians and Gynecologists (ACOG) has recommended including in PMR statistics only fetuses and neonates weighing

Table 14.1 Predictive Value of Antenatal Tests

Test	False-negative rate (%)	False-positive rate (%)
Contraction stress test (CST)	0.04	35–65
Nonstress test (NST)	0.2–0.8	55–90
Biophysical profile (BPP)	0.07–0.08	40–50
Modified biophysical profile (mBPP)	0.08	60

Source: Modified from Signore et al. [94].

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500 g or more [3]. For international comparisons, ACOG recommends counting fetuses and neonates weighing 1,000 g or more at delivery. Fetal death refers to the intrauterine death of a fetus prior to delivery regardless of the duration of pregnancy, where the pregnancy was not electively terminated or induced [4]. Fetal death prior to 20 completed weeks of gestation is referred to as *early fetal death*, between 20 and 27 weeks is referred to as *intermediate*, and beyond 28 weeks is referred to as *late*. The *fetal mortality rate* (FMR) generally refers to fetal deaths of 20 weeks or beyond per 1,000 live births [1].

Using the NCHS definition, the PMR has consistently declined in the United States over the past few decades. The PMR was 8.7 in 1991, 7.3 in 1997, 6.7 in 2004, and 6.24 in 2013 [1,2]. The rate of decline has slowed over time, dropping by less than 1% annually in recent years. Through the beginning of this century, drops in both infant and fetal mortality had contributed to the decline in PMR, FMR having fallen an average of 1.4% per year from 1990 to 2004. However, while infant mortality has continued to drop, FMR has plateaued in more recent years, with no appreciable decline between 2006 and 2013 [1,2]. In 2013 the FMR was 5.96, essentially unchanged from the rate in 2006. Early fetal mortality dropped slightly, whereas late fetal mortality was stable over this time period.

The PMR and FMR have declined over time among members of all races, though significant differences remain. The PMR for non-Hispanic blacks has been more than double that of non-Hispanic whites. In 1991 it was 15.7 versus 7.4, and in 2013 it was 10.5 versus 4.9 [1,2]. The increased PMR among blacks includes higher rates of both fetal and neonatal deaths. The reasons for the disparity in outcomes between these groups are not well understood, but differences in preterm delivery, income, access to care, stress and racism, cultural factors, and maternal preconception health have all been cited.

The infant mortality rate (infant death prior to 1 year of age/1,000) was the lowest ever in 2013, at 5.96 infant deaths per 1,000 live births [4]. This represents a 13% decline from 6.86 in 2005. Infant mortality during the past 20 years can be attributed most frequently to birth defects. In 1995, malformations were responsible for 22% of all infant deaths, one-third of which were caused by cardiac anomalies; chromosomal, respiratory, and nervous system defects were responsible for approximately 15% each [5]. In 2007, 20% of infant deaths were attributed to congenital malformations and chromosomal anomalies, followed by low birth weight and short gestation (17%), sudden infant death syndrome (SIDS, 8%), maternal complications of pregnancy (6%), and unintentional injuries (4%) [6].

The decline in the FMR may be attributed to improved methods of antepartum fetal surveillance, the prevention of Rh sensitization, improved ultrasound detection of intrauterine growth restriction (IUGR) and fetal anomalies, and improved care of maternal diabetes mellitus and preeclampsia. In Canada, Fretts et al. analyzed the cause of fetal death among 94,346 total deliveries weighing at least 500 g at the Royal Victoria Hospital in Montreal from 1961 to 1993 [7,8]. Overall, the fetal death rate declined by 70%, from 11.5/1,000 in the 1960s to 3.2/1,000 in 1990–3. Significant declines were seen in fetal deaths due to antepartum asphyxia (13.1–1.2/1,000), Rh disease (4.3–0.7/1,000), lethal anomalies (10.8–5.4/1,000), and intrauterine growth restriction (17.9–7.0/1,000). Fetal death due to anomalies declined primarily because of improved ultrasonographic detection and early pregnancy termination.

The pattern of perinatal death in the United States has also changed. According to data collected between 1959 and 1966 by the Collaborative Perinatal Project, 30% of perinatal deaths were attributed to complications of the cord and placenta [9]. Other major causes of perinatal death were unknown (21%), maternal and fetal infection (17%), prematurity (10%), congenital anomalies (8%), and erythroblastosis fetalis (4%). Lammer et al. reviewed the causes of 574 fetal deaths in Massachusetts in 1982 [10]. Overall, 30% of fetal deaths were attributed to maternal disease such as hypertension and diabetes, 28% to hypoxia, 12% to congenital anomalies, and 4% to infection. Ten percent of fetal deaths occurred in multiple gestations, giving a fetal mortality rate of 50/1,000, seven times the rate among singleton pregnancies. Fetal deaths were higher among women who were older than age 34, younger than age 20, unmarried, black, of parity of five or greater, and in those who received no prenatal care or care in the third trimester only. More recent population-based analyses of the causes of fetal deaths have confirmed these findings. In particular, a 2011 evaluation by the Stillbirth Collaborative Research Network used rigorous methods to classify more "unexplained" fetal deaths than in previous studies [1,6,11].

Most fetal deaths occur before 32 weeks' gestation. However, as pregnancy progresses, the risk of fetal death increases among high-risk patients. To plan a strategy for antepartum fetal testing, one must examine the risk of fetal death in a population of women still pregnant at that point in pregnancy [12,13]. When this approach is taken, one finds that fetuses at 40–41 weeks are at a threefold greater risk of intrauterine death than are fetuses at 28–31 weeks, and fetuses at 42 weeks or more are at a 12-fold greater risk [13].

To summarize the data on PMR, there has been a decline in rates of both fetal death and infant death in the United States over time, with persistent racial disparity in these rates and a shift in the conditions contributing to perinatal mortality. It is clear that many neonatal deaths have antenatal and perinatal antecedents. Therefore, it is useful to remember that even if a fetal death is averted due to antenatal interventions, a neonatal death may still occur due to events that preceded birth. In order to examine the impact that any of these antenatal interventions may have on PMR, we must examine the characteristics of tests of fetal well-being.

Sensitivity, Specificity, Positive and Negative Predictive Value

Any test of fetal well-being ideally should meet several criteria:

1. The test reliably predicts the fetus at risk for hypoxia.
2. The test reduces the risk of fetal death.
3. A false-positive test does not materially increase the risk of poor outcome to the patient or the fetus.
4. If an abnormality is detected, treatment options are available.
5. The test provides information not already apparent from the patient's clinical status.
6. The information is helpful to patient management.

Screening tests are applied broadly to healthy patients. The small screen-positive group subsequently undergoes costlier, potentially more invasive confirmatory testing. In obstetrics, the positive predictive value (PPV) of most tests is limited by a low prevalence of conditions that lead to intrauterine fetal death and by the variability of the normal fetal neurologic state.

When fetal tests are applied widely to populations with low disease prevalence, the tests' PPV is generally low. Because a missed diagnosis of fetal hypoxia may result in lifelong neurologic problems, most obstetricians accept tests of low PPV in clinical practice. While tests of high PPV are ideal, the low prevalence of the most worrisome obstetric conditions, coupled with the need to identify all fetuses at risk, has created acceptance of tests that have a high false-positive rate and a low PPV. When interpreting the results of studies of antepartum testing, the obstetrician must consider the application of that test to his or her own population. If the population is at greater risk of poor fetal outcomes, the likelihood is greater that an abnormal test will be associated with an abnormal fetus. If the population is generally low risk, an abnormal test will more likely be associated with a false-positive diagnosis.

Given the frequency of false-positive tests in obstetrics, to act on a single test could result in iatrogenic prematurity. In this setting, multiple tests may be helpful. Multiple normal tests tend to exclude disease, whereas additional abnormal tests support the diagnosis of disease and may merit intervention.

The Fetal Neurologic State

During the third trimester, the normal fetal neurologic state varies markedly [14,15], and this limits the sensitivity of fetal testing. The fetus may spend up to 25% of its time in quiet sleep, a condition during which fetal testing may appear nonreassuring. During quiet, non–rapid eye movement (REM) sleep, the fetal heart rate slows, and heart rate variability is reduced. Breathing and startle movements may be infrequent. Electrocortical activity recordings reveal high-voltage, low-frequency waves. Near term, periods of quiet sleep may last 20 minutes and those of active sleep approximately 40 minutes [15]. The mechanisms that control these periods of rest and activity in the fetus are not well established. Active sleep, in which the fetus spends approximately 60–70% of its time, is associated with REM. The fetus exhibits regular breathing movements; intermittent abrupt movements of its head, limbs, and trunk; increased variability of its heart rate; and frequent accelerations with movement, all of which are reassuring, as discussed below.

Biophysical Techniques of Fetal Evaluation

During the 1970s and early 1980s, biochemical tests such as human placental lactogen and estriol determinations were considered the optimal methods of fetal evaluation. These tests have since fallen out of favor,

replaced by more sensitive and less cumbersome biophysical surveillance techniques. The most commonly used tests are the CST, the NST, maternal perception of fetal movement, the BPP, and the mBPP.

Antenatal tests are limited in their scope. They can often identify chronic events such as progressive metabolic acidosis, though the point at which a fetus experiences long- or short-term negative sequelae from mild acidemia is unknown. Antenatal tests may not predict acute events such as umbilical cord accidents or placental abruption. The tests may be influenced by prematurity, maternal medication exposure, fetal sleep–wake cycle, and fetal anomalies.

Contraction Stress Test

The first widely adopted test of fetal well-being was the CST, also called the *oxytocin challenge test*. The CST mimics the first stage of labor with uterine contractions and thus indirectly assesses fetal-placental reserve. Uterine contractions reduce blood to the intervillous space, causing transient fetal hypoxia. The fetus at risk for uteroplacental insufficiency will demonstrate an abnormal response to contractions, forming the basis for this test. If fetal and placental reserve is poor, the fetus will often develop evidence of hypoxia that is not physiologic and may manifest late decelerations. A well-oxygenated fetus with good reserve should tolerate contractions without evidence of pathologic hypoxia. The CST is performed during the antepartum period.

The CST should take place in the labor and delivery suite or in an adjacent area with easy access to labor and delivery. The patient is placed in the semi-Fowler's position at a 30- to 45-degree angle, with a slight left tilt in order to avoid supine hypotension. Baseline fetal heart rate and uterine tone are simultaneously recorded for at least 10 minutes. Following this, the fetal heart rate is observed during three contractions of at least 40 seconds' duration within 10 minutes. If there are no spontaneous uterine contractions, oxytocin is administered by an infusion pump at a rate of 0.5 mIU/min. The infusion rate is doubled every 20 minutes until adequate contractions have been achieved [16]. Nipple stimulation may be used to initiate or augment contractions and may reduce testing time by half when used with oxytocin [17]. In one technique, the patient is instructed to rub one nipple through her clothing for 2 minutes or until a contraction appears. If a contraction does not appear, she should stop for 5 minutes and then repeat the process.

Although the CST has never been shown to cause premature labor [18], it is contraindicated when preterm labor is a significant risk, such as in the setting of premature rupture of the membranes, cervical insufficiency, or multiple gestation. The CST should also be avoided when labor is contraindicated, such as among patients with a prior classic cesarean delivery, placenta previa, or extensive uterine surgery.

How to Interpret the Test

The CST is interpreted as follows [19]:

- *Negative (normal):* No late or significant variable decelerations.
- *Positive:* Late decelerations following 50% or more contractions (regardless of contraction frequency).
- *Unsatisfactory:* Fewer than three contractions in 10 minutes or a tracing that cannot be interpreted
- *Equivocal suspicious:* Intermittent late decelerations or suspicious variable decelerations.
- *Equivocal hyperstimulatory:* Fetal heart rate decelerations in the presence of contractions lasting more than 90 seconds or more frequent than every 2 minutes

A negative (normal) CST is associated with good fetal outcome, permitting the obstetrician to prolong a high-risk pregnancy safely. The incidence of perinatal death within 1 week of a negative test is less than 1/1,000 [20,21]. A suspicious or equivocal CST should be repeated within 24 hours. A positive CST merits further evaluation and possibly delivery because it may indicate uteroplacental insufficiency. Variable decelerations seen during the CST suggest cord compression, often associated with oligohydramnios. In such cases, ultrasonography should be performed to assess amniotic fluid volume. Low amniotic fluid may reflect chronic stress as fetal blood is shunted preferentially to the brain and away from the kidneys. A positive CST has been associated with an increased incidence of intrauterine death, late decelerations in labor, low 5-minute Apgar scores, IUGR, and meconium-stained amniotic fluid [21]. A CST obtained between 28 and 33 weeks' gestation appears as accurate as a test performed at a greater gestational age.

The CST is limited by a high false-positive rate. Supine hypotension decreases uterine perfusion and may cause transient fetal heart rate abnormalities, heart rate tracings may be misinterpreted, oxytocin or nipple stimulation may cause uterine hyperstimulation, or the fetal condition may improve after the CST has been performed.

In addition to high-risk pregnancies, the CST has also been used to assess low-risk post-term pregnancies. There were no perinatal deaths among 679 prolonged pregnancies evaluated primarily with the CST [22]. When both the NST and the nipple-stimulation CST were used to determine the need for delivery, there were no antepartum deaths in a series of 819 patients tested at 40 weeks or more [23].

Druzin et al. found the CST to be most beneficial as a test to follow up a nonreactive NST [23]. In other situations, the CST did not significantly improve antepartum or intrapartum outcome. Merrill et al. evaluated all nonreactive NSTs with a CST and found that if the CST was negative and a biophysical profile (to be discussed later) was 6 or greater, the pregnancy could be prolonged for up to 13 days [24]. This approach should be used only when prematurity is an issue and when careful follow-up with daily assessment can be performed reliably.

In practice, the CST is used less frequently than other biophysical techniques described below due to the high false-positive rate and cumbersome, resource-intensive nature of performing the test.

The Nonstress Test

Fetal heart rate monitoring, or cardiotocography, was developed during the 1960s as a means of evaluating the fetus in labor. The concept of fetal monitoring was eventually extrapolated to the developing fetus with the NST, CST, and BPP. The antenatal use of the NST in the assessment of fetal well-being has become an integral part of obstetric care [16].

The NST is based on the observation that fetal heart rate accelerations reflect fetal well-being [25]. A *reactive* test is defined as the occurrence of two accelerations of 15 beats/minute above the fetal heart rate baseline lasting at least 15 seconds during any 20-minute period. A *nonreactive* test is one that does not meet the aforementioned criteria. A reactive NST suggests the absence of fetal hypoxia or asphyxia. The incidence of stillbirth within 1 week of a normal test, corrected for lethal congenital anomalies and unpredictable causes of in utero demise such as cord accidents or placental abruption, is approximately 1.9/1,000 [21].

The Basis for the NST

The premise behind the NST is that the well-oxygenated nonacidotic, nonimpaired fetus will temporarily accelerate its heart rate in response to movement. Regulation of the fetal heart rate and variability is complex and not entirely understood. The vagal nerve and the sympathetic nervous system modulate the fetal heart rate. As in the adult, the fetal heart has intrinsic pacemakers, including the sinoatrial (SA) and atrioventricular (AV) nodes. Both nodes are normally under continuous influence of the vagus nerve, which prevents the fetal heart from beating at its more rapid intrinsic rate. The interplay between the sympathetic and parasympathetic nervous systems results in beat-to-beat variability of the fetal heart rate, an important clinical predictor of fetal well-being.

In sheep, vagal influence increases fourfold during acute hypoxia [26], while the influence of the sympathetic nervous system increases to a lesser degree. In sum, vagal influence over the fetal heart dominates sympathetic influence during hypoxia. Baroreceptors located in the aortic arch and carotid sinus immediately signal the vagus or glossopharyngeal nerve, increasing vagal influence and slowing the heart rate. Fetal hypoxia results in a compensatory bradycardia with hypertension. The fetus also has functioning chemoreceptors in the medulla oblongata and carotid and aortic bodies. Interaction between the fetal chemoreceptors is poorly understood [26].

Uterine contractions reduce blood flow to the intervillous space, causing transient hypoxia. Using a sheep model, Parer demonstrated that the abrupt cessation of uterine blood flow for 20 seconds in normally oxygenated sheep resulted in a delayed deceleration in the fetal heart rate, known now as a *late deceleration* [26]. Pretreatment with atropine abolished any change in the fetal heart rate. The author concluded that chemoreceptors signal the vagus nerve to slow the heart during hypoxemic conditions, resulting in a deceleration of the heart rate following the contraction peak. Repetitive late decelerations suggest fetal hypoxemia.

When under hypoxic conditions, the fetus redistributes blood to its vital organs: the brain, heart, and adrenal glands. Blood is shunted away from the gut, spleen, and kidneys, leading to oligohydramnios. This, along with compensatory mechanisms such as

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decreased total oxygen consumption and anaerobic glycolysis, allows the fetus to survive for periods of up to 30 minutes in conditions of decreased oxygen.

Loss of reactivity is associated most commonly with a fetal sleep cycle but may result from any cause of CNS depression, the most ominous being fetal acidosis.

When to Perform the NST

Most patients deemed to be at increased risk for fetal death begin NSTs between 32 and 34 weeks and are tested weekly. The NST is generally not recommended prior to 26 weeks [19]. An NST should be performed only after viability, when intervention for a nonreassuring test is an option. The limit of viability is poorly defined. Recent survival rates of neonates born at 22 and 23 weeks have been reported at 21% and 30%, respectively [27]. However, given the significant morbidity associated with birth at these gestational ages, testing and intervention prior to 24 weeks' gestation are controversial and should be evaluated on a case-by-case basis.

How to Perform the Test

The fetal heart rate is monitored using a Doppler ultrasound transducer attached with a belt to the maternal abdomen. At the same time, a tocodynamometer is applied to the maternal abdomen to monitor for uterine contractions or fetal movement. Signals from the Doppler transducer and tocodynamometer are then relayed to tracing paper. Ideally, the patient should not have smoked cigarettes recently because this has been shown to interfere with the NST [28].

How to Interpret the Test

Using the most common definition, a normal or reactive test is seen when the fetal heart rate accelerates 15 beats/minute from baseline for 15 seconds twice during a 20-minute period [29]. A nonreactive NST is one that lacks these accelerations during 40 minutes of testing.

A reactive NST is associated with fetal survival for at least 1 week in more than 99% of patients [30]. In the largest series of NSTs, the stillbirth rate among 5,861 tests was 1.9/1,000 when corrected for lethal anomalies and unpredictable causes of demise [31]. The negative predictive value of the NST is 99.8% [21]. The low false-negative rate depends on the appropriate follow-up of significant changes in maternal status or perception of fetal movement. The false-positive rate of the nonreactive NST is quite high. A nonreactive NST must be evaluated further unless the fetus is extremely premature.

The fetal ability to generate a reactive heart rate tracing depends on gestational age because it likely reflects the maturation of the parasympathetic and sympathetic nervous systems. Druzin et al. demonstrated that among women who delivered infants with normal Apgar scores, 73% had nonreactive NSTs between 20 and 24 weeks' gestation, 50% were nonreactive between 24 and 32 weeks, and 88% became reactive by 30 weeks. Between 32 and 36 weeks, 98% were reactive [32].

The high incidence of the false-positive nonreactive NSTs is primarily due to the normal quiet fetal sleep state. The near-term fetus has four neurologic states, described as 1F, 2F, 3F, and 4F. State 1F is a period of quiet sleep in which the fetus spends approximately 25% of its time. This state may last up to 70 minutes. During this time, the fetal heart rate has few accelerations and reduced variability, and the fetus demonstrates only occasional gross body movements. The fetus spends 60–70% of its time in state 2F, or active sleep. During this time, heart rate variability and accelerations are increased, as are body and eye movements. During state 3F, eye and body movements are common, but accelerations are diminished. State 4F is characterized by continuous movement, and constant fetal heart rate accelerations and variability are seen. Whereas a nonreactive NST may reflect sleep state 1F, it alternatively might indicate fetal compromise and must be evaluated further.

Fetal bradycardia during routine antepartum testing is potentially ominous and merits further evaluation or delivery. Bradycardia, defined in some studies as a slowing of the fetal heart rate of 40 beats/minute from baseline or to 90 beats/minute or less lasting for at least 60 seconds, has been associated with stillbirth [33], significant cord compression, meconium passage, congenital abnormalities, and abnormal heart rate patterns in labor [34]. In a study of 121 cases of antepartum fetal bradycardia managed by active intervention and delivery, there were no fetal deaths [34].

Efficacy

To date, there are no prospective, double-blinded, randomized, controlled trials of the use of the NST to reduce perinatal morbidity or mortality. The NST was widely adopted without demonstration of benefit

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among well-conducted trials. Observational studies have shown a correlation between abnormal NSTs and poor fetal outcome [35].

Four randomized, controlled trials of the NST among intermediate- and high-risk patients failed to show reduction in perinatal morbidity or mortality due to asphyxia [36–39]. The study populations ranged from 300 to 550 patients and lacked sufficient power to assess low-prevalence events such as perinatal mortality. A meta-analysis of these four trials plus two additional trials comparing traditional NST with computerized NST analysis also lacked the power to demonstrate a difference [40]. The meta-analysis demonstrated a trend toward increased perinatal morbidity among the tested group, although most of the deaths in the tested group were considered unavoidable and reflect a weakness of the studies. NST did not lead to early delivery when compared with controls. The authors of the meta-analysis acknowledge that these trials are old, dating from the introduction and widespread use of NST, were not double blinded, and vary in quality. Practice styles and interpretation of the tests may have since changed.

Given the current medical-legal climate, a randomized, double-blinded, controlled trial is unlikely to be performed because use of the NST has become the standard of care. Further, given the fact that adverse outcomes such as fetal death are uncommon even among high-risk populations, any investigation would require enormous patient enrollment [41].

Several retrospective studies have suggested that the NST decreases perinatal mortality in the tested high-risk population. Schneider et al. reviewed their experience with antenatal testing from 1974 to 1983, before antenatal testing was widespread [42]. The authors used the contraction stress test for the first 2 years of the study period and the NST for the remaining 7 years. They found that perinatal mortality was 2.24% in the nontested population and 0.12% in the high-risk tested population. Studies such as these fueled the widespread adoption of the NST as a means of fetal assessment.

Vibroacoustic Stimulation

To determine whether a nonreactive NST is due to the quiet fetal sleep state or to fetal compromise, vibroacoustic stimulation (VAS) is performed. VAS entails the application of a vibratory stimulus to the patient's abdomen above the fetal vertex for at least 3 seconds, creating a startle response in the noncompromised fetus. VAS results in fetal heart accelerations [43], reducing testing time and the incidence of nonreactive tests [44]. VAS increases the NST's positive predictive value without adversely affecting perinatal outcome [45–47].

VAS reduces the incidence of "false" nonreactive NSTs without changing the predictive reliability of the test [43]. Smith et al. found that the incidence of fetal death within 7 days of a VAS-induced reactive NST was similar to that of a spontaneously reactive NST (1.9 versus 1.6/1,000 fetuses). There were no significant differences in Apgar scores, operative intervention, or meconium staining between groups.

The fetal response to VAS relies on an intact and mature auditory system. Anencephalic fetuses do not manifest heart rate accelerations in response to VAS [48]. The blink-startle response to VAS does not occur prior to 24 weeks and is seen consistently only after 28–31 weeks [49,50]. The incidence of reactivity after VAS increases significantly after 26 weeks [51].

The intensity and duration of the stimulus are important. A stimulus lasting for 3–5 seconds significantly increases fetal heart rate accelerations, while no difference is seen with a 1-second VAS [52].

If VAS fails to achieve a reactive NST, a BPP should be performed, as described later in this chapter. Though it is deemed safe, a case of supraventricular tachycardia was reported following VAS in a fetus with premature atrial contractions [53]. After 4 minutes, the tachyarrhythmia reverted to baseline. The authors cautioned against the use of VAS among fetuses with arrhythmias.

In lieu of VAS, manual fetal manipulation, the manual stimulation test (MST), is used in some parts of the world to reduce the incidence of a nonreactive fetal tracing. Previous trials did not show a benefit to the MST [54]. However, one recent study compared the MST with an NST alone and found that the time to reactivity was shorter and the incidence of reactivity was greater [55].

Maternal Perception of Fetal Movement

Maternal perception of fetal movement, or fetal *kick counts*, is an inexpensive, easily implemented, reliable test of fetal well-being and is often recommended for routine antepartum fetal surveillance in a low-risk population.

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The normal fetus is active. Studies using real-time ultrasound show that during the third trimester the fetus generates gross body movements 10% of the time, making 30 such movements each hour [56]. Most women can perceive 70–80% of gross body movements. The fetus also makes fine body movements, more difficult to perceive, such as limb flexion and extension, sucking, and hand grasping. Fine body movements probably reflect more coordinated CNS function. Decreased maternal perception of fetal movement often precedes fetal death, sometimes by several days [57]. Cessation of fetal movement has been correlated with a mean umbilical venous pH of 7.16 [58]. Several studies have shown that maternal awareness of changes in fetal activity can prevent unexplained fetal death.

There are several protocols for monitoring fetal movement that have been used in clinical and research settings. None have been proven to be superior, nor have any consistent results from randomized trials demonstrated that any program of fetal movement counting (FMC) is associated with a reduced risk of perinatal mortality. A 2007 Cochrane review of trials involving over 71,000 women randomized to FMC failed to find evidence of benefit. Nevertheless, given the ease of use and perceived low risk of implementation, it is the most commonly prescribed method of assessment of fetal well-being.

The optimal number of fetal movements has not been established. Methods studied include the Cardiff Count-to-Ten method, in which a woman starts counting fetal movements in the morning and records the time needed to reach ten movements, or counting number of movements per hour with a certain threshold indicating a negative test result. In one of the earlier randomized trials to show the promise of decreased fetal deaths with a program of FMC, Neldam et al. randomized 1,562 women to count movements three times a week 2 hours after their largest meal starting after 32 weeks' gestation. Fewer than three fetal movements each hour prompted further evaluation with NST and ultrasound. One stillbirth occurred in the monitored group, whereas 10 occurred in a comparable control group of 1,549 women ($p < 0.05$) [59].

While subsequent small and moderately sized trials appeared to confirm these results [60,61], the largest trial to date by Grant et al. found no benefit to FMC. This group randomized 68,000 European women to fetal movement counting using the Cardiff Count-to-Ten method or to standard care [62]. Women counted movements for nearly 3 hours per day. Approximately 7% of patients experienced at least one episode of decreased movement. The antepartum death rate for normal singleton fetuses was equal in both groups (2.9/1,000 among the study group versus 2.7/1,000 among controls). This study contained serious flaws and should be interpreted with caution. Compliance for reporting decreased fetal movement among the study group was low – only 46%. Compliance was even lower among study patients who suffered a fetal death. Of the 17 study patients who later experienced an intrauterine fetal demise, none received emergency intervention when she presented to the hospital complaining of decreased fetal movement. Why? Grant et al. ascribed the lack of intervention to errors of clinical judgment and to falsely reassuring follow-up testing [62]. One might conclude that this large prospective study disproves the benefit of fetal kick counts, especially if the low rate of compliance and inconsistent follow-up represent what can be expected from "usual" practice. An alternative interpretation is that the study demonstrates the need for appropriate interventions and follow-up of patients who complain of decreased fetal activity.

Maternal perception of fetal movement is influenced by several factors. An anterior placenta, polyhydramnios, and maternal obesity can decrease perception of fetal movement [63]. Movements lasting 20–60 seconds are more likely to be felt by the mother [64]. Fetal anomalies, sometimes associated with polyhydramnios, were linked in one study with decreased movement perception in 26% of cases compared with 4% of normal controls [65].

Fetal activity does not increase in response to food or glucose administration despite popular belief [66,67]. To the contrary, hypoglycemia is associated with increased fetal movement [68]. Normal fetal activity ranges widely, and each mother and fetus serves as its own control. Fetal movements tend to peak between 9 p.m. and 1 a.m. when maternal glucose levels are falling [69].

Intensive maternal surveillance of fetal activity helps to identify fetuses at risk for death due to chronic insult. Kick counts are unlikely to prevent an acute event such as fetal death caused by cord prolapse. Charting fetal movement may increase anxiety for some but generally reassures most women and may enhance maternal-fetal attachment [70,71]. When educated and encouraged, women are more

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likely to present early if they experience decreased fetal movement.

The Biophysical Profile

The discovery that decreased fetal activity is associated with hypoxia, combined with the 1970s development of B-mode ultrasound, which allowed for real-time observation of the fetus, led to the creation of the BPP. Hypoxic animals reduce activity in order to conserve oxygen. By decreasing movement and employing other protective mechanisms, the hypoxic fetus can reduce oxygen consumption by up to 19%, minutes into a hypoxic event [72]. Observation of such reduction in movement can provide clues into the fetus's acid-base status.

The BPP is based on a 10-point score. The lower the BPP score, the greater is the risk of fetal asphyxia. The fetus receives 2 points for the presence of each of the following:

1. Reactive NST
2. Fetal breathing movement
3. Gross body movement
4. Fetal tone
5. Sufficient amniotic fluid volume (AFV)

The BPP is performed by use of real-time ultrasound over a period of up to 30 minutes to observe the required fetal movements and amniotic fluid volume plus NST. Until recently, the AFV measurement most often incorporated in antenatal tests of fetal well-being was the amniotic fluid index (AFI). Using the AFI, oligohydramnios is diagnosed when the sum of amniotic fluid pockets at least 1 cm wide in each of four quadrants dividing the maternal abdomen is less than 5 cm. More recently, randomized comparisons have confirmed that use of the amniotic fluid single deepest vertical pocket (DVP) of at least 2 cm deep by 1 cm wide is equally predictive of fetal compromise as the AFI while being less time intensive and resulting in fewer labor inductions [19,73].

A BPP is typically performed to evaluate a nonreactive or nonreassuring NST. It may be used for other indications, such as the evaluation of a fetus with an abnormal cardiac rhythm, for whom NST would be difficult to interpret. Given the variation in the normal fetal neurologic state, an abnormal test should be evaluated by extending the testing time or repeating the test shortly thereafter to distinguish quiet sleep from asphyxia. VAS during the BPP can change the fetal behavioral state and improve the score without increasing the false-negative rate [74].

An abnormal BPP can predict an arterial cord pH of less than 7.20 with 90% sensitivity, 96% specificity, 82% PPV, and 98% negative predictive value (NPV) [75] and has been significantly associated with development of cerebral palsy (CP) [76]. The incidence of CP was 0.7/1,000 live births when the BPP was normal, 13.1/1,000 live births when the score was 6, and 333/1,000 live births when the score was zero in a study that controlled for birth weight and gestational age. The incidence of intrauterine fetal demise within 7 days of a normal BPP ranges from 0.411 to 1.01/1,000 [77].

The BPP correlates well with acid-base status. Manning et al. performed BPPs immediately prior to cordocentesis and found that a nonreactive NST with an otherwise normal BPP correlated with a mean umbilical vein pH of 7.28 (±0.11) [58]. Fetuses with abnormal movement had an umbilical vein pH of 7.16 (±0.08). Vintzileos et al. evaluated 124 patients undergoing cesarean delivery prior to labor [75]. All patients underwent a BPP prior to surgery, followed by cord pH at delivery. Reasons for delivery included severe preeclampsia, growth restriction, placenta previa, breech presentation, fetal macrosomia, and elective repeat cesarean section. The earliest biophysical signs of acidosis were a nonreactive NST and loss of fetal breathing movements. Among patients with a BPP of 8 or more, the mean arterial pH was 7.28; it was 6.99 among nine fetuses with BPPs of 4 or less. These data suggest that the NST is the most sensitive of the biophysical tests, followed by fetal breathing movements. Fetal movement is the least sensitive, ceasing at the lowest pH. Manning et al. postulated that the graded biophysical response to hypoxia is due to variation in sensitivity of the CNS regulatory centers [78]. When the other four components are normal, the NST may be eliminated from testing without fetal compromise [78].

Chronic hypoxemia may lead to an adaptive fetal response, lowering the pH threshold for the fetal biophysical response. This might explain why a chronically stressed fetus can die shortly after a reactive NST and why oligohydramnios, which often reflects chronic hypoxia and reshunting of blood from the kidneys to the brain, is associated with increased morbidity and mortality regardless of other test results. The lowered threshold likely results from a shift in the hemoglobin dissociation curve, improved fetal extraction of maternal oxygen, and

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an increase in fetal hemoglobin. Manning postulates that resetting of the CNS threshold may occur in part because some biophysical activity is necessary, especially for limb and lung development [77].

Recent studies suggest that antenatal corticosteroids may adversely affect the BPP, decreasing the score. Antenatal steroids are administered at between 24 and 34 weeks when premature delivery is anticipated. Kelly et al. reported that BPP scores were decreased in one-third of fetuses that received steroids between 28 and 34 weeks [79]. The effect was seen within 48 hours of corticosteroid administration. Repeat BPPs performed within 24–48 hours were normal in cases where the BPP score had decreased by 4 points. Neonatal outcome was not affected. Similarly, Deren et al. reported transient suppression of heart rate reactivity, breathing movements, and movement when corticosteroids were administered at less than 34 weeks' gestation, all of which returned to normal by 48–96 hours [80]. This effect must be considered at institutions where BPPs are used to evaluate the fetus.

As with other methods of antepartum fetal assessment, the BPP remains unproven via comparison with no testing or with other modalities in randomized, controlled trials, to reduce perinatal mortality. A 2008 Cochrane review of randomized trials of almost 3,000 women comparing BPP to NST found no differences in perinatal mortality, cesarean delivery rate, Apgar scores, or NICU admission [81].

The Modified Biophysical Profile

A mBPP, which uses only the NST and AFV assessment, may be used in lieu of the full BPP to identify the at-risk fetus [82]. If either the NST is nonreactive or the AFV measurement indicates oligohydramnios, further evaluation by full BPP or CST is recommended. Delivery is indicated if the fetus is full term.

The mBPP is an attractive option given that it incorporates assessment of both short- (NST) and longer-term (AFV) markers of placental function and fetal well-being and is easier to perform than a full BPP or CST. In addition, multiple studies have demonstrated that the mBPP has a comparable false-negative rate to the full BPP, of 0.8 fetal deaths per thousand within 1 week of a normal mBPP [31,82]. Additional evaluation for abnormal mBPP is required in about 10% of patients.

Doppler

Doppler ultrasound is used primarily to assess placental insufficiency and IUGR [83,84]. Blood through arteries supplying low-impedance vascular beds, such as the placenta, normally flows forward during systole and diastole. Diastolic forward flow in the umbilical artery is high during a normal pregnancy and increases more than systolic flow. As gestation advances, placental resistance normally decreases, and the systolic-to-diastolic (S/D) ratio should decrease [85]. An increased umbilical artery S/D ratio suggests an increased placental resistance [86,87].

If the placenta is compromised, umbilical arterial diastolic flow may be absent or reversed. This is seen most often in association and has a pathophysiologic link with IUGR. Absent end-diastolic flow is associated with increased perinatal morbidity and mortality. Reversed end-diastolic flow is even more predictive of poor perinatal outcome. Farine et al. summarized data from 31 studies of 904 fetuses demonstrating absent or reversed end-diastolic velocities [88]. Perinatal mortality was 36%. Eighty percent of the fetuses weighed less than the 10th percentile for gestational age. Abnormal karyotypes were found in 6% and malformations in 11%. Absent or reversed end-diastolic flow in the umbilical artery may be an indication for immediate delivery depending on gestational age and other fetal and maternal parameters; in the setting of extreme prematurity, it is considered an indication for intensive ongoing fetal surveillance. In those situations delivery is usually based on results of fetal heart rate monitoring or of the BPP.

Studies support the use of Doppler to assess high-risk pregnancies [89]. Among patients with IUGR, Doppler is a better predictor of fetal acid-base status than the NST and BPP [90], with a more consistent time course in relation to impending fetal death. A 2013 Cochrane review of 18 randomized trials including more than 10,000 high-risk women concluded that the use of Doppler ultrasound was associated with decreased perinatal deaths (risk ratio [RR] = 0.71, 95% confidence interval [CI] = 0.52–0.98) as well as significantly fewer inductions of labor and cesarean deliveries [91]. A 2010 systematic review of use of Doppler in over 14,000 low-risk pregnancies did not demonstrate benefit in reduction of fetal death [92].

Researchers have investigated the utility of Doppler studies of several different arteries, including

the middle cerebral and splenic arteries. The umbilical arteries are most commonly used because of their large size, lack of branches, and length, making them easy to study. Doppler studies are commonly conducted later in pregnancy. Prior to 15 weeks' gestation, one cannot consistently identify diastolic flow in the umbilical artery [93].

Fetuses with congenital malformations and chromosomal abnormalities may demonstrate markedly abnormal Doppler studies.

Choosing an Antenatal Testing Strategy

Who should receive antenatal testing, and which test(s) should be performed? Antenatal tests can identify the suboptimally oxygenated fetus and theoretically provide the opportunity for intervention before progressive metabolic acidosis results in morbidity or death. Therefore, patients with risk factors for uteroplacental insufficiency are assigned an antenatal testing strategy in common obstetric practice [94]. In general, these risk factors include

- Maternal disease and exposures:
  - Diabetes
  - Hypertensive disorders
  - Rh sensitization
  - Antiphospholipid syndrome
  - Poorly controlled thyroid disease
  - Hemoglobinopathies
  - Chronic renal disease
  - Systemic lupus erythematosus
  - Severe pulmonary disease
  - Smoking or illicit drug use
- Fetal-placental conditions:
  - IUGR
  - Decreased fetal movement
  - Oligo- or polyhydramnios
  - Multiple gestation with discordant growth or monochorionicity
  - Pregnancies past their due date
  - Placental abruption
  - Certain fetal anomalies
- Demographic features that confer increased risk of fetal death, though the pathophysiologic link may be poorly understood:
  - History of fetal death
  - Obesity
  - African-American race/ethnicity
  - Advanced maternal age

Identifying the appropriate time to initiate fetal testing depends on several factors, including the prognosis for neonatal survival, the risk of intrauterine fetal death, the degree of maternal disease, and the potential for a false-positive test leading to iatrogenic prematurity. There have been no randomized trials of timing of initiation of antenatal testing, nor of testing frequency [95]. However, a general sound practice would prescribe a series of tests to women for whom intervention via delivery based on a false-positive result could be harmful – such as those in the preterm period – with incentive to act only if multiple tests are abnormal [94,95]. In comparison, in situations for which provoking delivery based on an abnormal test has few costs, such as post-term pregnancy, acting on a single abnormal test is a typical strategy.

The choice of testing strategy ideally maximizes PPV and NPV and differentiates between patients at high risk of fetal death and those at low risk [96]. Table summarizes the relative predictive values of antenatal tests in common use:

Summary

Ideally, antepartum testing of fetal well-being should reduce perinatal morbidity and mortality by identifying the suboptimally oxygenated fetus accurately and before the onset of permanent damage or death. The predictive value of antepartum fetal tests is determined by the prevalence of an abnormal condition. When a test is applied widely to a low-prevalence population, the PPV of the test is reduced. Obstetric interventions are often employed when fetal compromise is suspected based on an abnormal fetal test despite the possibility of a false positive test result due to the severe consequences of a missed diagnosis. The complete clinical situation should be considered when decisions are made to intervene in a pregnancy based on results of fetal evaluation techniques.

Tests of fetal well-being include maternal assessment of fetal movement, CST, NST, BPP, and mBPP plus Doppler interrogation of the umbilical arteries for fetuses with growth restriction. The incidence of stillbirth within 1 week of a negative CST, BPP, or mBPP is less than 1/1,000, and for a reactive NST it is 1.9/1,000.

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The high false-positive rate of antepartum fetal tests is due in part to the fact that the near-term fetus spends approximately 25% of its time in a quiet sleep state. To design a strategy to reduce perinatal morbidity and mortality, maneuvers such as VAS, serial testing, and careful selection of patients tested should be employed given the low prevalence of the most serious conditions and high false-positive rates of available tests.

References

1. MacDorman MF, Gregory ECW. Fetal and perinatal mortality: United States, 2013. *National Vital Statistics Reports* 2015; **64**(8).
2. Gregory ECW, MacDorman MF, Martin JA. Trends in fetal and perinatal mortality in the United States, 2006–2012 (NCHS data brief, no 169), National Center for Health Statistics, Hyattsville, MD, 2014.
3. American College of Obstetricians and Gynecologists. *Perinatal and Infant Mortality Statistics: Committee Opinion 167. Washington*, DC: ACOG, 1995.
4. Osterman MJ, Kochanek KD, MacDorman MF, et al. Annual summary of vital statistics: 2012–2013. *Pediatrics* 2015; **135**(6): 1115–25.
5. Centers for Disease Control and Prevention. Trends in infant mortality attributable to birth defects: United States, 1980–1995. *MMWR Morb Mortal Wkly Rep* 1998; **47**: 773–8.
6. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2007 period linked birth/infant death data set. *National Vital Statistics Reports* 2011; **59**(6).
7. Fretts RC, Boyd ME, Usher RH, et al. The changing pattern of fetal death, 1961–1988. *Obstet Gynecol* 1992; **79**: 35–9.
8. Fretts RC, Schmittdiel J, McLean FH, et al. Increased maternal age and the risk of fetal death. *N Engl J Med* 1995; **333**: 953–7.
9. Naeye RL. Causes of perinatal mortality in the United States Collaborative Perinatal Project. *JAMA* 1977; **238**: 228–9.
10. Lammer EJ, Brown LE, Anderka MR, et al. Classification and analysis of fetal deaths in Massachussetts. *JAMA* 1989; **261**: 1757–62.
11. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA* 2011; **306**: 2459–68.
12. Grant A, Elbourne D. Fetal movement counting to assess fetal well-being. In Chalmers I, Enkin M, Keirse MJNC, eds., *Effective Care in Pregnancy and Childbirth*. Oxford University Press, 1989:440.
13. Cotzias CS, Paterson-Brown S, Fisk NM. Prospective risk of unexplained stillbirth in singleton pregnancies at term: population based analysis. *BMJ* 1999; **319**: 282–8.
14. Manning FA. Assessment of fetal condition and risk: analysis of single and combined biophysical variable monitoring. *Semin Perinatol* 1985; **9**: 168–83.
15. Van Woerden EE, VanGeijn HP. Heart-rate patterns and fetal movements. In Nijhuis J, ed., *Fetal Behaviour*. New York: Oxford University Press, 1992:41.
16. Antepartum fetal surveillance. ACOG Technical Bulletin Number 188: January 1994. *Int J Gynaecol Obstet* 1994; **44**: 289–94.
17. Huddleston JF, Sutliff G, Robinson D. Contraction stress test by intermittent nipple stimulation. *Obstet Gynecol* 1984; **63**: 669–73.
18. Braly P, Freeman R, Garite T, et al. Incidence of premature delivery following the oxytocin challenge test. *Am J Obstet Gynecol* 1981; **141**:5–8.
19. American College of Obstetricians and Gynecologists. Antepartum fetal surveillance (ACOG Practice Bulletin No. 145; replaces ACOG Practice Bulletin No. 9, October 1999). *Obstet Gynecol* 2014; **124**: 182–92
20. Nageotte MP, Towers CV, Asrat T, et al. The value of a negative antepartum test: contraction stress test and modified biophysical profile. *Obstet Gynecol* 1994; **84**: 231–4.
21. Freeman R, Anderson G, Dorchester W. A prospective multi-institutional study of antepartum fetal heart rate monitoring. I. Risk of perinatal mortality and morbidity according to antepartum fetal heart rate test results. *Am J Obstet Gynecol* 1982; **143**: 771–7.
22. Freeman R, Garite T, Mondanlou H, et al. Postdate pregnancy: utilization of contraction stress testing for primary fetal surveillance. *Am J Obstet Gynecol* 1981; **140**: 128–35.
23. Druzin ML, Karver ML, Wagner W, et al. Prospective evaluation of the contraction stress test and non-stress tests in the management of post-term pregnancy. *Surg Gynecol Obstet* 1992; **174**: 507–12.
24. Merrill PM, Porto M, Lovett SM, et al. Evaluation of the non-reactive positive contraction stress test prior to 32 weeks: the role of the biophysical profile. *Am J Perinatol* 1995; **12**: 229–37.
25. Hammacher K. The clinical significance of cardiotocography. In Huntingford P, Huter K, Saling E, eds., *Perinatal Medicine: 1st European Congress, Berlin*. San Diego, CA: Academic Press, 1969:80.
26. Parer JT. Fetal heart rate. In Creasy RK, Resnick R, eds., *Maternal-Fetal Medicine: Principles and Practice*, 3rd edn. Philadelphia: Saunders, 1994.

27. Lemons JA, Bauer CR, Oh W. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics* 2001; **107**: 1.
28. Graca LM, Cardoso CG, Clode N, *et al.* Acute effects of maternal cigarette smoking on fetal heart rate and fetal body movements felt by the mother. *J Perinat Med* 1991; **19**: 385–90.
29. Lavery J. Nonstress fetal heart rate testing. *Clin Obstet Gynecol* 1982; **25**: 689–705.
30. Schifrin B, Foye G, Amato J, et al. Routine fetal heart rate monitoring in the antepartum period. *Obstet Gynecol* 1979; **54**: 21–5.
31. Miller DA, Rabello YA, Paul RH. The modified biophysical profile: antepartum testing in the 1990s. *Am J Obstet Gynecol* 1996; **174**: 812–7.
32. Druzin ML, Fox A, Kogut E, et al. The relationship of the nonstress test to gestational age. *Am J Obstet Gynecol* 1985; **153**: 386–9.
33. Dashow EE, Read JA. Significant fetal bradycardia during antepartum heart rate testing. *Am J Obstet Gynecol* 1984; **148**: 187–90.
34. Druzin ML. Fetal bradycardia during antepartum testing. *J Reprod Med* 1989; **34**:1.
35. Phelan JP. The nonstress test: a review of 3000 tests. *Am J Obstet Gynecol* 1981; **139**: 7–10.
36. Brown VA, Sawers RS, Parsons RJ, et al. The value of antenatal cardiotocography in the management of high risk pregnancy: a randomised controlled trial. *Br J Obstet Gynaecol* 1982; **89**: 716–22.
37. Flynn A, Kelly J, Mansfield H, et al. A randomized controlled trial of non-stress antepartum cardiotocography. *Br J Obstet Gynaecol* 1982; **89**: 427–33.
38. Kidd L, Patel N, Smith R. Non-stress antenatal cardiotocography: a prospective randomized clinical trial. *Br J Obstet Gynaecol* 1985; **92**: 1156–9.
39. Lumley J, Lester A, Anderson I, et al. A randomised trial of weekly cardiotocography in high risk obstetric patients. *Br J Obstet Gynaecol* 1993; **90**: 1018–26.
40. Grivell RM, Alfirevic Z, Gyte GM, Devane D. Antenatal cardiotocography for fetal assessment. *Cochrane Database Syst Rev*. 2012; **12**: CD007863.
41. Thornton JG, Lilford RJ. Do we need randomised trials of antenatal tests of fetal wellbeing? *Br J Obstet Gynaecol* 1993; **100**: 197–200.
42. Schneider EP, Hutson JM, Petrie RH. An assessment of the first decade's experience with antepartum fetal heart rate testing. *Am J Perinatol* 1988; **5**: 134.
43. Smith CV, Phelan JP, Nguyen HN, et al. Continuing experience with the fetal acoustic stimulation test. *J Reprod Med* 1988; **33**: 365–8.
44. Sarno AP, Bruner JP. Fetal acoustic stimulation as a possible adjunct to diagnostic ultrasound: a preliminary report. *Obstet Gynecol* 1990; **76**: 668–90.
45. Tan KH, Smyth RD, Wei X. Fetal vibroacoustic stimulation for facilitation of tests of fetal wellbeing. *Cochrane Database Syst Rev* 2013; **12**:CD002963.
46. Serafini P, Lindsay MBJ, Nagey DA, et al. Antepartum fetal heart rate response to sound stimulation, the acoustic stimulation test. *Am J Obstet Gynecol* 1984; **148**: 41–5.
47. Divon MY, Platt LD, Cantrell CJ. Evoked fetal startle response: a possible intrauterine neurological examination. *Am J Obstet Gynecol* 1985; **153**: 454–6.
48. Ohel G, Simon A, Linder N, et al. Anencephaly and the nature of fetal response to vibroacoustic stimulation. *Am J Perinatol* 1986; **3**: 345–6.
49. Birnholz JC, Benacerraf BR. The development of fetal hearing. *Science* 1983; **148**: 41–5.
50. Crade M, Lovett S. Fetal response to sound stimulation: preliminary report exploring use of sound stimulation in routine obstetrical ultrasound examination. *J Ultrasound Med* 1988; **7**: 499–503.
51. Druzin ML, Edersheim TG, Hutson JM. The effect of vibroacoustic stimulation on the nonstress test at gestational ages of thirty-two weeks or less. *Am J Obstet Gynecol* 1989; **161**: 1476–8.
52. Pietrantoni M, Angel JL, Parsons MT, et al. Human fetal response to vibroacoustic stimulation as a function of stimulus duration. *Obstet Gynecol* 1991; **78**: 807–11.
53. Patrick J, Campbell K, Carmichael L, et al. Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. *Am J Obstet Gynecol* 1982; **142**: 363–71.
54. Pearson JF, Weaver JB. Fetal activity and fetal wellbeing: an evaluation. *Br Med J* 1976; **1**: 1305–7.
55. Laventhal NT, Dildy GA, Belfort MA. Fetal tachyarrhythmia associated with vibroacoustic stimulation. *Obstet Gynecol* 2003; **101**: 1116–18.
56. Tan KH, Sabapathy A, Wei X: Fetal manipulation for facilitating tests of fetal wellbeing. *Cochrane Database Syst Rev* 2013; **4**: CD003396.
57. Piyamongkol W, Trungtawatchai S, Chanprapaph P, et al. Comparison of the manual stimulation test and the nonstress test: a randomized controlled trial. *J Med Assoc Thai* 2006; **89**: 1999–2002.
58. Manning FA, Snijders R, Harman CR, et al. Fetal biophysical profile score. VI. Correlation with

antepartum umbilical venous pH. *Am J Obstet Gynecol* 1993; **169**: 755–63.

59. Neldam S. Fetal movements as an indicator of fetal well being. *Dan Med Bull* 1983; **30**: 274–8.
60. Moore TR, Piacquadio K. A prospective evaluation of fetal movement screening to reduce the incidence of antepartum fetal death. *Am J Obstet Gynecol* 1989; **160**: 1075–80.
61. Elbourne D, Grant A. Study results vary in count-to-10 method of fetal movement screening. *Am J Obstet Gynecol* 1990; **163**: 264–5.
62. Grant A, Valentin L, Elbourne D. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. *Lancet* 1989; **2**: 345–9.
63. Sorokin Y, Kierker L. Fetal movement. *Clin Obstet Gynecol* 1982; **25**: 719–34.
64. Johnson TR, Jordan ET, Paine LL. Doppler recordings of fetal movement. II. Comparison with maternal perception. *Obstet Gynecol* 1990; **76**: 42–3.
65. Rayburn W, Barr M. Activity patterns in malformed fetuses. *Am J Obstet Gynecol* 1982; **142**: 1045–8.
66. Phelan JP, Kester R, Labudovich ML. Nonstress test and maternal glucose determinations. *Obstet Gynecol* 1982; **60**: 437–9.
67. Druzin ML, Foodim J. Effect of maternal glucose ingestion compared with maternal water ingestion on the nonstress test. *Obstet Gynecol* 1982; **67**: 425–6.
68. Holden K, Jovanovic L, Druzin M, et al. Increased fetal activity with low maternal blood glucose levels in pregnancies complicated by diabetes. *Am J Perinatol* 1984; **1**: 161–4.
69. Schwartz RM, Luby AM, Scanlon JW, et al. Effect of surfactant on morbidity, mortality and resource use in newborn infants weighing 500–1,500 grams. *N Engl J Med* 1994; **330**: 1476–80.
70. Draper J, Field S, Thomas H. Women's views on keeping fetal movement charts. *Br J Obstet Gynaecol* 1986; **93**: 334–8.
71. Mikhail MS, Freda MC, Merkatz RB, et al. The effect of fetal movement counting on maternal attachment to fetus. *Am J Obstet Gynecol* 1991; **165**: 988–91.
72. Rurak DW, Gruber NC. Effect of neuromuscular blockade on oxygen consumption and blood gases. *Am J Obstet Gynecol* 1983; **145**: 258–62.
73. Nabhan AF, Abdelmoula YA: Amniotic fluid index versus single deepest vertical pocket as a screening test for preventing adverse pregnancy outcome. *Cochrane Database Syst Rev* 2009; **16**:CD006593
74. Inglis SR, Druzin ML, Wagner WE, et al. The use of vibroacoustic stimulation during the abnormal or equivocal biophysical profile. *Obstet Gynecol* 1993; **82**: 371–4.
75. Vintzileos AM, Gaffrey SE, Salinger IM, et al. The relationship between fetal biophysical profile score and cord pH in patients undergoing cesarean section before the onset of labour. *Obstet Gynecol* 1987; **70**: 196–201.
76. Manning F. Fetal assessment by evaluation of biophysical variables: fetal biophysical profile score. In Creasy R, Resnik R, eds., *Maternal-Fetal Medicine*, 3rd edn. Philadelphia: Saunders, 1999.
77. Manning FA. Fetal biophysical profile. *Obstet Gynecol Clin North Am* 1999; **26**: 557–77.
78. Manning FA, Morrison I, Lange IR, et al. Fetal biophysical profile scoring: selective use of the nonstress test. *Am J Obstet Gynecol* 1987; **156**: 709–12.
79. Kelly MK, Schneider EP, Petrikovsky BM, et al. Effect of antenatal steroid administration on the fetal biophysical profile. *J Clin Ultrasound* 2000; **28**: 224–6.
80. Deren O, Karaer C, Onderoglu L, et al. The effect of steroids on the biophysical profile and Doppler indices of umbilical and middle cerebral arteries in healthy preterm fetuses. *Eur J Obstet Gynecol Reprod Biol* 2001; **99**: 72–6.
81. Lalor JG, Fawole B, Alfirevic Z, Devane D. Biophysical profile for fetal assessment in high risk pregnancies. *Cochrane Database Syst Rev*. 2008; **1**: CD000038
82. Nageotte MP, Towers CV, Asrat T, et al. Perinatal outcome with the modified biophysical profile. *Am J Obstet Gynecol* 1994; **170**: 1672–6.
83. McCowan LME, Harding JE, Stewart AW, et al. Umbilical artery Doppler studies in small for gestational age babies reflect disease severity. *BJOG* 2000; **107**: 916–25.
84. Pollack RN, Divon MY. Intrauterine growth retardation: diagnosis. In Copel JA, Reed KL, eds., *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Raven Press, 1995: 171.
85. Itskovitz J. Maternal-fetal hemodynamics. In Maulik D, McNellis D, eds., *Reproductive and Perinatal Medicine (VIII): Doppler Ultrasound Measurement of Maternal-Fetal Hemodynamics*. Ithaca, NY: Perinatology Press, 1987: 13.
86. Morrow R, Ritchie K. Doppler ultrasound fetal velocimetry and its role in obstetrics. *Clin Perinatol* 1989; **16**: 771.
87. Copel JA, Schlafer D, Wentworth R, et al. Does the umbilical artery systolic/diastolic ratio reflect flow or acidosis? *Am J Obstet Gynecol* 1990; **163**: 751.
88. Farine D, Kelly EN, Ryan G, et al. Absent and reversed umbilical artery end-diastolic velocity. In Copel JA, Reed KL, eds., *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Raven Press, 1995: 187.

89. Divon MY, Ferber A. Evidence-based antepartum fetal testing. *Prenat Neonatal Med* 2000; **5**: 3–8.

90. Turan S, Turan OM, Berg C, et al. Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2007; **30**: 750–6.

91. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev*. 2013; **11**: CD007529

92. Alfirevic Z, Stampalija T, Gyte GM: Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev*. 2010; **8**: CD001450

93. Rizzo G, Arduini D, Romanini C. First trimester fetal and uterine Doppler. In Copel JA, Reed KL, eds., *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Raven Press, 1995: 105.

94. Signore C, Freeman RK, Spong CY: Antenatal testing: a reevaluation. Executive summary of a Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop. *Obstet Gynecol* 2009; **113**:687.

95. Scifres CM, Macones GA: Antenatal testing: benefits and costs. *Semin Perinatol* 2008; **32**: 318.

96. Kontopoulos EV, Vintzileos AM: Condition-specific antepartum fetal testing. *Am J Obstet Gynecol* 2004; **191**: 1546.

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Chapter 15

Intrapartum Evaluation of the Fetus

Israel Hendler and Daniel S. Seidman

Introduction

In 1958, Hon published the first set of data on 80 women who underwent successful electronic recording of fetal heart rate (FHR) throughout labor and delivery [1,2]. FHR monitoring was widely introduced into clinical practice in the 1970s. At the time, obstetric providers and researchers in fetal physiology believed that electronic fetal monitoring (EFM) would identify changes in the FHR and/or rhythm that reflect fetal acidosis [3–5]. It was presumed that detection would be early enough to allow clinical intervention that would prevent perinatal asphyxia [4].

The seeds of doubt began to emerge in the late 1970s, when the first randomized, controlled trials (RCTs) were published and failed to demonstrate any of the positive outcomes originally anticipated, with the exception of a decrease in neonatal seizures, in some studies [6]. Additionally, a frequently cited study of EFM and the prediction of cerebral palsy (CP) showed that the positive predictive value of a nonreassuring FHR tracing to predict CP was 0.14%, with a false-positive predictive rate exceeding 99% [7–10]. Despite 45 years of widespread use and multiple randomized clinical trials, FHR monitoring has not yet been shown to have a significant impact on perinatal mortality [11]. Moreover, some experts believe that the use of EFM leads to overdetection of nonreassuring FHR patterns, thereby directly contributing to the high rate of cesarean delivery in the United States [12].

Electronic fetal monitoring (EFM) has since become routine and widely used. In the United States, the use of EFM has increased from 73.4% in 1990 to 85.7% in 2004, a relative increase of 17% (95% confidence interval [CI] 16–18%) [13]. Despite its ubiquitous use, a meta-analysis of 12 RCTs noted that one additional cesarean delivery was performed for every 58 women monitored continuously and that 661 women needed to be monitored to avert one neonatal seizure [14]. In addition, EFM use was repeatedly found to increase the likelihood of vacuum, forceps, and cesarean deliveries.

Recently it was shown that this increase was associated with 2% decline in late neonatal deaths, as well as a 7% decline in the prevalence of low 5-minute Apgar score [15]. Increasing EFM use was associated with a 2–4% incremental increased rate of both cesarean delivery and operative vaginal delivery for fetal distress. Increasing EFM was not associated with any temporal changes in the rate of neonatal seizures [16].

This chapter reviews the physiology underlying FHR patterns and the possible reasons why randomized trials of EFM have so far failed to demonstrate efficacy. The current knowledge that guides interpretation of EFM in the intrapartum period will be discussed, with special emphasis on newer methods for intrapartum fetal surveillance such as ST-waveform analysis, fetal electrocardiogram (ECG), and fetal pulse oximetry.

The History of EFM

The common practice of monitoring the FHR during labor was stimulated by William Little in 1862. A London orthopedic surgeon who took care of spastic infants, he expressed the view that "the process of birth was responsible for the pathology of cerebral palsy."17 Edward Hon was a physician and engineer who in 1957 invented the "internal" monitor and fetal electrode that connects the fetus to the machine to collect the electrocardiographic information [1,2,18].

Soon thereafter, FHR monitoring was rapidly incorporated into routine use. Unfortunately, clinical practice swiftly proceeded, before controlled trials could establish a true cause-and-effect relationship between specific FHR patterns and fetal acidemia. In 1968, it was claimed that 90% of all fetal distress is caused by umbilical cord compression and that electronically monitoring the entire birth process from labor to delivery could save as many as 20,000 babies a year and reduce the number of injured babies by 50%

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[3]. A cost analysis published in 1975 concluded that EFM could enhance the quality of maternal-fetal healthcare, although it was clearly cited that "to date, there has been no definitive well-controlled study which has scientifically proven the value of this technique" [6]. A number of studies published in the 1970s pointed to the decline in perinatal morbidity and mortality that had occurred since the introduction of EFM and thought to attribute this to EFM. During a 10-year period from 1970 to 1979, the obstetric service at the University of Southern California found that after EFM was introduced in 1969, the perinatal mortality rate decreased. The cesarean delivery rate increased as well during this period, but the authors did not ascribe this increase to EFM [7].

The results of the first RCT of EFM were not in agreement with the conclusions reached in earlier studies using historical controls. In 1976, a prospective, randomized study in Denver of 483 high-risk patients in labor, monitored either electronically or with intermittent auscultation, found that the cesarean rate was significantly increased in the EFM group (16.5% versus 6.8%), but there was no difference in neonatal morbidity and mortality [19]. However, in 1979, a meta-analysis of 10 nonrandomized studies concluded that "there is now compelling evidence that the intrapartum stillbirth rate will decrease by 1–2 in 1,000 and neonatal deaths will be halved if monitoring is widely used" [20].

In a large randomized study performed in Dublin between 1981 and 1983, 12,964 women were randomized to either EFM or auscultation [8,9]. The cesarean delivery rate was 2.4% in the EFM group and 2.2% in the auscultation group. There were 14 stillbirths and neonatal deaths in each group. There were no apparent differences in the rates of low Apgar scores, need for resuscitation, or transfer to the special-care nursery. Cases of neonatal seizures and persistent abnormal neurologic signs followed by survival were twice as frequent in the intermittent auscultation group, but when the 9 children from the EFM group and the 21 children from the intermittent auscultation group who survived after neonatal seizures were followed up at 4 years of age, there were 3 children with CP in each group [10].

In 1995, Thacker et al. reviewed the results of 12 randomized trials with 58,855 patients undertaken from 1966 to 1994 [21]. They found that newborns who were monitored electronically had a relative risk of 0.5 for seizures versus a randomized group of patients managed by auscultation during labor (1.1% versus 0.8% of the newborns, respectively). With the exception of the reduction in the rate of neonatal seizures, the use of EFM had no measurable impact on morbidity and mortality. The long-term impact of the reduction in seizures was not demonstrated. In fact, the majority of newborns in some of these trials who developed CP were not in the group of fetuses who had FHR tracings that were considered ominous. The value of EFM in this meta-analysis was uncertain. These authors pointed out that EFM was introduced into widespread clinical practice before evidence from RCTs demonstrated either efficacy or safety and that widespread diffusion of this technology before efficacy was determined may have led to misuse, misunderstanding, and misinformation with regard to malpractice litigation.

We understand today that FHR monitoring may have a high sensitivity for the detection of fetal acidosis. However, several of the FHR patterns long considered abnormal do not reflect fetal acidosis. The specificity of this tool for the detection of hypoxic-ischemic injury is therefore very low [22]. Moreover, although CP can be a result of hypoxic-ischemic injury, apparently only about 10% of the children with CP had an asphyxial event during labor.

In a separate study, 78 term singleton children with the diagnosis of moderate to severe CP at age 3 were compared with 300 randomly selected term control children [23]. Although late decelerations (odds ratio [OR] 3.9, 95% CI 1.7–9.3) and decreased beat-to-beat variability (OR 2.7, 95% CI 1.1–5.8) were associated with an increased risk of CP, 57 of 78 (73%) children with CP did not have either of these abnormalities. The 21 children with CP who had severe changes on EFM represented only 0.2% of singleton infants at term who had these EFM findings, for a false-positive rate of 99.8% [23].

Larma et al. investigated the ability of EFM to detect metabolic acidosis and to predict hypoxic-ischemic encephalopathy, which is assumed to be one of the basic pathologies that leads to CP [22]. For the identification of hypoxic-ischemic encephalopathy, the sensitivity, specificity, and positive and negative predictive values were 15.4, 98.9, 66.7, and 89.4%, respectively, for bradycardia; 53.8, 79.8, 26.9, and 92.6%, respectively, for decreased variability; 92.3, 61.7, 2.7, and 82.9%, respectively, for nonreactivity; and 7.7, 98.9, 50.0, and 88.6%, respectively, for all three abnormalities combined. The authors concluded that fetal metabolic

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acidosis and hypoxic-ischemic encephalopathy are associated with significant increases in EFM abnormalities, but their predictive ability to identify these conditions is low [22]. Moreover, the assumption that hypoxic-ischemic encephalopathy is the main cause for CP remains debatable. In a meta-analysis published in 2008 for term infants, the incidence of an umbilical arterial pH of less than 7.0 at birth was 3.7/1,000, of which 51/297 (17.2%) survived with neonatal neurologic morbidity, 45 /276 (16.3%) had seizures, and 24/407 (5.9%) died during the neonatal period [24]. The incidence of neonatal neurologic morbidity and mortality for term infants born with a cord pH of less than 7.0 was 23.1%. The incidence of hypoxic-ischemic encephalopathy was 2.5/1,000 live births. The proportion of CP associated with intrapartum hypoxia-ischemia was 14.5%. The vast majority of cases of CP in term infants was not associated with intrapartum hypoxia-ischemia [24]. Despite the apparent lack of efficacy, the use of EFM during labor has continued to grow in hospital settings, and interpretation is being refined as knowledge of fetal physiology grows.

A Cochrane database review in 2013 assessed continuous cardiotocography (CTG) as a form of EFM for fetal assessment during labor [14]. Thirteen trials with over 37,000 women were included; only two were judged to be of high quality. Compared with intermittent auscultation, continuous CTG showed no significant improvement in overall perinatal death rate (risk ratio [RR] 0.86, 95% CI 0.59–1.23, n = 33,513, 11 trials) but was associated with a halving of neonatal seizures (RR 0.50, 95% CI 0.31–0.80, n = 32,386, nine trials). There was no significant difference in CP rates (RR 1.75, 95% CI 0.84–3.63, n = 13,252, two trials). There was a significant increase in caesarean sections associated with continuous CTG (RR 1.63, 95% CI 1.29–2.07, n = 18,861, 11 trials). Women were also more likely to have an instrumental vaginal birth (RR 1.15, 95% CI 1.01–1.33, n = 18,615, 10 trials). The authors concluded that continuous CTG during labor is associated with a reduction in neonatal seizures but no significant differences in CP, infant mortality, or other standard measures of neonatal well-being. However, continuous CTG was associated with an increase in caesarean sections and instrumental vaginal births [14].

A 2015 meta-analysis by the Cochrane collaboration assessed the use of antenatal CTG for fetal assessment [25]. Six studies involving 2,105 women were included. Overall, the studies were not of high quality, and only two had both adequate randomization sequence generation and allocation concealment. All the studies that were found acceptable for inclusion had enrolled only women at increased risk of complications. Comparison of traditional CTG versus no CTG showed no significant differences in their ability to identify perinatal mortality (RR 2.05, 95% CI 0.95–4.42, 2.3 versus 1.1%, n = 1,627, four studies, low-quality evidence) or potentially preventable deaths (RR 2.46, 95% CI 0.96–6.30, n = 1,627, four studies), though the meta-analysis was notably underpowered to assess this latter outcome. Similarly, no significant difference WAS identified in the rate of caesarean sections (RR 1.06, 95% CI 0.88–1.28, 19.7 versus 18.5%, n = 1,279, three trials, low-quality evidence). In addition, no significant differences were identified for secondary outcomes such as Apgar scores less than 7 at 5 minutes (RR 0.83, 95% CI 0.37–1.88, n = 396, one trial, very low-quality evidence) or admission to neonatal special-care units or neonatal intensive care units (RR 1.08, 95% CI 0.84–1.39, n = 883, two trials, low-quality evidence), nor for any of the other secondary outcomes that were assessed. The authors of this 2015 Cochrane collaboration meta-analysis concluded that at present there is no clear evidence that antenatal CTG improves perinatal outcome [21].

Physiology of the FHR

Fetal Oxygenation

The transfer of oxygen and carbon dioxide between the fetal and maternal circulations depends on the structure and adequate function of the uterine vasculature, the intervillous space, the fetal placenta, and the umbilical cord. Fetal umbilical vein blood, which carries oxygenated blood from the placenta to the fetus, has about the same partial pressure of oxygen (PO_2) as that in maternal uterine vein blood – approximately 35 mmHg. Gas exchange across the placenta is efficient, yet the PO_2 in fetal oxygenated blood is poor relative to arterial values in adults [26–28].

There are several physiologic mechanisms that enable the fetus to maintain normal metabolism in an environment with low PO_2 [29]:

1. High blood flow due to high heart rate. For instance, fetal myocardial oxygen needs are met through a 60% greater resting myocardial blood flow than that of the adult.

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2. Unique fetal hemoglobin (Hb) allows oxygen binding to Hb even at a low PO_2 values; thus more oxygen can be transported at a low PO_2.
3. Fetal blood has more hemoglobin than adult blood. The extra *carrying capacity* allows the fetus to extract maximal amounts of oxygen.
4. The pattern of blood flow in the fetus allows overperfusion of some organs with higher oxygen requirements, that is, improved cerebral blood flow.

The most common etiologies of interruption of oxygen delivery to the fetus during labor are acute decreases in uterine blood flow secondary to uterine contractions and a decrease in umbilical blood flow secondary to cord compression. The fetus is able to maintain normal aerobic metabolism during transient decreases in blood flow to the uterus. Certain FHR patterns, namely, variable decelerations, have been ascribed to transient umbilical cord compression in the fetus during labor. Manipulation of the maternal position, either to the lateral or Trendelenburg position, can sometimes abolish these patterns. Under normal conditions, the fetus compensates for short-term transient decreases in PO_2 without altering normal metabolic function [5,29–31].

Role of the Autonomic Nervous System

The parasympathetic and sympathetic nervous systems comprise the autonomic nervous system, which regulates FHR. FHR changes often result from moment-to-moment autonomic modulation from medullary cardiorespiratory centers in response to inputs from

- Chemoreceptors
- Baroreceptors
- Central nervous system (CNS) activities, such as arousal and sleep
- Hormonal regulation
- Blood volume control

The Parasympathetic Nervous System. Parasympathetic innervation of the heart is primarily mediated by the vagus nerve (tenth cranial nerve), which originates in the medulla oblongata. Fibers from this nerve supply the sinoatrial (SA) and atrioventricular (AV) nodes [29,31]. The two parasympathetic influences on the heart are

1. A chronotropic effect that slows FHR. Stimulation of the vagus nerve results in a relative slowing of SA node firing and a decrease in FHR, whereas medications (e.g., atropine) that block the release of acetylcholine from the vagus nerve lead to a relative increase in SA node firing and acceleration of the FHR (by approximately 20 beats/minute at term).
2. An oscillatory effect that alters R-wave intervals, resulting in FHR variability.

The Sympathetic Nervous System. Sympathetic nerves are distributed throughout the myocardium of the term fetus. Stimulation of the sympathetic nerves in the heart releases norepinephrine, resulting in an increase in FHR and an increase in cardiac contractility, a combination that results in an increase in cardiac output. Blockade of sympathetic activity decreases baseline FHR and blunts accelerations.

Effect of Gestational Age on FHR

The parasympathetic nervous system exerts a progressively greater influence on FHR as gestational age advances (i.e., advancing gestational age is associated with slowing of the baseline heart rate). As an example, at 20 weeks of gestation, the average FHR is 155 beats/minute, whereas at 30 weeks it is 144 beats/minute.

Maturation of the autonomic nervous system is accompanied by increasing FHR variability with a pronounced increase of parasympathetic activity. FHR variability is rarely present before 24 weeks of gestation, whereas its absence is abnormal after 28 weeks of gestation because the parasympathetic nervous system is consistently developed by the third trimester. Regardless of gestational age, loss of variability is an abnormal finding once a fetus has demonstrated that its heart rate responds to the oscillatory input of the parasympathetic nervous system.

Advancing gestational age is also associated with increased frequency and amplitude of FHR accelerations, which are modulated by the sympathetic nervous system [27]. Fifty percent of normal fetuses demonstrate accelerations with fetal movements at 24 weeks; this proportion rises to over 95 percent at 30 weeks of gestation [27,29,30]. Before 30 weeks, however, accelerations are typically only 10 beats/minute for 10 seconds rather than the 15 beats/minute sustained for 15 seconds noted after 30 weeks.

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Chemoreceptors, Baroreceptors, and Cardiac Output

Chemoreceptors are found in the carotid and aortic bodies of the aorta and the carotid sinus. In adults, when the central chemoreceptors perceive a decrease in circulating oxygen, a reflex tachycardia is initiated, presumably to circulate more blood. The fetus, in contrast, responds to hypoxia with a decrease in heart rate. The cardiovascular responses to hypoxia in the fetus are instituted rapidly and are mediated by both neural and hormonal mechanisms. Baroreceptors in the aortic arch and carotid sinus are small stretch receptors that are sensitive to changes in blood pressure. When blood pressure rises, impulses from the baroreceptors are sent to the brainstem via afferent fibers in the vagus and impulses are returned via vagal efferent fibers, rapidly resulting in a slowing of the FHR.

Cardiac output depends on heart rate, preload, afterload, and intrinsic contractility [32,33]. Each of these four determinants interacts dynamically to modulate the fetal cardiac output during physiologic conditions. The Frank-Starling mechanism is probably not well developed in the fetal heart. Because the fetal cardiac muscle is less developed than that of the adult, increases or decreases in preload do not initiate compensatory changes in stroke volume [34]. In addition, the fetal heart function appears to be highly sensitive to changes in the afterload, represented by the fetal arterial blood pressure. Increases in afterload elicit a dramatic reduction in the stroke volume or cardiac output. In clinical practice, it is reasonable to assume that with small variations of FHR, there are relatively small effects on the fetal cardiac output. However, at extremes, for example, a tachycardia above 240 beats/minute or a bradycardia below 60 beats/minute, cardiac output and umbilical blood flow are likely to be substantially decreased.

Other factors that either directly or indirectly alter FHR and the fetal circulation include CNS activity (sleep and awake cycles change the FHR variability), hormones, and blood volume shifts. The primary hormones involved in regulation of FHR, cardiac contractility, and distribution of blood flow in the fetus include epinephrine, norepinephrine, the rennin-angiotensin system, arginine vasopressin, prostaglandins, melanocyte-stimulating hormone, atrial natriuretic hormone, neuropeptide Y, and thyrotropin-releasing hormone. In addition, nitric oxide and adenosine can affect the fetal circulation.

Characteristics of the Normal FHR

The baseline features of the FHR, that is, predominant characteristics that can be recognized between uterine contractions, consist of the following [34–36] (Table 15.1).

Baseline Rate

The baseline FHR is the approximate mean FHR rounded to 5 beats/minute during a 10-minute segment, excluding

- Periodic or episodic changes
- Periods of marked FHR variability
- Segments of the baseline that differ by 25 beats/minute

In any 10-minute window, the minimum baseline duration must be at least 2 minutes; otherwise, the baseline for that period is indeterminate or saltatoric, in which case one may need to refer to the previous 10-minute segment(s). The normal baseline FHR is considered to be between 110 and 160 beats/minute. Values below 110 beats/minute are termed *bradycardia*, and those above 160 beats/minute are termed *tachycardia*.

Variability

Variability refers to the irregularity in the line one sees when examining an FHR monitor tracing. The FHR variability represents a slight difference in time interval between each beat as counted and recorded by the monitor. If all intervals between heartbeats were identical, the line would be regular or smooth. Baseline variability is defined as fluctuations in the baseline FHR of two cycles per minute or greater. Variability is a critical determinant of adequate perfusion and/or function in the CNS [22,37,38].

Accelerations

An acceleration is a visually apparent abrupt increase in FHR above the baseline, defined as onset of acceleration to peak in 30 seconds. The increase is calculated from the most recently determined portion of the baseline. The acme is 15 beats/minute above baseline, and the acceleration lasts between 15 seconds and 2 minutes from the onset to return to baseline (Figure 15.1).

Before 32 weeks of gestation, accelerations are defined as a rise of 10 beats/minute above baseline for a duration of at least 10 seconds [36,39]. A

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Table 15.1 Definitions of FHR Pattern

Pattern	Definition

Baseline	• The mean FHR rounded to increments of 5 beats/minute during a 10-minute segment, excluding
	  • Periodic or episodic changes
	  • Periods of marked FHR variability
	  • Segments of baseline that differ by more than 25 beats/minte

Baseline variability	• The baseline must be for a minimum of 2 minutes in any 10-minute segment
	• Fluctuations in the FHR of two cycles per minute or greater
	• Variability is visually quantitated as the amplitude of peak to trough in beats/minute
	  • Absent: amplitude range undetectable
	  • Minimal: amplitude range detectable but 5 beats/minute or fewer
	  • Moderate (normal): amplitude range 6–25 beats/minute
	  • Marked: amplitude range greater than 25 beats/minute

Acceleration	• A visually apparent increase (onset to peak in less than 30 seconds) in the FHR from the most recently calculated baseline • The duration of an acceleration is defined as the time from the initial change in FHR from baseline to the return of the FHR to baseline • At 32 weeks of gestation and beyond, an acceleration has an acme of 15 beats/minute or more above baseline, with a duration of 15 seconds or more but less than 2 minutes • Before 32 weeks of gestation, an acceleration has an acme of 10 beats/minute or more above baseline with a duration of 10 seconds or more but less than 2 minutes • Prolonged acceleration lasts 2 minutes or more but less than 10 minutes • If an acceleration lasts 10 minutes or longer, it is a baseline change
Bradycardia	• Baseline FHR less than 110 beats/minute
Early deceleration	• In association with a uterine contraction, a visually apparent gradual (onset to nadir 30 seconds or more) decrease in FHR with return to baseline • Onset, nadir, and recovery of the deceleration occur after the beginning, peak, and end of the contraction, respectively
Tachycardia	• Baseline FHR greater than 160 beats/minute
Variable deceleration	• An abrupt (onset to nadir less than 30 seconds), visually apparent decrease in the FHR below the baseline • The decrease in FHR is 15 beats/minute or more, with a duration of 15 seconds or more but less than 2 minutes
Prolonged deceleration	• Visually apparent decrease in the FHR below baseline • Deceleration is 15 beats/minute or more lasting 2 minutes or more but less than 10 minutes from onset to return to baseline

prolonged acceleration is more than 2 minutes and less than 10 minutes in duration. There is a close association between the presence of accelerations and normal FHR variability, and both accelerations and normal variability have the same positive prognostic significance of normal fetal oxygenation. It was found in 97 fetuses with birth weights less than 1,200 g that the absence of two FHR accelerations of 10 beats/minute for 10 seconds twice in a 20-minute window 1 hour before delivery was associated with intraventricular hemorrhage and/or periventricular leukomalacia ($p < 0.01$) and a significant risk for mental and psychomotor delays by Bayley testing ($p < 0.001$) [30].

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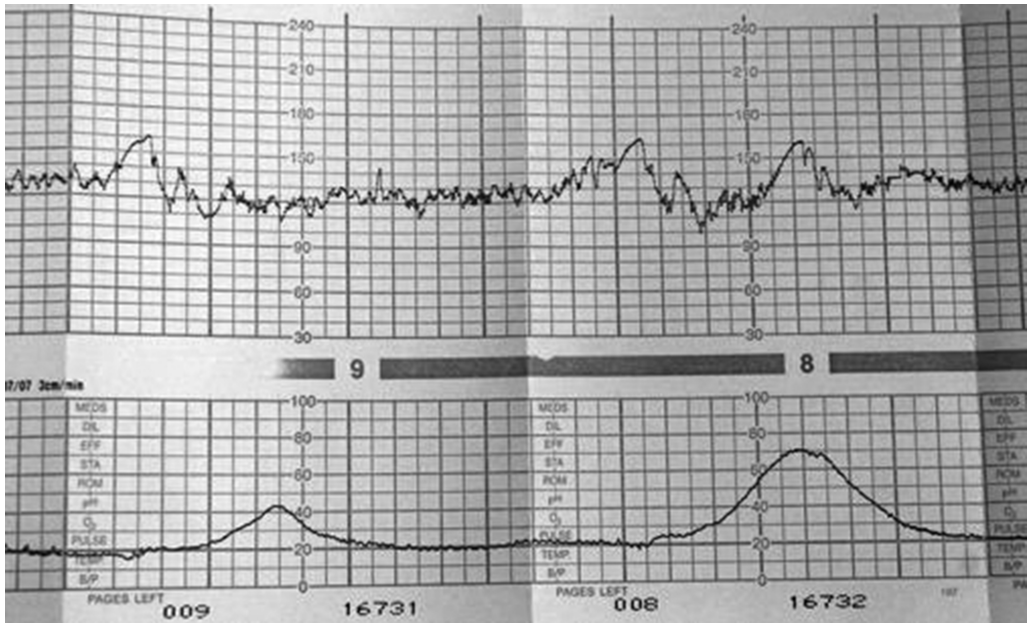


Figure 15.1 Normal FHR tracing. Within a 20-minute window, a normal FHR baseline is seen with good variability and two accelerations. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

Fetal Response to Hypoxia/Asphyxia

Fetal response to hypoxia is complicated because a number of physiologic control mechanisms are activated in response to acute hypoxia. These include both baroreceptors and chemoreceptors, as well as sympathetic and parasympathetic influences [40]. Fetal bradycardia occurs promptly in response to fetal hypoxia secondary to maternal hypoxia, reduced uterine blood flow, or umbilical cord occlusions. This bradycardia is variably associated with hypertension and therefore can occur as a result of activation of either chemoreceptors or baroreceptors. When fetal hypoxemia is maintained in pregnant sheep, there is a gradual return in the FHR to normal, followed by a tachycardia that is associated with elevations in fetal catecholamine levels. FHR returns to normal levels after 12–16 hours of hypoxia in the absence of progressive acidemia secondary to reduced uterine blood flow. A similar adaptation takes place with FHR variability [41].

Augmented beta-adrenergic activity may be important in maintaining cardiac output and umbilical blood flow during hypoxia by increasing the inotropic effect on the heart. Alpha-adrenergic activity is important in determining the regional distribution of blood flow in the hypoxic fetus by selective vasoconstriction.

The initial response to hypoxia includes a decrease in fetal oxygen consumption to values as low as 60% of control. This decrease is rapidly instituted, stable for periods of up to 45 minutes, proportional to the degree of hypoxia, and rapidly reversible on cessation of maternal hypoxia. It is accompanied by a fetal bradycardia of about 30 beats/minute below control and an increase in fetal arterial blood pressure. If hypoxia persists, metabolic acidosis develops. This is due to lactic acid accumulation as a result of anaerobic metabolism primarily in those partially vasoconstrictor beds where oxygenation is inadequate for normal basic needs [42].

In summary, the fetus responds to hypoxia with a redistribution of blood flow favoring certain vital organs – namely, heart, brain, and adrenal glands – and a decrease in blood flow to the gut, spleen, kidneys, and carcass [22,43,44]. In addition, there is bradycardia, decreased total oxygen consumption, and anaerobic glycolysis. These compensatory mechanisms enable a fetus to survive moderately long periods (e.g., 30–60 minutes) of limited oxygen supply without damage to vital organs. The response of blood flow to oxygen availability achieves a constancy of oxygen delivery in the fetal cerebral circulation and in the fetal myocardium.

During more severe asphyxia or sustained hypoxemia, the responses just described are no longer maintained, and decreases in cardiac output, arterial blood

pressure, and blood flow to the brain and heart have been described [44].

Variant FHR Patterns

Periodic Patterns: Late, Early, and Variable Decelerations

Periodic patterns are the alterations in FHR that are associated with uterine contractions. The three characteristic periodic patterns seen are late decelerations, early decelerations, and variable decelerations. Prolonged decelerations are a subcategory of variable or late decelerations. Episodic decelerations are similar to periodic patterns but do not have the same constant association with contractions [36].

Late deceleration of the FHR is a visually apparent gradual decrease (defined as onset of deceleration to nadir in less than 30 seconds) and return to baseline FHR associated with a uterine contraction. It is delayed in timing, with the nadir of the deceleration late in relation to the peak of the contraction. In most cases, the onset, nadir, and recovery are all late in relation to the beginning, peak, and end of the contraction, respectively [29,36] (Figure 15.2)

Originally, all late decelerations were thought to represent the fetal response to decreased oxygenation in the presence of significant uteroplacental insufficiency. More recent research has identified two different mechanisms. Late decelerations that have retained variability are neurogenic in origin. When a well-oxygenated fetus has an acute reduction in oxygenation during a contraction, chemoreceptors detect the hypoxemia and initiate the vagal bradycardic response. It takes a short time for hypoxemia to develop in this setting; thus the chemoreceptor reflex occurs as the hypoxemia is detected. The FHR baseline has a slower decline, and the nadir of the deceleration is late relative to the peak of the contraction. Because the fetus is centrally well oxygenated and not acidemic (i.e., the heart and CNS), variability is retained [22,37,38].

Late decelerations with decreased or absent variability are possibly asphyxial. Late decelerations with absent variability occur when there is insufficient oxygen for myocardial metabolism and/or normal cerebral function. These are likely to occur in the fetus with chronic and prolonged placental insufficiency [38].

Early deceleration of the FHR is similar to late deceleration in shape and duration. However, the nadir of the deceleration is coincident with the peak of the contraction. In most cases, the onset, nadir, and recovery are all coincident to the beginning, peak, and end of the contraction, respectively. Early decelerations are caused by fetal head compression during

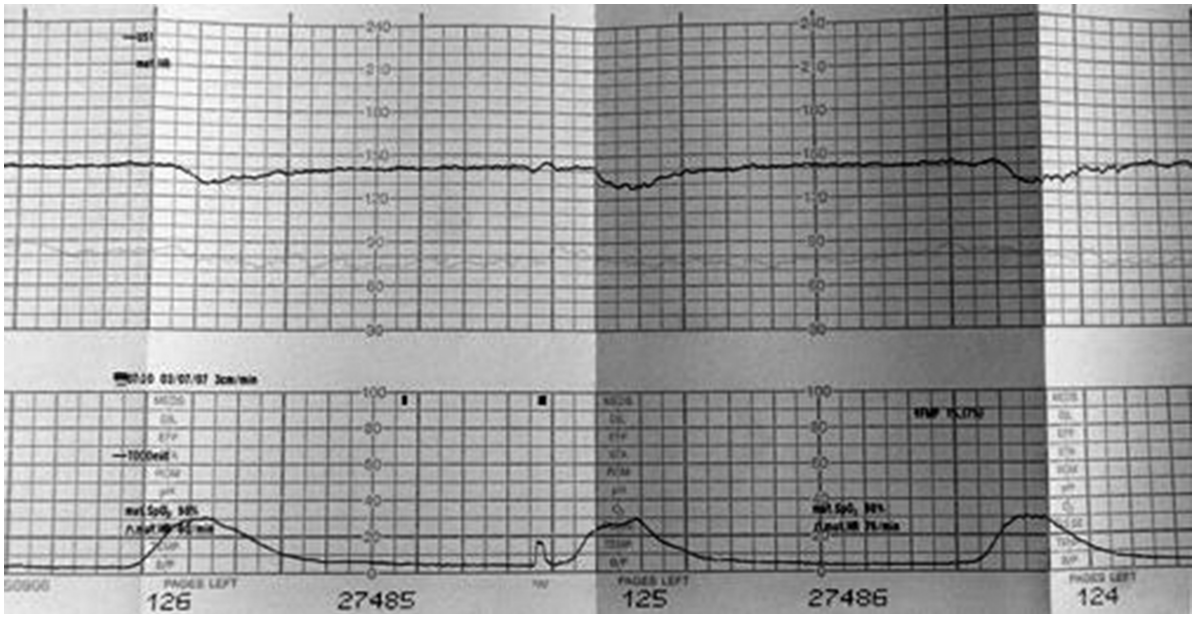


Figure 15.2 Late decelerations with decreased variability and normal baseline.

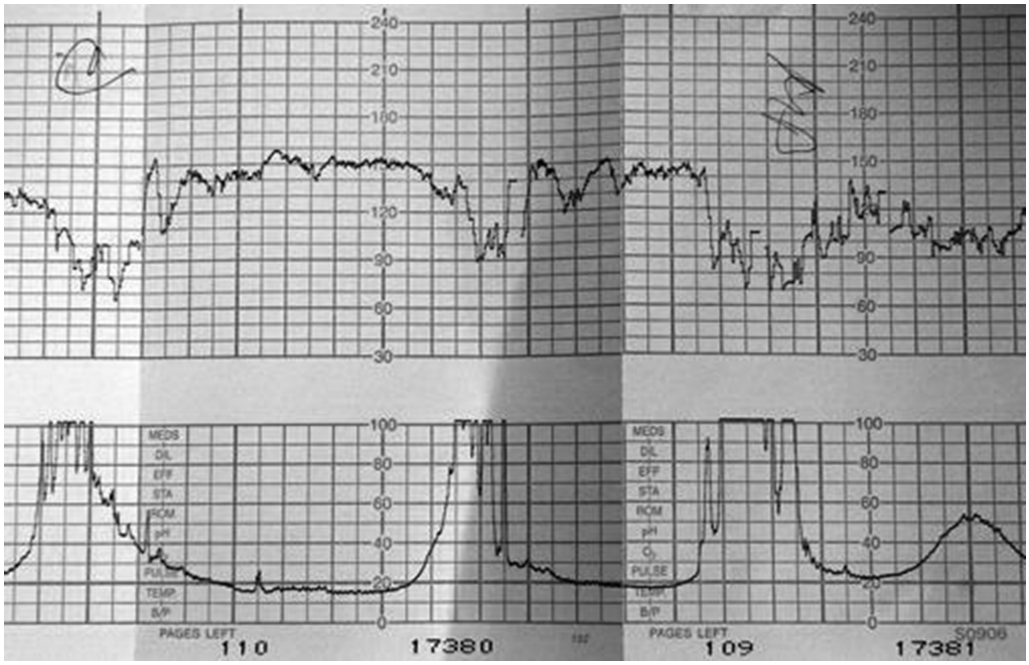


Figure 15.3 Moderate variable decelerations; the depth is between 70 and 80 beats/minute, and the duration is between 30 and 60 seconds.

uterine contraction, resulting in vagal stimulation and slowing of the heart rate. They are not associated with significant fetal academia [38].

Variable decelerations are visually apparent abrupt decreases in FHR from baseline, defined as the onset of deceleration to beginning of nadir within 30 seconds [42]. The decrease in FHR below baseline is at least 15 beats/minute, lasting (from baseline to baseline) between 15 seconds and 2 minutes. When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions (Figure 15.3).

Variable decelerations are secondary to umbilical cord compression that causes baroreceptor stimulation. Umbilical cord compression causes an increase in blood pressure secondary to umbilical artery occlusion. The sudden increase in blood pressure stimulates baroreceptors in the aortic arch. The baroreceptor reflex through the vagus to the medulla oblongata and back to the pacemaker of the heart is extremely fast, and the bradycardic response is quick – thus the abrupt descent of the FHR. If variable decelerations are persistent and/or severe, one may see the development of tachycardia, late return to baseline with progressive decelerations, and/or decreased variability. The evolution of moderate variables to variables with or without variability reflects developing fetal acidemia. Variable decelerations may be classified based on their depth and duration as mild, when the depth is above 80 beats/minute and the duration is less than 30 seconds; moderate, when the depth is between 70 and 80 beats/minute and the duration is between 30 and 60 seconds (Figure 15.3); and severe, when the depth is below 70 beats/minute and the duration is longer than 60 seconds (Figure 15.4). Variable decelerations are generally associated with a favorable outcome [38].

Episodic Decelerations: Prolonged Deceleration

A prolonged deceleration is a subcategory of variable deceleration. The decrease in FHR below the baseline is at least 15 beats/minute lasting more than 2 minutes but less than 10 minutes [29]. The definition refers to a change in baseline rate (e.g., bradycardia) if the prolonged deceleration is longer than 10 minutes in duration. Prolonged decelerations can lead to hypoxia. These patterns may reflect a stepwise decrease in fetal oxygenation secondary to an acute asphyxial insult [43]. The stimulus may be anything that causes a sudden drop in blood flow to the intervillous space (e.g., maternal hypotension or tetanic contractions).

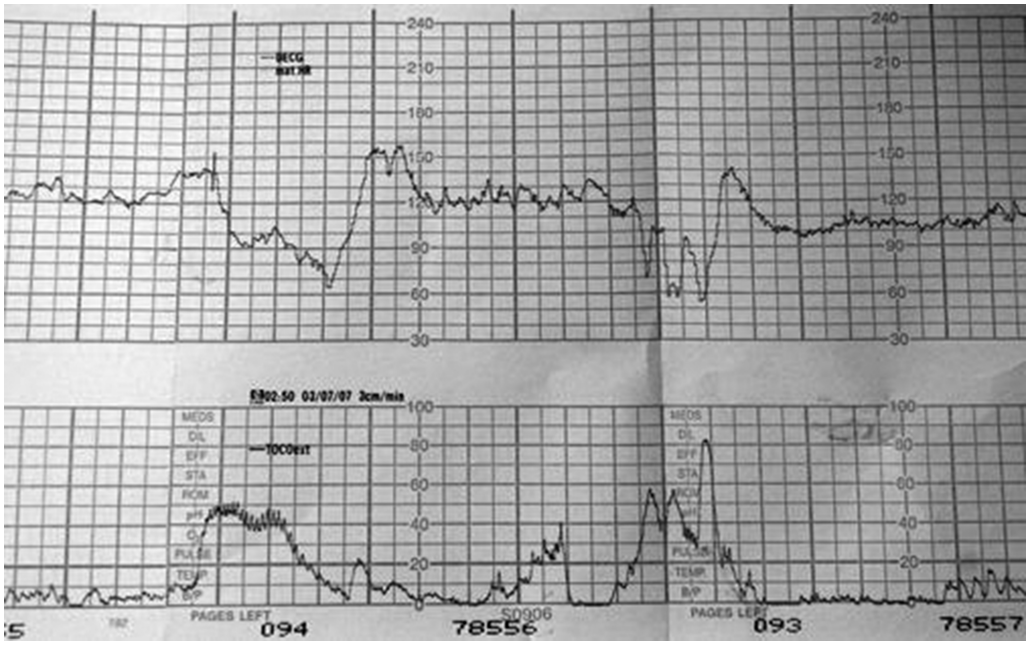


Figure 15.4 Severe variable decelerations; the depth is below 70 beats/minute and the duration is longer than 60 seconds.

Changes in Baseline Rate: Tachycardia and Bradycardia

Nonasphyxial causes of fetal tachycardia include the administration of some drugs such as beta-sympathomimetics or atropine. Nonasphyxial causes that may develop into asphyxia include maternal fever, fetal infection, and fetal cardiac tachyarrhythmia. Tachycardia signifying fetal acidemia is seen most frequently with absent variability, recurrent late decelerations, recurrent variable decelerations, or a combination of these patterns [38]. Mild tachycardia with normal variability and no periodic changes is not associated with fetal academia [30,37,43,45]. Tachycardia can also be seen transiently when the fetus recovers from an acute hypoxial stress. This tachycardia is considered a physiologic response secondary to adrenal stimulation with release of catecholamines.

By definition, bradycardia refers to a baseline rate of less than 110 beats/minute [36]. Uncomplicated bradycardias of more than 80 beats/minute with retained variability are not associated with fetal academia [37,38,40,42]. Nonasphyxial causes of bradycardia include complete heart block and treatment with significant doses of beta-adrenergic blockers. Occasionally, a fetus will have a baseline below 110 beats/minute without pathologic implications.

Like the patterns described earlier, bradycardial episodes in the fetus may cause hypoxia. Bradycardias that occur during the final moments of the second stage (end-stage bradycardias) are an example of an FHR pattern that can lead to hypoxia if sufficiently prolonged and severe. These bradycardias can be secondary to head compression and vagal stimulation or to acute umbilical cord occlusion. The fetus can tolerate end-stage bradycardias as long as the baseline remains above 80 beats/minute and variability is retained [22,43].

If a bradycardia becomes severe, oxygen and carbon dioxide transfer will become impaired, a metabolic acidosis will develop, and variability will diminish. Bradycardias that result from severe hypoxia do not return to baseline and have decreased or absent variability [46]. The progressive flat-line bradycardia can be seen following a period of severe late or variable decelerations. This evolution from severe periodic changes to progressive bradycardia with minimal or absent variability is associated with metabolic acidemia and eventually fetal hypotension. It may be seen in uterine rupture, extensive placental abruption, or just prior to fetal death.

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Sinusoidal Patterns

The sinusoidal pattern was first described in a group of severely affected Rh-isoimmunized fetuses [47,48] but has been noted subsequently in association with fetuses that are anemic for other reasons, such as fetal-maternal bleeding, and in severely asphyxiated infants. This pattern appears as a regular, smooth sine wave–like baseline with a frequency of approximately three to six per minute and an amplitude range of up to 30 beats/minute. The regularity of the waves distinguishes this pattern from long-term variability complexes, which are more crudely shaped and irregular. In addition, sinusoidal patterns exhibit an absence of beat-to-beat or short-term variability. The essential characteristic of a true sinusoidal pattern is extreme regularity and smoothness.

Sinusoidal patterns have also been described in cases of normal infants born without depression or acid-base abnormalities, although in these cases there is dispute about whether the patterns are truly sinusoidal or whether, because of the moderately irregular pattern, they are variants of long-term variability. Such patterns, called *pseudosinusoidal*, are sometimes seen after administration of narcotics to the mother.

The presence of a sinusoidal pattern in an Rh-sensitized patient suggests fetal anemia, generally with a hematocrit below 25%. In cases of fetal-maternal bleeding, the appearance of a striking sinusoidal pattern has given rise to the belief that the pattern is caused by acute anemia rather than by a slow development of anemia, as seen usually with erythroblastosis fetalis [47]. However, there may be a less striking blunted variant in Rh-affected babies. As yet there is little evidence for this, although the association of the acute anemia in fetal arginine vasopressin levels is consistent with the theory. If the pattern is irregularly sinusoidal or pseudosinusoidal, intermittently present, and not associated with intervening periodic decelerations, it is unlikely to indicate fetal compromise [47].

Absent or Minimal Variability

Minimal variability can be secondary to fetal sleep, medication, or early hypoxia. Minimal variability without decelerations is almost always nonasphyxial [40,43]. Absent variability can be asphyxial or nonasphyxial as well. Examples of nonasphyxial causes include CNS depressants, anencephaly, defective cardiac conduction system, and congenital neurologic abnormalities. Conversely, absent variability is seen when the fetus has cerebral asphyxia with accompanying loss of either fine-tuning within the cardioregulatory center in the brain and/or direct myocardial depression. Loss of variability, especially in the presence of other periodic patterns during labor, is the most sensitive indicator of metabolic acidemia in a fetus [22,37,38,43,49] (Figure 15.5).

In summary, when assessing periodic or episodic FHR patterns, variability is the key reflection of intact cerebral oxygenation. Periodic FHR patterns have specific physiologic mechanisms, but because such variant patterns are common during labor, the degree of hypoxia or asphyxia experienced by an individual fetus is not well predicted by them.

Inter- and Intraobserver Variability

There is a wide variation in the way obstetricians interpret and respond to EFM tracings. When four obstetricians, for example, examined 50 CTGs, the interobserver variability (they agreed in only 22% of the cases) and intraobserver variability were wide [37,50,51]. When identical tracings were analyzed by the same personnel 2 months later, the clinicians interpreted 21% of the tracings differently than they did during the first evaluation. Once the tracings were found reassuring, there was less inter- and intraobserver variability [15,37,50,51]. However, knowledge of the neonatal outcome and retrospective review of fetal tracings significantly influenced the analysis of FHR monitoring.

Role of EFM in Predicting Perinatal Asphyxia

The link between the FHR pattern and the actual acid-base status of the fetus is not well defined. Thirty-nine percent of the intrapartum FHR tracings obtained during labor displayed periodic FHR patterns, yet only 2% of all newborns have evidence of metabolic acidemia (pH = 7.1 with a base excess of −12 mmol/L) [15,21,37,49,52].

The original outcome measures used in early studies of FHR monitoring were intrapartum stillbirth and CP. FHR monitoring has been associated with a virtual disappearance of intrapartum stillbirths. Prior to the introduction of FHR monitoring, approximately one-third of all stillbirths or 3/1,000 births occurred in the intrapartum period [4,42]. Currently, the overall incidence of intrapartum stillbirth is at most 0.5/1,000 births. The hope that EFM during labor would abolish

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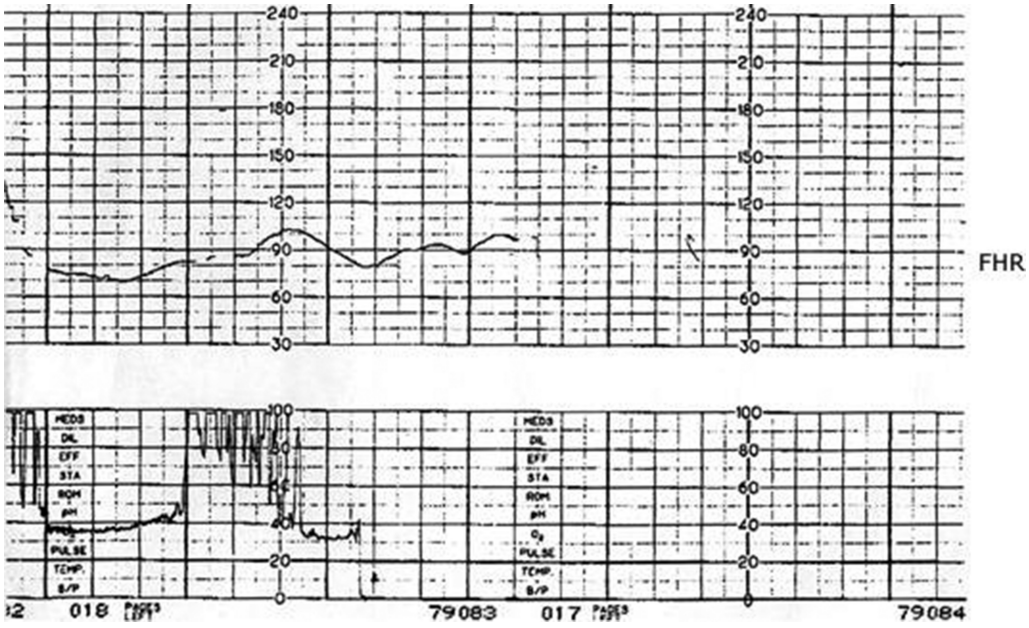


Figure 15.5 No variability and bradycardia. Loss of variability, especially in the presence of other periodic patterns during labor, is the most sensitive indicator of metabolic acidemia in a fetus.

CP through the diagnosis of "fetal distress" and early intervention has proven to be an unrealistic goal because the majority of children with CP develop the disorder prior to labor. In fact, the incidence of CP due to intrapartum asphyxia is on the order of 0.025%, that is, more than 1,000-fold less than the incidence of variant FHR patterns during labor [53]. However, normal baseline rate, moderate variability, accelerations, and absence of periodic patterns are highly predictive of the absence of fetal acidemia. While the presence of absent variability, severe bradycardia, late decelerations (mild or severe), and/or severe variable decelerations is predictive of newborn acidemia.

In summary, CP and neonatal seizures are extremely rare events, and variant heart rate patterns are common. Although there are no specific FHR patterns or groups of patterns that reliably predict brain damage, there is a growing literature that suggests a correlation between absent variability with severe periodic decelerations or bradycardia and progressive metabolic acidemia in the fetus. The degree of acidemia that reliably predicts newborn complications is as yet to be defined.

A full description of an EFM tracing requires a qualitative and quantitative description of

1. Uterine contractions
2. Baseline FHR
3. Baseline FHR variability
4. Presence of accelerations
5. Periodic or episodic decelerations
6. Changes or trends in FHR patterns over time

In April 2008, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine partnered to sponsor a 2-day workshop to revisit nomenclature, interpretation, and research recommendations for intrapartum electronic FHR monitoring [35]. They developed a three-tier system for the categorization of FHR (Figure 15.6). Category I FHR tracings are normal. These tracings are strongly predictive of normal fetal acid-base status at the time of observation. Category I FHR tracings may be followed in a routine manner, and no specific action is required. Category II FHR tracings are indeterminate. These tracings are not predictive of abnormal fetal acid-base status, yet we do not have adequate evidence at present to classify these as Category I or Category III. Category II FHR tracings require evaluation and continued surveillance and reevaluation, taking into account the entire associated clinical circumstances. Category III FHR tracings are abnormal. These tracings are predictive of abnormal fetal acid-base status at the time of observation.

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Category I

Category I fetal heart rate tracings include all of the following:

- Baseline rate: 110–160 beats per minute (bpm)
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

Category II

Category II FHR tracings include all FHR tracings not categorized as Category I or Category III. Category II tracings may represent as appreciable fraction of those encountered in clinical care. Examples of Category II FHR tracings include any of the following:

Baseline rate

- Bradycardia not accompanied by absent baseline variability
- Tachycardia

Baseline FHR variability

- Minimal baseline variability
- Absent baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations

- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations

- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration ≥2 minutes but <10 minutes
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots", or "shoulders"

Category III

Category III FHR tracings include either:

- Absent baseline FHR variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Figure 15.6 The three-tier system for fetal monitoring assessment. (*Source:* Macones et al. [53a].)

Category III FHR tracings require prompt evaluation. Depending on the clinical situation, efforts to expeditiously resolve the abnormal FHR pattern may include, but are not limited to, provision of maternal oxygen, change in maternal position, discontinuation of labor stimulation, and treatment of maternal hypotension.

Soncini et al. studied the intrapartum FHR tracings of 314 singleton fetuses at 37 weeks or more using the NICHD three-tier system for interpretation: category I (normal), category II (indeterminate), and category III (abnormal) [37]. Category II was further divided into category IIA, with moderate FHR variability or accelerations, and category IIB, with minimal/absent FHR variability and no accelerations. The mean values of pH and base excess decreased proportionally as tracings worsened ($p < 0.001$). Interpretation of FHR tracings based on a strictly standardized system was closely associated with umbilical artery acid-base status at delivery.

Management of Nonreassuring FHR

In the case of an EFM tracing with decreased or absent variability without spontaneous accelerations, an effort should be made to elicit one. A meta-analysis of 11 studies of intrapartum fetal stimulation noted that four techniques are available to stimulate the fetus: (1) fetal scalp sampling, (2) Allis clamp scalp stimulation, (3) vibroacoustic stimulation, and (4) digital scalp stimulation [54,56]. Vibroacoustic stimulation and scalp stimulation are the preferred methods to be used because they are less invasive than the other two methods. When there is an acceleration following stimulation, acidosis is unlikely, and labor can continue [56]. When a nonreassuring FHR

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tracing persists and neither spontaneous nor stimulated accelerations are present, a scalp blood sample for the determination of pH or lactate can be considered. Fetal blood sampling from the fetal scalp after adequate dilatation of the cervix was developed at about the same time as continuous electronic FHR monitoring and, in fact, for a time was a competitor to FHR monitoring for primary screening of fetal condition during labor. Later, a combination of the two techniques, with FHR monitoring as the screening tool and fetal blood sampling as a follow-up in cases of uncertainty, was recommended by a number of investigators. Such an approach was used with great enthusiasm by tertiary institutions. However, the sensitivity and positive predictive value of a low scalp pH (defined in the study as less than 7.21 because it was the 75th percentile) to predict umbilical arterial pH less than 7 were 36% and 9%, respectively. More important, the sensitivity and positive predictive value of a low scalp pH to identify a newborn with hypoxic-ischemic encephalopathy were 50% and 3%, respectively [57,58]. These results made the technique impractical, and it never penetrated to any great extent to community hospitals, where the vast majority of North America's 4 million births per year are carried out. Nowadays, the use of lactate measurement in fetal blood sampling is considered more reliable. In a recent Cochrane database review, two completed RCTs and two ongoing trials were analyzed. The two published RCTs considered outcomes for 3,348 mother-baby pairs allocated to either lactate or pH estimation of fetal blood samples when clinically indicated in labor. No statistically significant between-group differences were found for neonatal encephalopathy or death. Fetal blood sampling attempts for lactate and pH estimation were successful in 98.7% and 79.4% of procedures, respectively [58].

Fetal Pulse Oximetry

In May 2000, the Food and Drug Administration (FDA) granted conditional approval of the OxiFirst Fetal Oxygen Saturation Monitoring System for use as an adjunct to EFM [59]. This new technology was designed to improve knowledge of the fetal condition by continuously measuring fetal oxygen saturation in the presence of a nonreassuring FHR pattern. With this technology, a specialized sensor that is positioned against the fetal face is inserted through the dilated cervix after the membranes have ruptured. Once in contact with the fetal skin, the device permits continuous measurement of fetal oxygen saturation during labor [60]. Conditional approval of the device was based primarily on the results of a trial in which 1,010 women with labors complicated by nonreassuring FHR patterns were randomly assigned to either EFM alone or EFM plus continuous fetal pulse oximetry [59]. There was a reduction in the rate of cesarean delivery for the indication of a nonreassuring FHR from 10.2–4.5% ($p = 0.007$) when fetal oximetry was used. However, the rate of cesarean delivery for the indication of dystocia in the oximetry group more than doubled, and thus there was no overall difference in the rate of cesarean delivery between the two groups. The discrepancy in the effect of the oximeter between the two indications for cesarean delivery was unanticipated and not easily explained. In the year 2006, the Maternal-Fetal Medicine Network of the NICHD published a randomized, controlled multicenter study of more than 5,000 women delivering at 14 university hospitals throughout the United States. Knowledge of intrapartum fetal oxygen saturation had no significant effect on either the overall rates of cesarean delivery or specifically for the indications of a nonreassuring FHR or dystocia – or on infant outcomes. Findings for the subgroup of women with FHR abnormalities before randomization were similar to those for the overall cohort [61]. Currently, the ACOG does not support the routine use of fetal pulse oximetry in clinical practice [31].

ST-Waveform Analysis (STAN)

ST-waveform changes in the fetal electrocardiogram (FECG) can provide continuous information during labor about myocardial function and in particular regarding fetal hypoxia [26]. When the fetal heart uses myocardial glycogen by anaerobic metabolism, there is an increase in the T-wave amplitude. An elevation of the ST-segment and T wave, quantified by the ratio between T-wave and QRS amplitudes (T/QRS), identifies fetal heart muscle responding to hypoxia by a surge in stress hormones (catecholamines) that leads to use of glycogen stored in the heart as an extra source of energy. However, when the heart is not fully capable of responding to stress, ST-segment depression and negative T waves can be observed. The ST waveform of the FECG provides continuous information on the ability of the fetal heart muscle to respond to the stress of labor. ST-waveform analysis requires appropriate technology,

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and continuous development of the STAN device has taken place over the years. The STAN S21 and S31 (Neoventa Medical, Moelndal, Sweden) saw the full use of digital signal processing with automatic detection of ST-waveform changes. It combines visual assessment of FHR tracings with automated analysis of the FECG. STAN uses computerized FECG analysis to detect ST-interval changes that may predict myocardial hypoxia.

In 2001, the first Swedish RCT regarding the use of STAN S21 was published [62]. The size of the trial allowed an assessment of outcome related to mode of surveillance among the 351 babies who were admitted to the special-care baby unit. The use of STAN during labor in accordance with fetal heart monitoring reduced the number of babies showing signs of neonatal mortality/morbidity as a consequence of adverse events in labor from 1.0–0.017% (OR 0.17, 95% CI 0.03–0.78, $p < 0.01$). Moreover, there was a significant reduction in moderate or severe neonatal encephalopathy in term newborns with the use of STAN clinical guidelines from 3.3 to 0.4/1,000 (OR 0.12, 95% CI 0.01–0.94, $p < 0.02$). Data from two large RCTs that included 6,826 cases showed that with the support of ST-waveform analysis, the number of babies born with cord artery metabolic acidosis could be reduced from 1.46% to 0.65% (OR 0.44, $p < 0.003$) [63–66]. At the same time, the rate of operative deliveries for fetal distress rates was reduced from 9.2% to 6.8% (OR 0.72, $p < 0.001$), and the rate of moderate or severe encephalopathy was reduced from 3.3 to 0.5/1,000. Thus the use of STAN was shown to reduce the rate of cesarean deliveries for nonreassuring FHR and concomitantly decreased the rate of neonatal encephalopathy.

In 2012, a Dutch meta-analysis reviewed five RCTs that included 15,352 patients and compared ST-waveform analysis and conventional CTG for intrapartum fetal monitoring of singleton pregnancies [67]. ST-waveform analysis showed a nonsignificant reduction in metabolic acidosis (RR 0.72, 95% CI 0.43–1.19, number needed to treat [NNT] 357). ST-waveform analysis significantly reduced the incidence of additional fetal blood sampling (RR 0.59, 95% CI 0.44–0.79, NNT 11), operative vaginal deliveries (RR 0.88, 95% CI 0.80–0.97, NNT 64), and total operative deliveries (RR 0.94, 95% CI 0.89–0.99, NNT 64). There was no reduction in the incidence of metabolic acidosis at birth.

Currently, more than 200 European hospitals are using the STAN methodology as an adjunct to FHR analysis. However, the Maternal-Fetal Medicine Network of the NICHD recently published a multicenter trial in which 11,108 women in labor with a singleton fetus at term were randomly assigned to "open" ($n = 5,532$) or "masked" ($n = 5576$) monitoring with fetal ST-segment analysis [68]. The masked system functioned as a normal FHR monitor. The open system displayed additional information for use when uncertain FHR patterns were detected. The primary outcome was a composite of intrapartum fetal death, neonatal death, an Apgar score of 3 or less at 5 minutes, neonatal seizure, an umbilical artery blood pH of 7.05 or less with a base deficit of 12 mmol/L or more, intubation for ventilation at delivery, or neonatal encephalopathy. The primary outcome occurred in 52 fetuses or neonates of women in the open group (0.9%) and 40 fetuses or neonates of women in the masked group (0.7%) ($p = 0.20$). Only the frequency of a 5-minute Apgar score of 3 or less differed significantly between neonates of women in the open group and those in the masked group (0.3% versus 0.1%, $p = 0.02$). There were no significant between-group differences in the rate of cesarean delivery or any operative delivery. In this large randomized American study, fetal ECG ST-segment analysis used as an adjunct to conventional intrapartum electronic FHR monitoring did not improve perinatal outcomes or decrease operative delivery rates [68].

Innovations in Fetal Monitoring

Noninvasive Fetal ECG (NI-FECG)

NI-FECG can theoretically be performed at an early stage of the pregnancy. However, the NI-FECG always manifests as a mixture of (significant) noise, fetal activity (from each fetus), and a much larger amplitude of maternal activity [69]. The signals overlap in both the time and frequency domains, and therefore, accurate extraction and analysis of the FECG waveform are challenging. The FECG was first observed more than a century ago. Despite significant advances in adult clinical electrocardiography, signal-processing techniques, and the potency of digital processors, few significant advances have been made in the extraction and analysis of NI-FECG. Moreover, there is a less complete clinical knowledge concerning fetal cardiac function and development than for adult cardiology. Another significant barrier to the analysis of NI-FECG is the

paucity of (public) "gold standard" databases with expert annotations and objective signals such as independent measures of the FECG (through direct scalp electrodes), heart rate, ischemia, and rhythm [70].

Some studies have shown that FECG morphology is promising in identifying actionable abnormalities [70]. This includes the QT interval, QRS morphology, and the ST segment. In particular, it is known that QT interval reacts to situations of stress and exercise. It has been shown that a significant shortening of the QT interval is associated with intrapartum hypoxia (resulting in metabolic acidosis) irrespectively of changes in FHR, whereas in normal labor these changes do not occur [69,71,72]. To date, two NI-FECG devices have obtained FDA clearance (and there are two regularly published papers [70] on NI-FECG analysis): the Monica AN24 monitor (Monica Healthcare, Nottingham, UK) and the MERIDIAN monitor from MindChild Medical (North Andover, MA). Both monitors have proved to be accurate in detecting the FHR, and early work on extracting morphologic information has been published. However, these studies are still limited in number and population size, and the positive outcomes of these devices on fetal monitoring are yet to be established.

Newer Fetal Heart Monitoring Technologies

Although voltage-based technologies are most active in the fetal monitoring space, developers are working on other technologies as well. Lifewave, Inc. (Los Altos, CA), is developing a FHR monitoring system based on radiofrequency technology similar to radar that emits a low-energy electromagnetic signal and analyzes the return waveform that has bounced off moving fetal structures in order to calculate a heart rate. The device has the potential to be very small and portable, but it is not yet approved for use by the FDA, and published data are lacking [73].

Significant advances also are being made in areas of fetal magnetocardiography and fetal magnetic resonance imaging (MRI), but both technologies require expensive, fixed equipment. Magnetocardiography uses minute shifts in the magnetic fields produced by fetal electrical cardiac activity; in addition to evaluating anatomy, functional MRI sequences can be used to obtain metabolic information about the developing fetus. Although both magnetocardiography and MRI are poised to make major contributions to the understanding of fetal cardiology, anatomic abnormalities, and metabolic disorders in coming years, neither is likely to have a role in intrapartum management or routine antepartum evaluation [73].

Informatics is playing a major role in helping obstetricians do more with the data they have. For example, automated systems that identify abnormalities in traditional FHR tracings and warn clinicians before a high-risk pattern is ignored may reduce the risk of adverse newborn outcomes [74].

Home Fetal Monitoring

The current communication capabilities allow for remote fetal monitoring and enable women to use fetal monitoring devices at home. The market for fetal Doppler home monitoring is at continuous growth, and gravidas worldwide feel more secure when they have the ability to listen to their fetal heartbeats at home. The biggest concern expressed by healthcare professionals about daily home use of a fetal monitor is that mothers might rely on the monitor rather than consulting the midwife or doctor, and this can lead to false reassurance. This was described in a case study published by the *British Medical Journal* of a woman who falsely reassured herself via fetal home monitor about the condition of her fetus and delayed her arrival to the medical center [75]. This could eventually lead to fetal demise. However, another case (personal communication) described a woman so stressed after being unable to grasp her fetal heart beat via a home Doppler device that when rushing to the hospital experienced a fatal motor vehicle accident.

The current communication capabilities allow for remote fetal monitoring and enable women to use fetal monitoring devices at home and send the fetal tracing in real time to the physician.

On September 9, 2015, Apple announced that mothers can now hear their baby's heart rate in real time using the Apple Watch on their wrist. Apple announced that physicians can now remotely monitor FHR, as well as contractions and the mother's heart rate. Moreover, 3.5 million women have already monitored their pregnancies using Airstrip, a HIPPA-compliant application that works on mobile devices from Android, Microsoft, and Apple and now on the Apple Watch.

The pregnancy care capabilities are possible through AirStrip's subapp called *Sense4Baby*, which pairs with sensors that pregnant women place on their

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bellies. It can distinguish the mother's heart rate from that of her baby. Physicians can send a request to the mother to perform a nonstress test (NST). When the test is complete, the data can be sent to the physician using the Apple Watch.

Current Recommendations

The fetus lives in a state of decreased oxygen tension relative to the adult yet has similar metabolic needs. The physiologic mechanisms that enhance oxygen delivery to fetal tissue are intricate and able to accommodate varying degrees of lowered PO_2 without pathologic sequelae. The biochemical events that herald irreversible asphyxial injury have not been determined in terms of acid-base indices, and because there is wide variability in physiologic responses from fetus to fetus, acid-base status at birth may never be a perfect predictor. To date, there are no clinical markers or specific FHR patterns that reliably predict intrapartum asphyxia. Neither are there any single neonatal indices, such as Apgar scores, umbilical cord gases, or neonatal seizures, that reliably correlate with intrapartum asphyxia severe enough to cause brain injury. The combination of mixed acidemia, a 5-minute Apgar score of 3 or less, seizures within 24 hours of birth, and multiorgan dysfunction, as a constellation, are the indicators most strongly associated with intrapartum asphyxia.

Given these complexities, the goal of clinical FHR monitoring is the detection of patterns that herald a significant risk of acidemia at a value well before irreversible damage occurs. Absent or minimal variability, especially in the presence of late or severe variable decelerations, and bradycardias are the patterns most clearly associated with severe fetal acidemia. Many measures that were developed over the years to improve the prediction of fetal academia fared no better than basic FHR monitoring. These measures include the use of STAN combined with FHR monitoring, fetal scalp blood sampling for pH or lactate determination, and the use of fetal pulse oximetry. The future lies in better tools to detect and analyze FHR monitoring, as well as the development of new approaches, such as the noninvasive FECG monitor and fetal e-health biotelemetry monitoring systems. However, careful assessment of these new technologies must be performed because beyond the apparent advantages, new potential risks may emerge.

References

1. Hon EH. The electronic evaluation of the fetal heart rate: preliminary report. *Am J Obstet Gynecol* 1958; **75**(6): 1215–30.
2. Hon EH, Hess OW. Instrumentation of fetal electrocardiography. *Science* 1957; **125**(3247): 553–4.
3. Benson RC, et al. Fetal heart rate as a predictor of fetal distress: a report from the collaborative project. *Obstet Gynecol* 1968; **32**(2): 259–66.
4. Lilien AA. Term intrapartum fetal death. *Am J Obstet Gynecol* 1970; **107**(4): 595–603.
5. Jepson JH. Factors influencing oxygenation in mother and fetus. *Obstet Gynecol* 1974; **44**(6): 906–14.
6. Quilligan EJ, Paul RH. Fetal monitoring: is it worth it? *Obstet Gynecol* 1975; **45**(1): 6–100
7. Yeh SY, DIaz F, Paul RH. Ten-year experience of intrapartum fetal monitoring in Los Angeles County/University of Southern California Medical Center. *Am J Obstet Gynecol* 1982; **143**(5): 496–500.
8. MacDonald D, et al. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. *Am J Obstet Gynecol* 1985; **152**(5): 524–39.
9. Parer JT. Roundtable: Part I. The Dublin trial of fetal heart rate monitoring: the final word? *Birth* 1986; **13**(2): 119–21.
10. Grant A, et al. Cerebral palsy among children born during the Dublin randomised trial of intrapartum monitoring. *Lancet* 1989; **8674**(2): 1233–6.
11. Banta HD, Thacker SB. Electronic fetal monitoring. Lessons from a formative case of health technology assessment. *Int J Technol Assess Health Care* 2002; **18**(4): 762–70.
12. Centers for Disease Control. Rates of cesarean delivery–United States, 1991. *MMWR Morb Mortal Wkly Rep* 1993; **42**(15): 285–9.
13. Chez BF, Baird SM. Electronic fetal heart rate monitoring: where are we now? *J Perinat Neonatal Nurs* 2011; **25**(2): 180–92.
14. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. *Cochrane Database Syst Rev* 2013; **5**: CD006066.
15. Maso G, et al. Intrapartum fetal heart rate monitoring interpretation in labour: a critical appraisal. *Minerva Ginecol* 2015; **67**(1): 65–79.
16. Redman C. 45 years of fetal heart rate monitoring in BJOG. *BJOG* 2015; **122**(4): 536.
17. Little WJ. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of

.016

the child, especially in relation to deformities. *Clin Orthop Relat Res* 1966; **46**: 7–22.

18. Hon EH. Apparatus for continuous monitoring of the fetal heart rate. *Yale J Biol Med* 1960; **32**(5): 397–9.
19. Haverkamp AD, et al. The evaluation of continuous fetal heart rate monitoring in high-risk pregnancy. *Am J Obstet Gynecol* 1976; **125**(3): 310–20.
20. Parer JT. Fetal heart-rate monitoring. *Lancet* 1979; **2**(8143): 632–3.
21. Thacker SB, Stroup DF, Peterson HB. Efficacy and safety of intrapartum electronic fetal monitoring: an update. *Obstet Gynecol* 1995; **86**(4 Pt 1): 613–20.
22. Larma JD, et al. Intrapartum electronic fetal heart rate monitoring and the identification of metabolic acidosis and hypoxic-ischemic encephalopathy. *Am J Obstet Gynecol* 2007; **197**(3): 301.e1–8.
23. Nelson KB, et al. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. *N Engl J Med* 1996; **334**(10): 613–8.
24. Spong CY. Electronic fetal heart rate monitoring: another look. *Obstet Gynecol* 2008; **112**(3): 506–7.
25. Grivell RM, et al. Antenatal cardiotocography for fetal assessment. *Cochrane Database Syst Rev* 2015; **9**: CD007863.
26. Finnemore A, Groves A. Physiology of the fetal and transitional circulation. *Semin Fetal Neonatal Med* 2015; **20**(4): 210–6.
27. Thornburg KL, Louey S. Uteroplacental circulation and fetal vascular function and development. *Curr Vasc Pharmacol* 2013; **11**(5): 748–57.
28. Zhang L. Uteroplacental circulation and maternal/fetal health. *Curr Vasc Pharmacol* 2013; **11**(5): 543.
29. Richardson BS. Fetal adaptive responses to asphyxia. *Clin Perinatol* 1989; **16**(3): 595–611.
30. Sadovsky G, Nicolaides KH. Reference ranges for fetal heart rate patterns in normoxaemic nonanaemic fetuses. *Fetal Ther* 1989; **4**(2–3): 61–8.
31. Martin CB, Gingerich B. Uteroplacental physiology. *JOGN Nurs* 1976; **5**(5 Suppl.):16s–25s.
32. Anderson PA, et al. In utero right ventricular output in the fetal lamb: the effect of heart rate. *J Physiol* 1987; **387**: 297–316.
33. Anderson PA, et al. The effect of heart rate on in utero left ventricular output in the fetal sheep. *J Physiol* 1986; **372**: 557–73.
34. National Institute of Child Health and Human Development. Electronic fetal heart rate monitoring: research guidelines for interpretation. National Institute of Child Health and Human Development Research Planning Workshop. *Am J Obstet Gynecol* 1997; **177**(6): 1385–90.
35. Parer JT, Ikeda T, King TL. The 2008 National Institute of Child Health and Human Development report on fetal heart rate monitoring. *Obstet Gynecol* 2009; **114**(1): 136–8.
36. American College of Obstetrics and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles (ACOG Practice Bulletin No. 106). *Obstet Gynecol* 2009; **114**(1): 192–202.
37. Soncini E, et al. Intrapartum fetal heart rate monitoring: evaluation of a standardized system of interpretation for prediction of metabolic acidosis at delivery and neonatal neurological morbidity. *J Matern Fetal Neonatal Med* 2014; **27**(14): 1465–9.
38. Parer JT, Ikeda T. A framework for standardized management of intrapartum fetal heart rate patterns. *Am J Obstet Gynecol* 2007; **197**(1): 26.e1–6.
39. Park YS, et al. Difference of fetal heart rate accelerations based on 10 and 15 beats per minute. *J Obstet Gynaecol Res* 2010; **36**(2): 291–5.
40. Salamalekis E, et al. Computerized analysis of fetal heart rate variability using the matching pursuit technique as an indicator of fetal hypoxia during labor. *J Matern Fetal Neonatal Med* 2006; **19**(3): 165–9.
41. Ross MG, et al. Correlation of arterial fetal base deficit and lactate changes with severity of variable heart rate decelerations in the near-term ovine fetus. *Am J Obstet Gynecol* 2013; **208**(4): 285.e1–6.
42. Paul RH, et al. Clinical fetal monitoring. VII. The evaluation and significance of intrapartum baseline FHR variability. *Am J Obstet Gynecol* 1975; **123**(2): 206–10.
43. Parer JT, et al. Fetal acidemia and electronic fetal heart rate patterns: is there evidence of an association? *J Matern Fetal Neonatal Med* 2006; **19**(5): 289–94.
44. Ozden S, Demirci F. Significance for fetal outcome of poor prognostic features in fetal heart rate traces with variable decelerations. *Arch Gynecol Obstet* 1999; **262**(3–4): 141–9.
45. Pillai M, James D. The development of fetal heart rate patterns during normal pregnancy. *Obstet Gynecol* 1990; **76**(5 Pt 1): 812–6.
46. Honjo S, Yamaguchi M. Umbilical artery blood acid-base analysis and fetal heart rate baseline in the second stage of labor. *J Obstet Gynaecol Res* 2001; **27**(5): 249–54.
47. Reddy A, Moulden M, Redman CW. Antepartum high-frequency fetal heart rate sinusoidal rhythm: computerized detection and fetal anemia. *Am J Obstet Gynecol* 2009; **200**(4): 407.e1–6.
48. Egley C. The clinical significance of intermittent sinusoidal fetal heart rate. *Am J Obstet Gynecol* 1999; **181**(4): 1041–2.

16:14:56
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49. Frasch MG, et al. Correlating multidimensional fetal heart rate variability analysis with acid-base balance at birth. *Physiol Meas* 2014; **35**(12): L1–12.

50. Uccella S, et al. Interobserver reliability to interpret intrapartum electronic fetal heart rate monitoring: does a standardized algorithm improve agreement among clinicians? *J Obstet Gynaecol* 2015; **35**(3): 241–5.

51. Torres J, De Vries R, Low LK. Consumer information on fetal heart rate monitoring during labor: a content analysis. *J Perinat Neonatal Nurs* 2014; **28**(2): 135–43.

52. Yudkin PL, et al. Assessing the contribution of birth asphyxia to cerebral palsy in term singletons. *Paediatr Perinat Epidemiol* 1995; **9**(2): 156–70.

53. Nelson KB, Blair E. Prenatal factors in singletons with cerebral palsy born at or near term. *N Engl J Med* 2015; **373**(10): 946–53.

53a. Macones GA, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol* 2008; **112**: 661–6.

54. Skupski DW, Eglington GS. Intrapartum fetal stimulation tests: a meta-analysis. *Obstet Gynecol* 2002; **100**(4): 830.

55. Lazebnik N, et al. Response of fetal heart rate to scalp stimulation related to fetal acid-base status. *Am J Perinatol* 1992; **9**(4): 228–32.

56. East CE, et al. Vibroacoustic stimulation for fetal assessment in labour in the presence of a nonreassuring fetal heart rate trace. *Cochrane Database Syst Rev* 2013; **1**: CD004664.

57. Westgren M, et al. Lactate compared with pH analysis at fetal scalp blood sampling: a prospective randomised study. *Br J Obstet Gynaecol* 1998; **105**(1): 29–33.

58. East CE, et al. Intrapartum fetal scalp lactate sampling for fetal assessment in the presence of a non-reassuring fetal heart rate trace. *Cochrane Database Syst Rev* 2015; **5**: CD006174.

59. Garite TJ, et al. A multicenter controlled trial of fetal pulse oximetry in the intrapartum management of nonreassuring fetal heart rate patterns. *Am J Obstet Gynecol* 2000; **183**(5): 1049–58.

60. Yam J, Chua S, Arulkumaran S. Intrapartum fetal pulse oximetry. I. Principles and technical issues. *Obstet Gynecol Surv* 2000; **55**(3): 163–72.

61. Bloom SL, et al. Fetal pulse oximetry and cesarean delivery. *N Engl J Med* 2006; **355**(21): 2195–202.

62. Amer-Wahlin I, et al. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomised controlled trial. *Lancet* 2001; **358** (9281): 534–8.

63. Potti S, Berghella V. ST waveform analysis versus cardiotocography alone for intrapartum fetal monitoring: a meta-analysis of randomized trials. *Am J Perinatol* 2012; **29**(8): 657–64.

64. Salmelin A, et al. Fetal monitoring with computerized ST analysis during labor: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2013; **92**(1): 28–39.

65. Kessler J, Moster D, Albrechtsen S. Delay in intervention increases neonatal morbidity in births monitored with cardiotocography and ST-waveform analysis. *Acta Obstet Gynecol Scand* 2014; **93**(2): 175–81.

66. Olofsson P, et al. A critical appraisal of the evidence for using cardiotocography plus ECG ST interval analysis for fetal surveillance in labor. I. the randomized controlled trials. *Acta Obstet Gynecol Scand* 2014; **93**(6): 556–68.

67. Westerhuis ME, et al. Identification of cases with adverse neonatal outcome monitored by cardiotocography versus ST analysis: secondary analysis of a randomized trial. *Acta Obstet Gynecol Scand* 2012; **91**(7): 830–7.

68. Belfort MA, et al. A randomized trial of intrapartum fetal ECG ST-segment analysis. *N Engl J Med* 2015; **373**(7): 632–41.

69. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. *Cochrane Database Syst Rev* 2013; **5**: CD000116.

70. Sletten J, Kessler J. QRS abnormalities of the fetal electrocardiogram, and their implications for ST-interval analysis during labor. *Acta Obstet Gynecol Scand* 2015; **94**(10): 1128–35.

71. Stampalija T, et al. Fetal and maternal heart rate confusion during intra-partum monitoring: comparison of trans-abdominal fetal electrocardiogram and Doppler telemetry. *J Matern Fetal Neonatal Med* 2012; **25**(8): 1517–20.

72. Signorini MG, Fanelli A, Magenes G. Monitoring fetal heart rate during pregnancy: contributions from advanced signal processing and wearable technology. *Comput Math Methods Med*, 2014; **2014**: 707581.

73. Adam J. The future of fetal monitoring. *Rev Obstet Gynecol* 2012; **5**: 132e–136e.

74. Hamilton EF, Warrick PA. New perspectives in electronic fetal surveillance. *J Perinat Med* 2013; **41**(1): 83–92.

75. Chakladar A, Adams H. Dangers of listening to the fetal heart at home. *BMJ* 2009; **339**: b4308.

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Chapter 16

Clinical Manifestations of Hypoxic-Ischemic Encephalopathy

Jin S. Hahn

Introduction

Hypoxic-ischemic encephalopathy (HIE) is a well-recognized clinical syndrome and the most common cause of acute neurologic impairment and seizures in the neonatal period [1–5]. *Neonatal encephalopathy* is a term used to describe newborns with acute neurologic syndromes and encephalopathy that may be caused by diverse processes including hypoxia-ischemia, infections, inflammation, trauma, and metabolic disorders. Neonatal encephalopathy due to perinatal asphyxia can lead to neurologic sequelae and cerebral palsy (CP), but recent literature has shown that only a small percentage of children with CP had intrapartum asphyxia as a possible etiology [6–8]. More emphasis has been placed on antenatal events as having a greater association with CP [9]. Although newborns with neonatal encephalopathy may have antenatal risk factors associated with other findings, such as delayed onset of respiration, arterial cord blood pH of less than 7.1, and multiorgan failure, the MRI most often shows signs of acute perinatal insult [10]. Therefore, hypoxic-ischemic injury during the perinatal period can lead to a neurologic syndrome in the newborn period, that is, HIE, and subsequent neurologic sequelae in the survivors. Recognizing and understanding HIE is therefore important.

Clinical Features and Management

The clinical features in the infant with HIE are presented here by first describing a general approach to the evaluation. Then the specific clinical features, diagnostic studies, prognosis, and management of these infants are described.

General Evaluation

The initial assessment of the infant with suspected HIE relies on obtaining a thorough history and carrying out a careful physical examination. The history should be directed toward determining whether there were any specific antenatal factors that might account for the disorder. Review of the maternal history, fetal monitoring studies, fetal ultrasonographic findings, and fetal acid-base measurements is essential. Information regarding examination of the placenta should also be obtained. Special attention should be paid to any possible history of maternal infection and chorioamnionitis. Family history is also important because genetic factors may play a role in determining the severity of the HIE after a hypoxic-ischemic insult.

A general physical examination is required to establish the infant's gestational age, cardiopulmonary status, presence of congenital anomalies, and growth parameters. A carefully performed neurologic examination is essential to obtain information about the infant's current status. This information is used to determine additional evaluations that are critical in establishing a prognosis. Many studies have shown that the neonatal neurologic examination is a valuable predictor of outcome [2,11]. A detailed neurologic examination provides the most information about the localization and severity of the encephalopathy, but a clinical grading of encephalopathy should be performed initially [11].

Neurologic Assessment in HIE

If the degree of hypoxic-ischemic insult at or shortly before delivery is of sufficient magnitude to cause long-term neurologic sequelae, newborns will manifest signs of neurologic dysfunction shortly after birth, often within hours. Conversely, the absence of significant neonatal encephalopathy during the newborn period during the first 24 hours of life implies the absence of significant hypoxic-ischemic insult during the intrapartum period.

Neurologic dysfunctions due to hypoxic-ischemic insult include altered level of consciousness and reactivity, altered tone, and seizures. There is a correlation

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between the severity and duration of the hypoxic-ischemic insult and the severity of the encephalopathy. Careful documentation of the neurologic examination and grading of the encephalopathy will help to determine the severity of the hypoxic-ischemic insult and ultimate outcome.

Several grading systems have been developed to assess the severity of HIE. One of the more widely used scales is the staging system developed by Sarnat and Sarnat, in which the clinical stages of HIE are divided into three levels [12]. The major clinical features that are used in the assessment are the infant's level of consciousness, cranial nerve findings, muscle tone, deep tendon reflexes, neonatal reflexes, spontaneous motor activity, and autonomic function (Table 16.1). The degree of encephalopathy is then graded as mild, moderate, or severe. An updated version has been used by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network to identify newborn infants who may be eligible for hypothermia and neuroprotective treatments [13]. Encephalopathy is graded on the basis of six categories: (1) level of consciousness, (2) spontaneous activity, (3) posture, (4) tone, (5) primitive reflexes, and (6) autonomic nervous system. Serial examinations may be performed to track the evolution of the encephalopathy.

Infants with a *mild* degree of encephalopathy (stage 1) often have variable levels of consciousness with periods of irritability and hyperalertness. They often feed poorly, have disturbed sleep-wake cycles with a preponderance of active sleep, and are described as "jittery." Jitteriness is best described as a spontaneous or stimulus-induced myoclonus (nonepileptic). Findings on cranial nerve examination are normal. Muscle tone is normal or increased, and the deep tendon reflexes are hyperactive. The Moro reflex is often exaggerated, but other neonatal reflexes are normal. Pupillary dilation and tachycardia are observed frequently. Mild encephalopathy usually lasts for less than 24 hours and is generally associated with a favorable prognosis [12,14].

Newborn term infants with *moderate* encephalopathy (stage 2) manifest lethargy, hypotonia, hyporeflexia, and seizures. Although lethargic, they can be aroused with auditory and tactile stimuli. Feeding is extremely poor. Muscle tone is decreased, with a

Table 16.1 Clinical Staging and Outcome of HIE

Severity of encephalopathy	Mild	Moderate	Severe
Level of consciousness	Alert or hyperalert	Lethargy	Stupor or coma
Tone	Normal or hypertonia	Hypotonia (focal or general)	Flaccidity
Tendon reflexes	Increased	Increased	Depressed or absent
Primitive reflexes			
Suck	Weak	Weak to absent	Absent
Moro	Exaggerated	Incomplete	Absent
Autonomic function			
Pupils	Dilated	Constricted	Deviated, dilated, or nonreactive to light
Heart rate	Tachycardia	Bradycardia	Variable
Respiration	Normal	Periodic breathing	Apnea
Others	Irritability, jitteriness	Brainstem dysfunction	±Elevated intracranial pressure
Seizures	Absent	±	Frequent, often refractory to anticonvulsants
EEG background	Normal	Low voltage, periodic or paroxysmal	Periodic or isoelectric
Outcome	Normal	20–40% abnormal	Death or 100% abnormal

Sources: Based on Sarnat and Sarnat [12], Roland and Hill [4], and Shankaran et al. [13].

prominent head lag, a positive scarf sign, and a poor response to the Landau maneuver. Exaggerated deep tendon reflexes with clonus are elicited. Jaw clonus may be observed. Cranial nerve examination reveals a weak suck and decreased gag reflex. Spontaneous motor activity is decreased, and the observed movements may include spontaneous myoclonus or signs of extrapyramidal dysfunction. Pupils are often constricted, and periodic breathing associated with bradycardia may be present. Seizures may occur and must be differentiated from other abnormal movements and behaviors. The duration of moderate encephalopathy is usually 2–14 days. Recovery is heralded by the disappearance of myoclonus, increased alertness, and improved suck. Neurologic sequelae occur in approximately 20–40% of infants with moderate encephalopathy [14,15], especially if the abnormal neurologic signs persist for over 1 week.

Infants who are profoundly affected display *severe* encephalopathy (stage 3), characterized by stupor or coma, flaccidity, and unresponsiveness to noxious stimuli [12]. They also have episodic decerebrate (extensor) posturing and poor brainstem function. Deep tendon and neonatal reflexes are absent. The pupils are poorly reactive or fixed, and the oculocephalic reflex and sucking reflex are absent. Seizures are very common. The infant often has bradycardia, systemic hypotension, irregular respirations, periodic breathing, and apnea. The duration of this stage ranges from hours to weeks. Mortality rate is high, and nearly all the survivors will develop neurologic sequelae [14]. If the infant recovers, a period of extensor hypertonia and brainstem dysfunction (abnormal swallowing, sucking movements) may occur.

Newborns with perinatal hypoxic-ischemic brain injury may transition from one stage to another. Most infants who initially manifest mild encephalopathy also develop moderate encephalopathy before recovering [12]. More severely affected infants begin in the moderate encephalopathic state shortly after delivery. Often the clinical manifestations of severe encephalopathy may not be apparent until day 2 or 3 after birth, when cerebral edema is at its maximum. Clinically, when severe cerebral edema is present, the anterior fontanel is often bulging or tense, and the cranial sutures are splayed.

During the first week, infants with moderate or severe encephalopathy may show signs of neurologic improvement. However, abnormalities in tone, bulbar function, hyperactive reflexes, and seizures may persist for days or weeks. If infants remain in moderate or severe encephalopathic states for more than 7 days, there is a high incidence of long-term neurologic sequelae [12].

Hypothermia treatments may alter the evolution of the stages of encephalopathy. In the NICHD study, encephalopathy improved steadily over the first 3 days in infants treated with hypothermia, whereas improvements occurred later in the control group [16]. Persistence of severe stage of encephalopathy after being treated with hypothermia is associated with greater likelihood of death or sequelae. It is also important to take into account medications, and metabolic derangements may suppress cerebral function, making it difficult to assess the true severity of encephalopathy.

Laboratory Evaluations

Laboratory investigations in infants with HIE should include measurements of cord blood gases, arterial blood gas and pH levels, serum electrolyte levels (including calcium and magnesium), and serum glucose, blood urea nitrogen, creatinine, and hepatic enzyme levels. A lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure, cell count, and protein and glucose levels should be performed if there is a clinical concern for CNS infection.

Many studies have evaluated various biomarkers in blood, urine, and CSF that would be useful for clinical assessment or prognostication. These include lactate, creatine kinase brain isoenzyme (CK-BB), and neuron-specific enolase in CSF and serum catecholamines, S100β, interleukin 6 (IL-6), IL-8, and IL-1β in blood [17]. However, a systematic review found that most of these biomarkers are not specific for HIE and correlate poorly with neurologic outcome [18]. The abnormalities found in the majority of these parameters reflect the severity of the systemic insult rather than the severity of the insult to the brain. The optimal timing for measuring the biomarker is also not well understood. A recent pilot study suggests that glial fibrillary acidic protein (GFAP) and other inflammatory markers may be useful biomarkers [19], but larger controlled studies are needed before these tests can be used clinically.

Electroencephalography

The electroencephalogram (EEG) is a valuable measure of cerebral function that can be performed at the bedside. It complements the clinical examination in

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establishing the severity of the encephalopathy and in determining the prognosis [20]. The diagnosis of seizures in this age group depends on the EEG because a significant number of abnormal behavior patterns thought to represent seizures actually represent nonepileptic phenomena [3,21]. Furthermore, the clinical seizure type in these infants may often be subtle and fragmentary or masked by anticonvulsant therapy, making the EEG essential for the diagnosis of seizures. The EEG is also helpful in assessing the degree of cerebral dysfunction and providing information about neurologic prognosis. Severely depressed backgrounds, such as a suppression-burst or isoelectric pattern, indicate severe cerebral dysfunction and usually portend a poor prognosis. The presence of status epilepticus on the EEG also carries an unfavorable prognosis. EEG patterns with less severe background disturbance that revert to normal after the first week usually indicate a more favorable prognosis. The application of EEG in the evaluation of the encephalopathic newborn is described in detail in Chapter 17.

Amplitude-integrated EEG (aEEG) is often used to monitor neonates with HIE. This method provides a bedside display of the time-compressed EEG background patterns, which can be useful for assessing the severity of the encephalopathy and monitoring for seizures [22]. In HIE, aEEG changes are classified by (1) voltage criteria (normal, moderately abnormal, or severely abnormal) and (2) background patterns (continuous normal voltage, discontinuous normal voltage, burst suppression, continuous low voltage, or flat trace) [17].

A systematic review and meta-analysis of prognostic tests found EEG and aEEG performed during the first week to be the most valuable [23]. Combining aEEG abnormality with the grade of encephalopathy may further improve prognostic value [17].

Other neurophysiologic measures of nervous system function, such as somatosensory, brainstem, and visual evoked potential (VEP), have been used to evaluate newborns with HIE [24] but are not routinely used as part of the acute evaluation. Among the evoke potential tests, VEP has the highest predictive value [23].

Neuroimaging Studies

Neuroimaging studies are an essential component of the assessment of the newborn with HIE. It is helpful for determining the nature, severity, and extent of the hypoxic-ischemic brain injury.

Cranial ultrasonography has proven to be a valuable technique in the diagnosis of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), which primarily affect premature infants. This study can be readily carried out at the bedside in newborns. However, the predictive accuracy is poor in term infants with hypoxic-ischemic insults.

Computed tomography (CT) is widely used to assess the nature and extent of cerebral injury, especially in term infants. It is more useful in assessing cortical and hemorrhagic injury. It can be obtained rapidly, often without the need for sedation. CT scans in asphyxiated newborns may show focal or multifocal areas of decreased attenuation in the cerebral gray or white matter. These abnormal areas likely represent areas of ischemia or cerebral edema. Diffuse cerebral edema can manifest as loss of gray-white matter differentiation, effacement of sulcal spaces, and slitlike ventricles. CT is also useful for detecting acute intracranial hemorrhage.

Magnetic resonance imaging (MRI) is the method of choice to assess the newborn brain. MRI has been used to document in the neonate various clinicopathologic syndromes of hypoxic-ischemic brain injury, including basal ganglia and thalamic injury, parasagittal cerebral injury, PVL, focal ischemic lesions, and selective neuronal necrosis [25–28]. Diffusion-weighted MRI and magnetic resonance spectroscopy have also been used to assess the extent of cerebral injury and provide valuable prognostic information [23,29–31]. The ideal time to assess for brain injury is between the fourth and eighth day after HIE onset [23]. The disadvantages of MRI include the prolonged scanning time and impaired ability to monitor the mechanically ventilated sick newborns. Further details on neuroimaging studies in the newborn are available in Chapter 18.

Patterns of Injury and Clinical Syndromes

The cerebral injury from perinatal hypoxic-ischemic brain injury results in specific patterns of regional injury, the topography of which is maturation dependent. This regional vulnerability is caused in part by dysregulation of cellular processes that are critical for normal brain development. For example, the increased density of glutamate receptors normally present in rapidly developing brain regions (e.g., the basal ganglia) renders these areas exquisitely sensitive

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to hypoxic-ischemic insults. The specific type of lesion also varies with the characteristics of the primary insult and the subsequent management. MRI neuroimaging studies have correlated the specific patterns of neuroradiologic alterations with the specific clinicopathologic syndromes. Recognition of these disorders provides an understanding of the mechanisms leading to their development and allows prediction of possible neurologic disabilities. The neuropathologic changes can be divided into lesions that are the result of primary damage to specific types of cells and structures and those due to hemorrhage.

The pathologic changes observed in the term infant are different from those seen in the premature infant (Table 16.2). The term infant most commonly is observed to have neuropathologic changes involving primarily the gray matter and specific neuroanatomic structures in both the cortical and subcortical regions. IVH occurs in the term infant, but the pathogenic mechanisms are different from those in the preterm infant. On the contrary, periventricular hemorrhage or intraventricular hemorrhage is the most common neuropathologic finding in the premature infant. Pathologic changes in the white matter are the next most common disorder, followed by lesions involving selected neuronal populations.

The patterns of brain injury observed in the term newborn can be categorized into lesions involving four major areas of the CNS: cortex, deep gray matter nuclei, brainstem, and cerebellum. There is often an overlap of these pathologic processes, but primary involvement of one of these regions results in specific clinical characteristics both acutely and in the long term. The clinicopathologic correlates of the major types of hypoxic-ischemic brain injury are presented here.

Table 16.2 Patterns of Injury in Neonatal HIE

Full-term newborn	Preterm newborn
Parasagittal border-zone "watershed" lesions	Intraventricular or periventricular hemorrhage
Necrosis of deep gray nuclei Basal ganglia Thalamus Diencephalon	Periventricular leukomalacia
Perirolandic gyri and posterior limb of internal capsule	
Brainstem necrosis Selective nuclei	
Selective nuclei	
Diffuse cerebral edema	
Focal brain injury Arterial occlusion Venous occlusion	

Parasagittal Border Zone Injury

This form of cortical injury resulting from a general decrease in the cerebral blood flow (ischemia) is referred to as the *watershed infarction* because the disorder involves the border zones of the three major arterial supply zones. The injury is bilateral and usually symmetric. *Ulegyria*, a term describing cortical gyri that are atrophic, particularly at the depth of sulci, is the chronic lesion resulting from this particular brain injury (Figure 16.1). In one autopsy series of neurologically handicapped children, 30 of 153 subjects had this lesion in the parasagittal watershed region [32]. This type of injury most often affects the term infant and appears to be due to mild to moderate hypotension in the peripartum period [27]. The hypotension leads to subacute *partial hypoxic-ischemic injury* that primarily involves the vascular border zones. More prolonged partial hypoxic-ischemic injury may lead to a more diffuse neuronal necrosis with relative sparing of the deep gray matter.

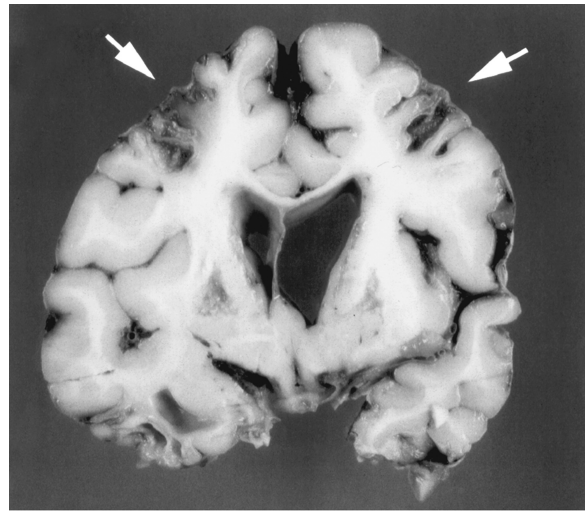


Figure 16.1 Coronal section of a 13-year-old boy who had spastic quadriplegia and intellectual disability as a result of perinatal brain injury shows bilateral parasagittal (border-zone) atrophy and necrosis (arrows). The cortex in these regions shows thinning (ulegyria) and laminar necrosis that are consistent with remote anoxic/ischemic injury.

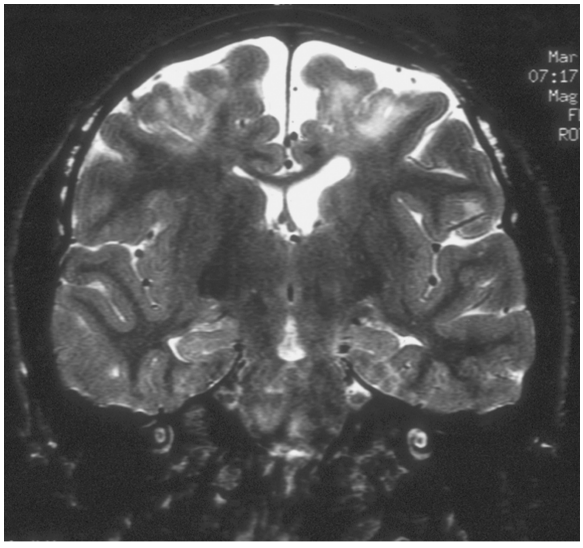


Figure 16.2 Coronal T2-weighted MRI (TE 93/Ef, TR6000) of a 12-year-old girl who had a history of neonatal hypoxic-ischemic encephalopathy and seizures shows bilateral parasagittal signal hyperintensities consistent with border-zone ischemia.

Cortical infarcts in the watershed regions are difficult to diagnose in the neonatal period. This is most likely because computed tomographic (CT) and ultrasound techniques do not visualize this region well. Radioisotope studies and positron-emission tomography have identified infants with decreased cerebral blood flow in the parasagittal cortex [33,34]. MRI is useful in identifying these infants earlier in the course, especially when coronal images are obtained (Figure 16.2).

Newborns with parasagittal injury often have a moderate encephalopathy in the neonatal period and may show evidence of weakness of the shoulder girdles and the proximal extremities. Seizures can be observed, especially in more severely affected infants. The neurologic sequelae often include a spastic quadriparesis with varying degrees of intellectual impairment. The topographic localization (i.e., preferential injury to the parietal, posterior temporal, and occipital cortices) may account for the frequent occurrence of language and visuospatial disabilities.

Selective Injury

Deep Gray Nuclei

Lesions in the deep gray nuclei (thalamus and basal ganglia) have been described for more than a century

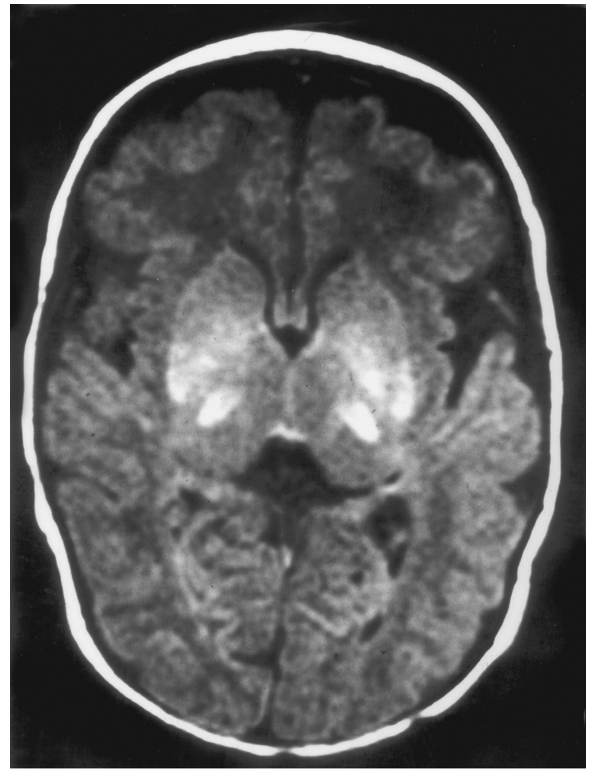


Figure 16.3 Axial T1-weighted MRI (TE 16 ms, TR 600 ms) of a 7-day-old term infant who had an unexplained cardiorespiratory arrest at 12 hours of age shows bilateral symmetric areas of high signal intensity in the basal ganglia and thalami. These areas were low in signal intensity on T2-weighted images. At 1 year of age, this child manifested hypotonia, ataxia, and bulbar dysfunction.

in children with presumed birth injury who exhibited choreoathetosis and dystonia [35]. Infants with this pathologic lesion have been identified in the neonatal period by neuroimaging studies (Figure 16.3) [36].

Acute near-total asphyxia can lead to specific symmetric lesions in the putamen and the thalamus with sparing of the globus pallidus [37]. The posterior putamen and lateral thalami are more affected. The mechanism for this pattern appears to be impairment of energy substrates that selectively damage areas with higher metabolic requirements [27]. This type of injury may occur in the setting of severe umbilical cord prolapse, uterine rupture, or severe placental abruption. Affected newborns often manifest evidence of brainstem dysfunction such as facial diplegia and abnormal eye movements due to concomitant brainstem injury (see below). Children with this type of injury later often develop extrapyramidal cerebral

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palsy manifested by dystonia, rigidity, axial hypotonia, dysphagia, and abnormal vocalization.

Early in the course there is often hemorrhage and infarction in these structures on neuropathologic examination. Eventually, cystic changes develop, particularly in the neostriatum. The neurons and penetrating vessels become calcified. The basal ganglia and thalamus develop a chronic pathologic lesion termed *status marmoratus*. This lesion, characterized by neuronal loss, gliosis, and hypermyelination, was observed in 173 of 198 cases of presumed perinatal birth injury in one report [38]. The lesions are probably the result of both impairment of blood flow through the deep penetrating arteries and the high level of metabolic activity of this structure. These children usually have a poor long-term outcome. Infants with status marmoratus of the basal ganglia develop choreoathetosis, dystonia, tremor, and intellectual deficits. The movement disorder has a delayed onset and may deteriorate over a period of 1–2 years.

In infants who manifest injury to the basal ganglia and thalamus, there is often concomitant injury to the corticospinal tract and hippocampi. Abnormal magnetic resonance (MR) signals are often seen in the posterior limbs of the internal capsules bilaterally. The perirolandic cortex is also often affected, resulting in abnormal MR signal and loss of gray-white differentiation in the perirolandic gyri.

Brainstem

Pathologic changes of the brainstem are rarely isolated, and other structures, especially the thalamus, are also involved. Brainstem injury usually occurs in the setting of acute hypotension [39]. Selective necrosis of specific brainstem nuclei has been observed, and the nuclei adjacent to the floor of the fourth ventricle are more often affected. These nuclei include the inferior colliculi, fifth and seventh cranial nerve nuclei, and nucleus ambiguus (ninth and tenth cranial nerves). An MRI pattern involving the dorsomesencephalic structure has been recognized but appears to occur relatively infrequently [27].

Cerebellum

The cerebellum is especially vulnerable to hypoxic-ischemic insult, and the Purkinje cells are the most vulnerable type of cell. The cerebellum is often affected by bilateral lesions at the boundaries of the superior and inferior cerebellar arterial zones or by lesions of the foliar cortex. White matter edema and small hemorrhages accompany the neuronal loss. Chronic lesions are referred to as *cerebellar sclerosis*. In this condition there is a loss of Purkinje cells and an increase in Bergmann's astrocytes. The folia are narrowed, and there is an increased space between them.

Cerebellar involvement is often observed concurrently with deep gray nuclei and brainstem lesions. Impairment of the posterior circulation due to hyperextension of the neck at the time of delivery has been suggested as being a factor in the pathogenesis of this lesion [40]. Hypotonia and ataxia are observed as sequelae of cerebellar involvement. Intellectual impairment is common and may be severe.

Infants with disease involving the deep gray matter nuclei, brainstem, and cerebellum usually have moderate to severe encephalopathy in the neonatal period. A history of an acute process that causes near-total asphyxia, such as severe umbilical cord prolapse, uterine rupture, or significant placental abruption, is often found. Acutely bifacial weakness, gaze abnormalities, and tongue fasciculations have been described in an infant with brainstem involvement due to "acute" near-total asphyxia [41–43]. Infants with more extensive brainstem involvement may require prolonged ventilatory support. Infants with brainstem involvement have bulbar dysfunction associated with poor feeding, failure to thrive, and recurrent aspiration. Interestingly, in this pattern of injury there may be complete or relative sparing of the cortex and white matter. Also, since the hypoxic-ischemic insult occurs acutely, there is little time for shunting of blood away from extracerebral organs. Hence there is less evidence of multiorgan dysfunction.

Although there seems to be a different topographic distribution of injury caused by hypotension (parasagittal border-zone injury) and acute near-total asphyxia (deep gray nuclei and brainstem), there is often an overlap between the two pathophysiologic syndromes. Furthermore, when the nature of the hypoxic-ischemic injury is severe and prolonged, diffuse injury to the brain occurs. This manifests in the first few days as diffuse cytotoxic edema on MRI in addition to the thalamic and basal ganglia injury [27]. Neurologic examination reveals encephalopathy, brainstem dysfunction, flaccid quadriparesis, and respiration abnormalities. Most such infants require mechanical ventilation. As the encephalopathy evolves, the infants are described as having clinical seizures, the brainstem signs persist, and temperature

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instability may be observed. The injured areas will evolve into multicystic encephalomalacia.

Focal Brain Injury

Cortical injury may result from occlusion of an artery (i.e., ischemic stroke) resulting in necrosis of all cellular elements in the distribution of a single vessel. Arterial occlusions occur most often in the term infant and have been observed in 5–9% of autopsy series [44,45]. The middle cerebral artery is most frequently involved. Most are thought to be due to embolic or thrombotic processes. Although the actual etiology is infrequently found, coagulopathy, congenital heart disease, and trauma are common associated disorders. As the infarction evolves, there is dissolution of brain parenchyma and formation of a cavity (porencephalic cyst). If multiple vessels are involved, multicystic encephalomalacia or hydranencephaly may result.

Infants with neonatal strokes often present with early-onset seizures with absence or only a mild degree of encephalopathy [46]. Neonatal strokes are the second most common cause of seizures in the newborn period after global hypoxic-ischemic insult and often occur in the absence of intrapartum difficulties [10]. Focal clonic seizures are often exhibited, and these seizures can be readily diagnosed by clinical criteria [3]. Focal findings may be noted on neurologic examination but are often subtle. The EEG usually demonstrates lateralized abnormalities and allows assessment of the severity of the encephalopathy in other cortical regions. CT scan and MRI show a wedge-shaped area of abnormal signal that is in the distribution of a single artery. Diffusion-weighted MRI provides a sensitive way of detecting infarcts early in the course.

Infants may develop spastic hemiparesis as a long-term sequela. Because of the frequent involvement of the middle cerebral artery distribution, the upper extremities are more impaired. The extent and location of the pathologic lesion are important factors in determining whether intellectual impairment and epilepsy will also develop [47].

Focal cerebral injury may also occur with venous occlusions. Venous occlusions often involve the sinuses or major veins, leading to superficial cortical infarcts, which are frequently hemorrhagic. MRI has been particularly useful for diagnosing venous sinus thrombosis and focal injury due to venous occlusions [48]. Venous sinus thrombosis may also cause secondary intraventricular (choroid plexus) hemorrhages in the term newborn. A more severe encephalopathy is noted with venous occlusion because of frequently associated hemorrhage. Seizures are also common [48,49].

White Matter Injury

Preterm infants have a predilection for white matter injury as a result of hypoxic-ischemic insult. *Periventricular leukomalacia* (PVL) is the term frequently used to describe this disorder, which is characterized by necrosis of the white matter and may include hemorrhage [50]. The lesion is readily identified by ultrasonography, and prospective studies have determined that the incidence is 4–26% in low-birthweight infants [51–53]. Grossly, the acute lesions are characterized by white or white-yellow spots in the periventricular white matter, which occasionally show hemorrhagic infiltration. Microscopically, focal coagulative necrosis is observed. Petechial hemorrhages may also be seen within these lesions. These areas often develop into cystic lesions and later contract into gliotic scars (Figure 16.4). The lesions are observed most frequently in the corona radiata, occipital and temporal horns of the lateral ventricles, and just anterior to the anterior horn of the lateral ventricles. In the term infant, the lesions are usually hemorrhagic and are associated with a coagulopathy or congenital heart disease.



Figure 16.4 Coronal section of a 1-week-old infant (gestational age 34 weeks) shows periventricular leukomalacia with bilateral areas of congestion and hemorrhage (arrows) in the white matter and a periventricular cyst (arrowhead). The pregnancy was complicated by nonimmune hydrops, and an ultrasound study on the first day after birth revealed extensive bilateral periventricular cysts.

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The clinical characteristics of infants with PVL include decreased tone in the lower extremities associated with increased neck extensor tone [54]. Apnea, pseudobulbar palsy with poor feeding, and irritability have been described. Clinical seizures without EEG confirmation have been reported in 10–30% of the infants. The diagnosis of PVL can be made by ultrasonography (<28 days), but MRI in later infancy better defines the extent of the disease and the associated abnormalities of myelination [56]. Spastic diplegia with varying degrees of intellectual impairment, especially visual-motor dysfunction, is the usual sequela.

Periventricular/Intraventricular Hemorrhages

Periventricular or intraventricular hemorrhage is the most common neuropathologic change observed in the premature infant. It is observed in 31–43% of low-birth-weight infants in prospective neuroimaging studies [57,58]. The hemorrhage arises from the germinal matrix at the ventromedial angle of the lateral ventricle. Cerebral hypoxic ischemia leads to impaired autoregulation of cerebral blood flow and injury to the germinal matrix and capillary endothelium, which have a high level of oxidative metabolism. Changes in the systemic blood pressure, platelet and coagulation disturbances, and increased cerebral venous pressure also contribute to the pathogenesis of this lesion.

The pathologic findings include subarachnoid hemorrhage with blood in the basal and pontine cisterns and cisterna magna. The hemorrhage may range from a small area of bleeding in the subependymal matrix zone to massive distension of the ventricular system associated with extension of blood into the centrum semiovale. Hydrocephalus may be a complication in infants with this disorder. The hydrocephalus is often secondary to an obstruction at the aqueduct or the foramina exiting from the fourth ventricle, or it may be due to impairment of reabsorption of CSF over the convexities.

Intraventricular hemorrhage (IVH) in the term infant often arises from the choroid plexus, and trauma, venous thrombosis, and hypoxia are thought to be important pathogenic factors [59,60]. In 25% of term infants with this disorder there is no identifiable cause for the hemorrhage [60].

Periventricular or intraventricular hemorrhages are often clinically silent in the preterm neonate. Severe hemorrhage may present with an acute syndrome, characterized by rapid deterioration of the level of consciousness, brainstem dysfunction, decerebrate posturing, and tonic seizures. A subacute presentation is more common, with intermittent neurologic symptoms superimposed on slowly progressive encephalopathy. The newborn may have episodes of abnormal eye movements, hypotonia, and decreased spontaneous motor activity. A fall in the hematocrit level is often an important sign. Ultrasonography is usually diagnostic and can be done serially at the bedside.

The prognosis is extremely variable, and many infants have no sequelae. The prognosis is most closely correlated with the degree of parenchymal involvement rather than the extent of the hemorrhage. Progressive posthemorrhagic ventricular dilatation may develop in some infants and worsen the neurodevelopmental outcome [61].

References

1. Finer NN, Robertson CM, Peters KL, et al. Factors affecting outcome in hypoxic-ischemic encephalopathy in term infants. *Am J Dis Child* 1983; **137**: 21–5.
2. Finer NN, Robertson CM, Richards RT, et al. Hypoxic–ischemic encephalopathy in term neonates: perinatal factors and outcome. *J Pediatr* 1981; **98**: 112–17.
3. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology* 1987; **37**: 1837–44.
4. Roland EH, Hill A. Clinical aspects of perinatal hypoxic-ischemic brain injury. *Semin Pediatr Neurol* 1995; **2**:57–71.
5. Vannucci R. Hypoxic-ischemic encephalopathy. *Am J Perinatol* 2000; **17**: 113–20.
6. Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr* 1988; **112**: 515–19.
7. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: multivariate analysis of risk. *N Engl J Med* 1986; **315**: 81–6.
8. Nelson KB. What proportion of cerebral palsy is related to birth asphyxia? *J Pediatr* 1988; **112**: 572–4.
9. Naeye RL, Peters EC. Antenatal hypoxia and low IQ values. *Am J Dis Child* 1987; **141**: 50–4.
10. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.
11. Levene MI, Grindulis H, Sands C, et al. Comparison of two methods of predicting outcome in perinatal asphyxia. *Lancet* 1986; **1**: 67–9.

.017

12. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; **33**: 696–705.
13. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–84.
14. de Vries L, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy *Arch Dis Child Fetal Neonatal Ed* 2010; **95**: F220–4.
15. Mwaniki MK, Atieno M, Lawn JE, Newton CRJ. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet* 2012; **279**: 445–52.
16. Shankaran S, Laptook AR, Tyson JE, et al. Evolution of encephalopathy during whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 2012; **160**: 567–72.e3
17. Merchant N, Azzopardi D. Early predictors of outcome in infants treated with hypothermia for hypoxic-ischemic encephalopathy. *Dev Med Child Neurol* 2015; **57**(Suppl. 3): 8–16.
18. Ramasawmy V, Horton J, Vandermeer B, et al. Systematic review of biomarkers of brain injury in term neonatal encephalopathy. *Pediatr Neurol* 2009; **40**: 215–26.
19. Chalak LF, Sánchez PJ, Adams-Huet B, et al. Biomarkers for severity of neonatal hypoxic-ischemic encephalopathy and outcomes in newborns receiving hypothermia therapy. *J Pediatr* 2014; **164**: 468–74.
20. Takeuchi T, Watanabe K. The EEG evolution and neurological prognosis of neonates with perinatal hypoxia. *Brain Dev* 1989; **11**: 115–20.
21. Scher MS, Painter MJ, Bergman I, et al. EEG diagnosis of neonatal seizures: clinical correlations and outcome. *Pediatr Neurol* 1989; **5**: 17–24.
22. Toet MC, Hellström-Westas L, Groenendaal F, et al. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxicischemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F19–23.
23. Van Laerhoven H, de Haan, TR, Offriga M, et al. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review. *Pediatrics* 2013 **131**: 88–98.
24. Scalais E, François-Adant A, Nuttin C, et al. Multimodality evoked potentials as a prognostic tool in term asphyxiated newborns. *Electroencephalogr Clin Neurophysiol* 1998; **108**: 199–207
25. Kuenzle C, Baenziger O, Martin E, et al. Prognostic value of early MR imaging in term infants with severe perinatal asphyxia. *Neuropediatrics* 1994; **25**: 191–200.
26. Baenziger O, Martin E, Steinlin M, et al. Early pattern recognition in severe perinatal asphyxia: a prospective MRI study. *Neuroradiology* 1993; **35**: 437–42.
27. Triulzi F, Parazzini C, Righini A. Patterns of damage in the mature neonatal brain. *Pediatr Radiol* 2006; **36**: 608–20.
28. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005; **146**: 153–60.
29. Chau V, Poskitt KJ, Dunham CP, et al. Magnetic resonance imaging in the encephalopathic term newborn. *Curr Pediatr Rev* 2014; **10**: 28–36.
30. Hüppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics* 2001; **107**: 455–60.
31. Robertson RL, Ben-Sira L, Barnes PD, et al. MR line-scan diffusion-weighted imaging of term neonates with perinatal brain ischemia. *Am J Neuroradiol* 1999; **20**: 658–70.
32. Myer JE. Uber die Lokalisation frühkindlicher Hirnshäden in arteriellen Grenzgebieten. *Arch Psychiatr Zeitschr Neurol* 1953; **190**: 328–41.
33. Volpe JJ, Herscovitch P, Perlman JM, et al. Positron emission tomography in the asphyxiated term newborn: parasagittal impairment of cerebral blood flow. *Ann Neurol* 1985; **17**: 287–96.
34. Volpe JJ, Pasternak JF. Parasagittal cerebral injury in neonatal hypoxic-ischemic encephalopathy: clinical and neuroradiological features. *J Pediatr* 1979; **91**: 472–6.
35. Friede RL. *Developmental Neuropathology*, 2nd edn. New York: Springer-Verlag, 1989.
36. Voit T, Lemburg P, Neuen E, et al. Damage of thalamus and basal ganglia in asphyxiated full-term neonates. *Neuropediatrics* 1987; **18**: 176–81.
37. Johnston MV, Hoon AH. Possible mechanisms in infants for selective basal ganglia damage from asphyxia, kernicterus, or mitochondrial encephalopathies. *J Child Neurol* 2000; **15**: 588–91.
38. Malamud N, Hirano A. *Atlas of Neuropathology*, 2nd edn. Berkeley:University of California Press, 1974.
39. Gilles FH. Hypotensive brain stem necrosis: selective symmetrical necrosis of tegmental neuronal aggregates following cardiac arrest. *Arch Pathol* 1969; **88**: 32–41.
40. Rorke LB. *Pathology of Perinatal Brain Injury*. New York:Raven Press, 1982.
41. Roland EH, Hill A, Norman MG, et al. Selective brainstem injury in an asphyxiated newborn. *Ann Neurol* 1988; **23**: 89–92.

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42. Pasternak JF, Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. *Pediatr Neurol* 1998; **18**: 391–8.
43. Natsume J, Watanabe K, Kuno K, et al. Clinical, neurophysiologic, and neuropathological features of an infant with brain damage of total asphyxia type (Myers). *Pediatr Neurol* 1995; **13**: 61–4.
44. Barmada MA, Moossy J, Shuman RM. Cerebral infarcts with arterial occlusion in neonates. *Ann Neurol* 1979; **6**: 495–502.
45. Banker BQ. Cerebral vascular disease in infancy and childhood. I. Occlusive vascular disease. *J Neuropathol Exp Neurol* 1961; **20**: 127–40.
46. Koelfen W, Freund M, Varnholt V. Neonatal stroke involving the middle cerebral artery in term infants: clinical presentation, EEG and imaging studies, and outcome. *Dev Med Child Neurol* 1995; **37**: 204–12.
47. Levine SC, Huttenlocher P, Banich MT, et al. Factors affecting cognitive function of hemiplegic children. *Dev Med Child Neurol* 1987; **29**: 27–35.
48. Rivkin MJ, Anderson ML, Kaye EM. Neonatal idiopathic cerebral venous thrombosis: an unrecognized cause of transient seizures or lethargy. *Ann Neurol* 1992; **32**: 51–6.
49. Wong VK, LeMesurier J, Franceschini R, et al. Cerebral venous thrombosis as a cause of neonatal seizures. *Pediatr Neurol* 1987; **3**: 235–7.
50. Banker BQ, Larroche JC. Periventricular leukomalacia of infancy. *Arch Neurol* 1962; **7**: 386–410.
51. Guzzetta F, Shackleford GD, Volpe S, et al. Periventricular intraparenchymal echodensities in the premature newborn: critical determination of neurologic outcome. *Pediatrics* 1986; **78**: 995–1006.
52. Fawer CL, Calame A, Perentes E, et al. Periventricular leukomalacia: a correlation study between real-time ultrasound and autopsy findings. *Neuroradiology* 1985; **27**: 292–300.
53. Trounce JQ, Rutter N, Levene MI. Periventricular leucomalacia and intraventricular haemorrhage in the preterm neonate. *Arch Dis Child* 1986; **16**: 1196–202.
54. Trounce JQ, Shaw DE, Leverne MI, et al. Clinical risk factors and periventricular leucomalacia. *Arch Dis Child* 1988; **63**: 17–22.
55. Sarkar S, Shankaran S, Laptook AR et al. Screening cranial imaging at multiple time points improves cystic periventricular leukomalacia detection. *Am J Perinatol* 2015; **32** (epub ahead of print).
56. De Vries LS, Connell JA, Dubowitz LMS, et al. Neurological, electrophysiological and MRI abnormalities in infants with extensive cystic leukomalacia. *Neuropediatrics* 1987; **18**: 61–6.
57. Dolfin T, Skidmore MB, Fong KW, et al. Incidence, severity, and timing of subependymal and intraventricula hemorrhages in preterm infants born in a perinatal unit as detected by serial real-time ultrasound. *Pediatrics* 1983; **71**: 541–6.
58. Enzmann D, Murphy-Irwin K, Stevenson D, et al. The natural history of subependymal germinal matrix hemorrhage. *Am J Perinatol* 1985; **2**: 123–33.
59. Scher MS, Wright FS, Lockman LA, et al. Intraventricular haemorrhage in the full-term neonate. *Arch Neurol* 1982; **39**: 769–72.
60. Volpe JJ. Intracranial hemorrhage:subdural, primary subarachnoid, cerebellar, intraventricular (term infant), and miscellaneous. In *Neurology of the Newborn*, 5th edn. Philadelphia: Saunders. 2008: 483–516.
61. Bouwer AJ, Groenendaal F, Benders MJ, de Vries LS. Early and late complications of germinal matrix-intraventricular haemorrhage in the preterm infant: what is new? *Neonatology* 2014; **106**: 296–303.

Chapter 17

The Use of EEG and aEEG in Assessing the Term and Preterm Brain

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EEG Use in the Newborn

Introduction to EEG

Electroencephalography (EEG) remains a valuable mainstay of the neurologic evaluation of the neonate. While neuroimaging allows assessment of brain structure, EEG allows direct measurement of brain function. An understanding of EEG fundamentals is helpful in using this tool in the care of neonates.

EEG Acquisition

EEG uses multiple electrodes placed on the scalp to directly measure electrical potentials at each location. Differences in voltage are compared between various pairs of electrodes, and these voltage differences are displayed graphically over time, with each pair of electrodes generating one channel of EEG on the display. In this sense, EEG works in a manner very similar to electrocardiography (ECG). In describing EEG in simple terms, it can be said that EEG "records brainwaves" – it records and displays brain activity (Figure 17.1).

Recordings are typically performed by an EEG technologist (alternately called a *neurodiagnostic technologist*), an allied health professional with specialized training and certification in clinical neurophysiology. The technologist applies electrodes, initiates recordings, and ensures adequate recording quality. Technologists perform stimulation at the bedside and make notes regarding behavioral correlates during recordings. In many centers, EEG technologists also provide a preliminary interpretation of the recording. The recording is then reviewed by a neurophysiologist, a physician with additional specialized training in EEG interpretation. There are various professional guidelines regarding the specific technical requirements of EEG recording and interpretation (for examples, see the American Clinical Neurophysiology Society website, www.acns.org, or the International Federation of Clinical Neurophysiology website, www.ifcn.info) [1–3].

Neonatal EEG is recorded using one of a variety of electrode types. Most commonly, metal disk-shaped electrodes are used. These are applied to the neonatal scalp using an electrolyte paste and secured with breathable tape. In some cases, an additional gauze wrap is placed around the head to help keep the electrodes in place. In order to ensure good contact with the scalp, the patient's hair must be moved as much as possible away from the electrode site. This usually may be achieved by combing and parting the hair. When hair is particularly thick, it may even be necessary to trim it at electrode sites. The skin must be cleaned to prepare the scalp for electrode application; particular care is needed in doing this for the fragile skin of preterm neonates so as to avoid excessive skin abrasion. Skin should be checked at least daily for signs of irritation at electrode sites [4]. In older children, instead of paste and tape, collodion glue is typically used to secure electrodes for prolonged recordings. However, collodion is rarely necessary for critically ill neonates and has the disadvantages of requiring a special solution to remove the electrodes, and it has an increased risk of skin irritation. Alternatives to conventional metal disk electrodes include special plastic or gold cup electrodes, designed to be MRI compatible. While commercially available with published data to suggest safety, many of these electrodes are not yet specifically approved by the Food and Drug Administration (FDA) for use during MRI and thus may or may not be acceptable to individual medical centers or radiology groups. Other alternatives include disposable electrodes, with advantages for infection control and ease of use but with higher long-term cost. Subdermal needle electrodes may be easier to apply and ensure good contact regardless of hair, but they carry needlestick risk and may be unacceptable to parents and providers.

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Figure 17.1 Example of a normal neonatal EEG recorded at typical settings. Sensitivity 7 μV, paper speed 15 seconds per page. The bottom five channels record eye movements (left and right), body movements, respirations, and ECG, respectively.

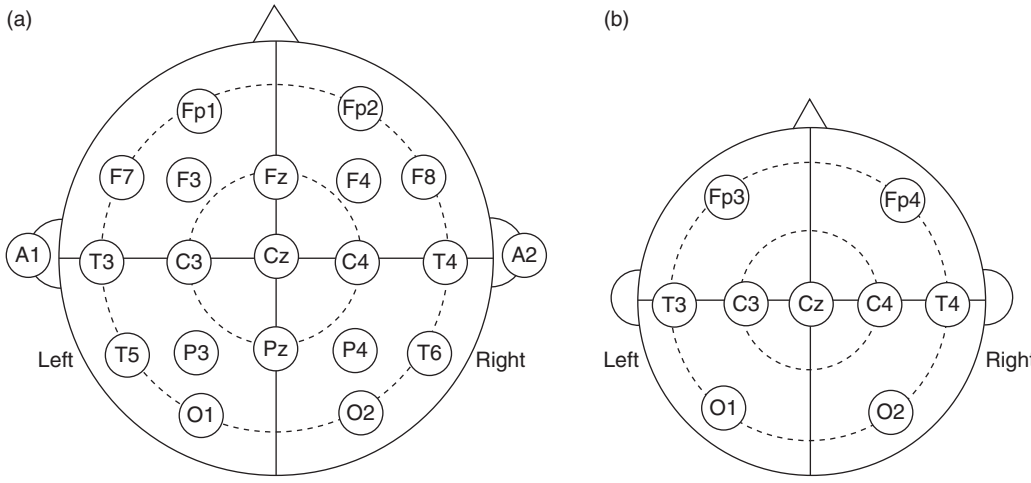


Figure 17.2 Electrode nomenclature using the international 10-20 system. (A) Most commonly used electrodes for recordings outside the neonatal period. (B) More limited set of electrodes used for neonates. Note the slightly more lateral placement of the frontopolar electrodes.

Electrode placement is according to a standard system, the International 10–20 System, modified for the smaller neonatal head [5] (Figure 17.2). In a term neonate, this includes 9–11 electrodes placed at specific points on the scalp according to precise measurements. In very preterm neonates, small head size may require a reduced number of electrodes. The use of standardized electrode placement ensures reproducibility of electrode location both across neonatal patients and between multiple recordings for the same patient over time. "Cap" and "net" electrode systems are sometimes used as a shorthand for individual electrode placement using precise measurements; while caps and nets have the advantage of being much faster to apply, they have the disadvantage of less precise electrode location and the potential for electrode movement or slippage during the course of a recording. Locations of electrodes are indicated using a letter-number naming convention. Letters designate the anteroposterior location of the

electrode; numbers indicate the left-to-right location. Frontopolar electrodes are designated "Fp," temporal electrodes "T," central electrodes "C," and occipital electrode "O." Less often used in neonates are frontal ("F") and parietal ("P") electrodes. Odd numbers indicate electrodes on the left side of the head, even numbers the right side, and the letter "Z" indicates midline placement. In addition to scalp electrodes to record cerebral activity, neonatal EEG should be performed with additional electrodes to simultaneously record electrocardiogram, respiration, electromyogram (EMG, often recorded at the chin), and eye movements. These additional electrodes allow identification of common artifacts, recognition of breathing and movement patterns to identify sleep or wake state, and correlation of EEG seizures with movement and/or changes in ECG or respiration.

The bedside caregiver plays an essential role during EEG acquisition, particularly during long-term or continuous EEG recording. The bedside team records behavioral observations, which are necessary for proper interpretation of the EEG. These include identifying and noting any unusual behaviors concerning for seizure, noting any external factors that might introduce artifacts into the recording (e.g., patting or performing care), and documenting time of administration of neuroactive medications. The protocol for documentation of these observations varies between centers: methods range from log sheets posted at the bedside to pushbutton markers connected to the EEG equipment or keypads for entering notes directly onto the digital recording.

Some centers use sedation such as chloral hydrate to facilitate recording pediatric EEGs. This is rarely or never required for neonates. Neonates may move during electrode application and recording, but even the squirmiest newborn is unable to effectively preclude electrode placement. Likewise, while movement during a nonsedated recording may necessitate a longer recording to ensure that periods of EEG are obtained without artifact, a recording of 60 minutes' duration typically ensures enough good-quality recording for adequate interpretation. Sedation may affect the EEG background and carries some risk for the patient; it should be avoided.

Types of EEGs

Different types of EEGs are used in neonates; these must be distinguished by ordering clinicians (see the following box). The EEGs described here all use a full array of electrodes; reduced-array amplitude-integrated EEG is discussed later in this chapter.

Types of EEGs

- **Routine EEG:** 30- to 60-minute full-array EEG, referred to as a *spot EEG* at some centers.
- **cEEG:** Continuous EEG monitoring. This is a full-array (minimum of eight electrodes) EEG recorded continuously for at least 12 hours, with or without accompanying video. Also referred to as *video-EEG* or *vEEG* at some centers.
- **qEEG:** Quantitative EEG. This is a processed EEG displaying limited quantitative features over time to better allow visualization of trends. Examples include *density spectral array* (DSA) and *amplitude-integrated EEG* (aEEG).
- **aEEG:** Amplitude-integrated EEG. This is a reduced-array EEG (typically two or three channels) recorded continuously and displayed as a time-compressed quantitative trend with an accompanying two- to three-channel source EEG available for review.

A *routine* or *spot EEG* is typically performed at the bedside for a short period in order to record a brief sample of brain activity. EEG duration is 40–60 minutes in order to capture both awake and asleep states [1], with files then transferred to a reader station for later interpretation. Routine EEG allows for evaluation of the baseline brain activity, or *EEG background pattern*. Routine EEGs are most useful when the goal is to evaluate EEG background, such as when using serial EEG to assess brain maturation in preterm neonates.

Continuous EEG (cEEG), or *long-term EEG monitoring*, refers to an EEG that uses a full array of electrodes to record EEG continuously over a prolonged period, typically 24 hours or longer. This allows for evaluation of the EEG background as it evolves over a greater period of time and is also useful when there is concern for possible seizures. While a routine EEG may or may not capture seizures during the recording period, cEEG allows a longer sample for superior seizure detection. cEEG is the recommended test for evaluation of suspected neonatal seizures whenever available; it is preferable over routine EEG for this purpose [2,6]

Video-EEG (vEEG) refers to an EEG that is acquired with simultaneous video recording. This

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has the advantage of recording patient behaviors to provide better correlation with the EEG for the interpreting neurophysiologist. For example, information regarding sleep or clinical manifestations of seizures seen on video can be correlated with EEG patterns. Similarly, video recording greatly enhances identification of common artifacts, such as the artifact caused by patting a newborn. Commonly, the term *video-EEG monitoring* is used to refer to cEEG monitoring, though video-EEG can be performed for any duration of time.

In addition to the traditional display of EEG recorded in any of the abovementioned ways, EEG can be displayed using quantitative trends as *quantitative EEG* (qEEG). qEEG processes the EEG signal, simplifies the display to show information about a subset of features, and time compresses the display to allow better identification of trends over time. This is useful both as a bedside display for easy screening and for use by the neurophysiologist to quickly identify areas in prolonged recordings that warrant more detailed review. Examples of qEEG include color density spectral array (CDSA), asymmetry index, and amplitude-integrated EEG (aEEG). aEEG is by far the most popular type of qEEG used in the neonatal population and is discussed further later.

Indications for EEG

As mentioned earlier, EEG is indicated in neonates for whom an assessment of brain function is needed. For most healthy neonates, the neurologic examination is sufficient to assess brain function; a normal examination suggests normal brain function. However, in cases where there is encephalopathy – abnormal brain function manifesting as altered mental state – an EEG can be helpful. The initial recording provides information regarding background brain activity, which can contribute to diagnosis. Furthermore, information about EEG background has prognostic value in a variety of conditions, including in hypoxic-ischemic encephalopathy (HIE), and in preterm neonates. Serial EEG can be especially useful for evaluating changes in the EEG background over time.

EEG is also indicated in neonates at risk for or suspected of having seizures. In some neonates, paroxysmal clinical events are the indication for EEG. These can include abrupt and unusual movements, autonomic fluctuations, or stereotyped behaviors such as bicycling or lip smacking. In such cases, when a clinical event is witnessed and concerning for seizures, cEEG is indicated to confirm that the event of interest is a seizure [2]. Proper confirmation will guide further management either by confirming an electrographic correlate and that the event is an electroclinical seizure or by showing that there is no electrographic correlate and thus treatment with antiseizure medications is not indicated. Up to 70% of clinical events though to be seizures by bedside caregivers are found not to be seizures on EEG; cEEG confirmation is crucial to confirm the diagnosis of seizures to target treatment appropriately [7]. When cEEG is performed for the differential diagnosis of suspected clinical seizures, it is recommended to continue recording until the typical events of interest have been captured or for at least 24 hours [2]. If the events are found to be seizures, cEEG should be continued to guide management.

Some neonates are at such high risk for seizures that cEEG is indicated as routine practice to evaluate for subclinical seizures. Neonatal seizures are frequently subclinical, with no outward clinical signs present during up to 90% of the time a baby is seizing and absent in up to 80% of neonates having seizures [7,8]. Because of this high rate of subclinical seizures, cEEG is indicated to accurately identify seizures among populations at risk. An example is term neonates with HIE. Multiple studies have shown that seizures occur in approximately 40% of term neonates with HIE during cooling treatment [9,10]. A significant proportion of neonates with HIE will have only subclinical seizures, and of those with seizures, about half will have their first seizure after the first 24 hours of cooling [10]. As such, it is now recommended that all neonates with HIE receive EEG or other brain monitoring for the duration of therapeutic hypothermia to evaluate for seizures [2,11]. Other conditions with high seizure risk warranting consideration of cEEG to screen for seizures have been identified in the American Clinical Neurophysiology Society guidelines on cEEG in neonates [2](Table 17.1).

If seizures are identified, cEEG should be continued to facilitate management. As discussed in Chapter 43, even in the minority of cases in which seizures initially have outward clinical signs, antiseizure medications such as phenobarbital or phenytoin will suppress outward clinical signs without resolving electrographic seizures in over 50% of cases [12]. This phenomenon, known as *uncoupling*, makes

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Table 17.1 High-Risk Conditions for Seizures

Category	Examples
Acute neonatal encephalopathy	HIE, postnatal collapse
Cardiac or pulmonary risk for brain injury	Extracorporeal membrane oxygenation (ECMO), congenital head defects perioperatively
CNS infection	Meningitis, encephalitis
CNS trauma	Subarachnoid bleeding, nonaccidental trauma
Inborn errors of metabolism	Various
Stroke	Arterial stroke, venous thrombosis
At-risk preterm infants	Acute grade III or IV intraventricular hemorrhage (IVH)
Genetic/syndromic disease	Cerebral dysgenesis, multiple abnormalities with encephalopathy

clinical observation alone highly unreliable for assessing response to antiseizure medication. Because of this, cEEG is needed to assess response to treatment in any neonate with seizures. It is recommended to continue cEEG until seizures have resolved for at least 24 hours. In some neonates needing only short-term antiseizure treatment, such as those with symptomatic seizures from acute brain injury, cEEG may also be useful after stopping seizure medication to ensure the lack of recurrence [2].

EEG Findings and Interpretation

EEG interpretation requires specialized experience and expertise by a neurophysiologist; neonatal EEG interpretation can be particularly challenging because it requires recognition of patterns and findings not seen in older children and adults. The interpreting neurophysiologist relies on the information provided with the EEG to facilitate accurate interpretation. In particular, it is crucial to know the patient's postmenstrual age (PMA = gestational age, measured from the time of the last menstrual period + chronological age). A difference of only a few weeks corresponds to a difference in the expected patterns seen on the EEG. Therefore, an EEG for a "2-day-old neonate" would be interpreted differently depending on whether that neonate was born at 36 weeks' gestational age or 41 weeks' gestational age. Providing the PMA in the EEG request is very helpful in ensuring accurate interpretation. Other useful details include any neuroactive medications administered (because these can affect the EEG pattern), whether the child is receiving hypothermia, and the suspected clinical diagnosis.

While interpretation of the neonatal EEG is beyond the scope of this book, it is helpful to recognize some of the most commonly used terms in neonatal EEG interpretation and reporting and to understand their significance.

Normal Background

Normal, awake EEG background in a term neonate is a continuous, symmetric mixture of normal amplitude (>25 μV) activity, with waveforms having a frequency of mostly 1–7 Hz (delta and theta range), with some faster frequencies intermixed. This overall pattern is called *activité moyenne* (Figure 17.3). In sleep, activity remains continuous and symmetric, with alternating higher and lower amplitudes; this is called *tracé alternant* (Figure 17.4). Of special note: a normal neonatal EEG contains some scattered sharp waves (Figure 17.5). This is a key difference from EEG in older children or adults – in those age groups, sharp waves indicate an increased risk of seizures or epilepsy. However, in a normal term neonate, some scattered sharp waves are expected. In particular, frontal sharp waves called *encoche frontales* are normal and expected. A common pitfall in neonatal EEG interpretation is mistaking all sharp waves to be indicators of coexisting seizures – this is not the case. A more subtle analysis of sharp-wave features is needed to determine whether they are abnormal or normal; this interpretation should be included in the neurophysiologist's report. In a term neonate, a normal EEG background with normal sleep and wake architecture is reassuring for normal brain activity and suggests a good prognosis.

Preterm neonates have less mature EEG findings while awake or asleep. The specific findings depend on the exact age of the neonate. In very preterm neonates, background activity is not continuous. This means there are pauses or breaks in the EEG pattern where the activity recorded is less than 25 μV in amplitude. Periods of higher-amplitude activity

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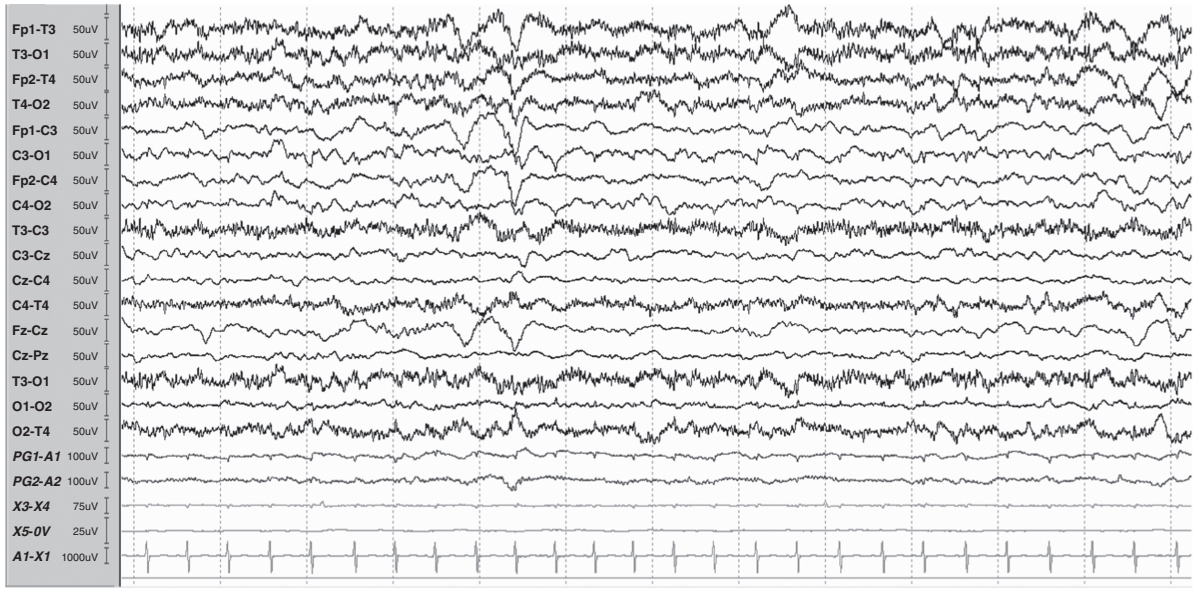


Figure 17.3 Example of a typical activité moyenne pattern. This is a normal pattern in a term neonate who is awake or in active sleep, consisting of a mixture of frequencies and amplitudes, with continuous activity seen in every channel.

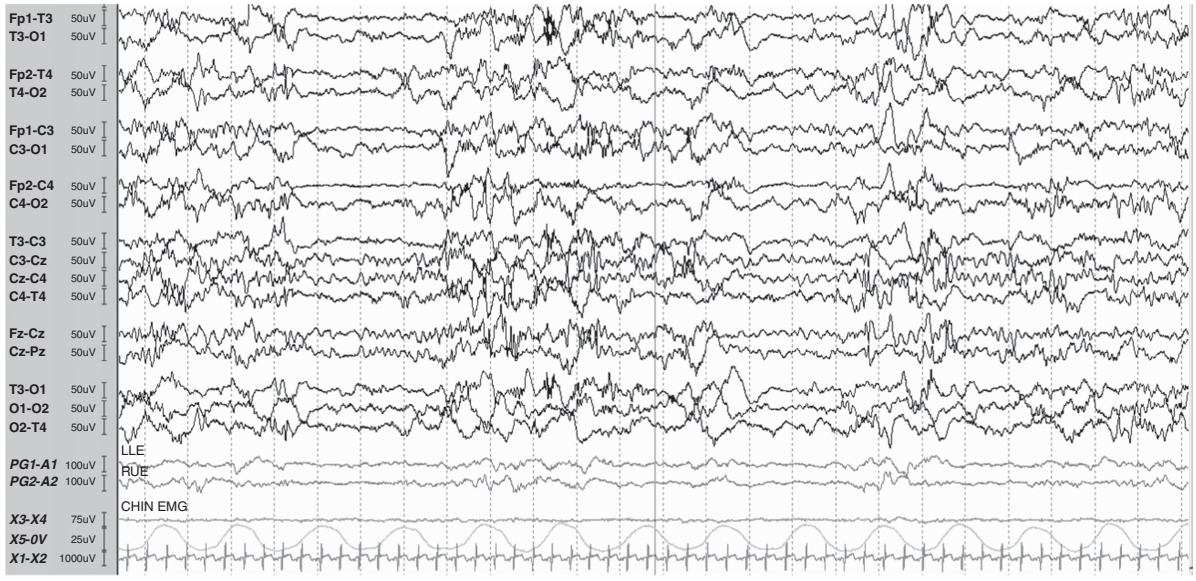


Figure 17.4 Example of tracé alternant pattern. This pattern is seen in normal sleep in a term neonate and is characterized by alternating amplitude of activity. (Paper speed has been adjusted to 30 seconds per page to allow visualization of this alternating pattern.)

may be called *bursts*, with lower-amplitude periods called *interburst intervals*. This should not be confused with the very abnormal pattern of *burst suppression*, discussed later. The expected duration of pauses, or *degree of discontinuity*, is greater in premature neonates with lower gestational age. In a preterm neonate under 30 weeks' PMA, it can be normal to have interburst intervals up to 35 seconds [13]. As mentioned earlier, by term-equivalent age, the EEG should no longer have interburst intervals longer than 2–6 seconds; the record should be continuous.



Figure 17.5 Example of normal sharp waves in the EEG of a term neonate. The arrow indicates physiologic frontal sharp waves (also called *encoches frontales*), which are a normal finding.

Background Abnormalities

When EEG background is not normal, the specific pattern of abnormalities can provide useful clues to the diagnosis and prognosis. One of the most common EEG abnormalities is excessive discontinuity for age. In a term neonate, any degree of discontinuity is abnormal. Excess discontinuity is a nonspecific marker of abnormal brain function, or encephalopathy. Mild to moderate discontinuity may also result from sedating medications, such as phenobarbital or morphine, though typical doses would not be expected to cause marked suppression or very low-voltage activity [14,15]. Excess discontinuity also reflects abnormal brain function due to underlying pathology. It is a common finding in HIE, with the degree of discontinuity reflecting the severity of injury [13]. At the most extreme end of the spectrum, the EEG may consist entirely of low-amplitude activity (<25 μV), with few or no bursts of higher-amplitude activity. This pattern may be described as *extremely low voltage* and carries a particularly poor prognosis [13].

Burst suppression refers to a specific abnormal EEG pattern with features beyond just discontinuity (Figure 17.6). A burst suppression pattern contains very low-amplitude suppressed periods, with amplitudes (<5 μV) even lower than those seen in excessive discontinuity. Bursts are high amplitude and consist of abnormal activity. The EEG in burst suppression is also invariant and unreactive, with no change over time even with stimulation. Burst suppression may be seen in severe brain injury; in these cases, prognosis is poor [13]. Burst suppression may also be seen in some neonatal-onset epilepsies, such as Ohtahara syndrome. In these patients, the EEG finding may be helpful in clarifying the specific diagnosis of an epilepsy syndrome.

Dysmaturity describes an EEG pattern with features that are not as mature as the neonate's corrected gestational age (CGA). For example, a 36-week CGA neonate having an EEG typical of a 32-week neonate would be said to have a dysmature EEG background. Dysmature EEG, particularly a persistently dysmature EEG, conveys an increased risk of later neuromotor disability and cognitive impairment in preterm neonates [16].

Asymmetry indicates lateralized or focal brain dysfunction. Asymmetry describes an EEG background in which there is a significant difference in activity between the two hemispheres. When asymmetry is noted on the EEG, neuroimaging is indicated to look

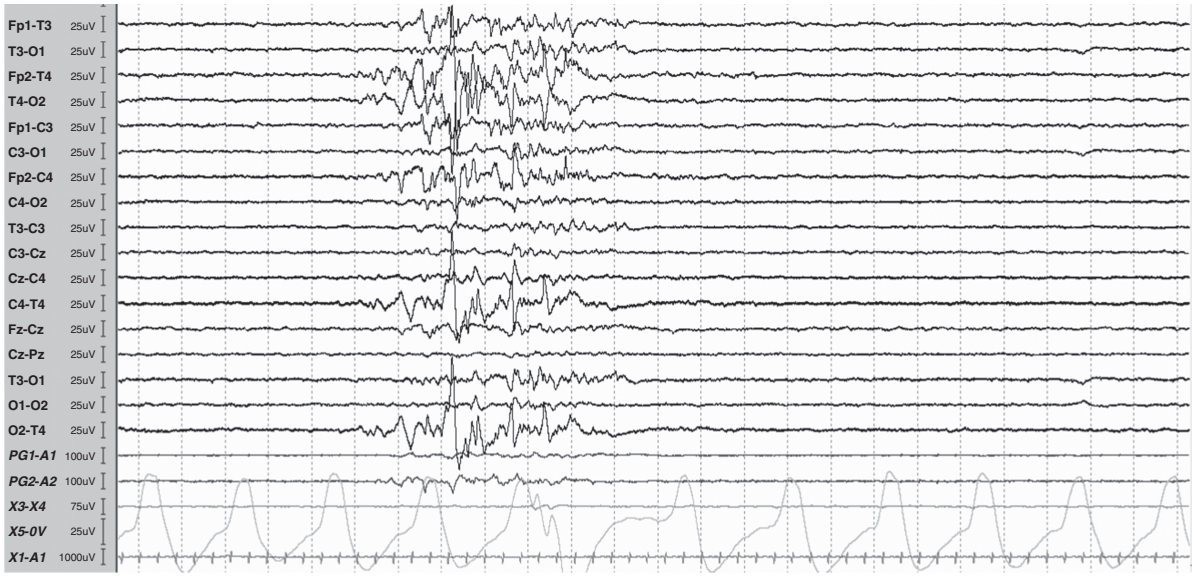


Figure 17.6 Example of burst suppression in a neonatal EEG. Note the brief burst of abnormal activity amid the very suppressed background. (Paper speed has been adjusted to 30 seconds per page to allow full visualization of the pattern.)

for a structural cause of asymmetric brain function, such as stroke or hemorrhage.

Sharp waves with certain features are abnormal in a neonatal EEG. Sharps that are excessive in quantity are abnormal and are nonspecific indicators of encephalopathy. While excess sharps are abnormal, they do not necessarily indicate an increased risk of seizures. Sharp waves are also abnormal if they occur in runs or trains, in which case they may indicate an increased risk of seizures. Sharp waves clustered in one particular region are concerning for focal brain dysfunction, as well as increased risk of seizures [3].

Seizures

Neonatal seizures are defined as abnormal paroxysmal electrical activity in the brain. Seizures are characterized on EEG by a rhythmic pattern of activity that evolves in either frequency, amplitude, morphology, or location [3] (Figure 17.7). The abnormal pattern must last for 10 seconds to be considered a seizure; abnormal, rhythmic, evolving patterns lasting less than 10 seconds are called *brief rhythmic discharges* (BRDs). BRDs are often seen in patients who also have seizures; their presence on EEG should increase suspicion for coexisting seizures.

When seizures are very frequent or prolonged, a neonate is said to have *status epilepticus*. Status epilepticus in a neonate is defined as seizures occupying greater than half of any 1-hour segment of the EEG. Thus a neonate who either has a single continuous seizure lasting 31 minutes or has repeated brief seizures with a summed duration greater than 30 minutes in any 60-minute window has status epilepticus. Status epilepticus is the extreme of high seizure burden and has been associated with the worse outcomes in a number of conditions [17]. For further discussion of neonatal seizures, see Chapter 43.

Common EEG Artifacts

EEG recordings can be affected by a number of interfering signals, both internal and external to the patient. These artifacts can be mistaken for abnormal brain activity and often require neurophysiologist input to discern. At the same time, recognition of common artifacts in neonatal EEG by the bedside caregiver can avoid unnecessary worry and, in some cases, even prevent unnecessary use of antiseizure medications. Patting artifact is very common in a neonatal EEG and is often mistaken for seizures (Figure 17.8). This is so because patting typically starts slowly and with lower amplitude and then increases in frequency and/or intensity before slowly dying down. The resulting movement of the baby and electrodes can result in an artifact on EEG that has many similarities with EEG seizures. Video correlation is the easiest way to distinguish patting artifact from



Figure 17.7 Example of neonatal seizure. Note the repetitive, rhythmic sharp-wave discharges, seen in multiple channels of the EEG.

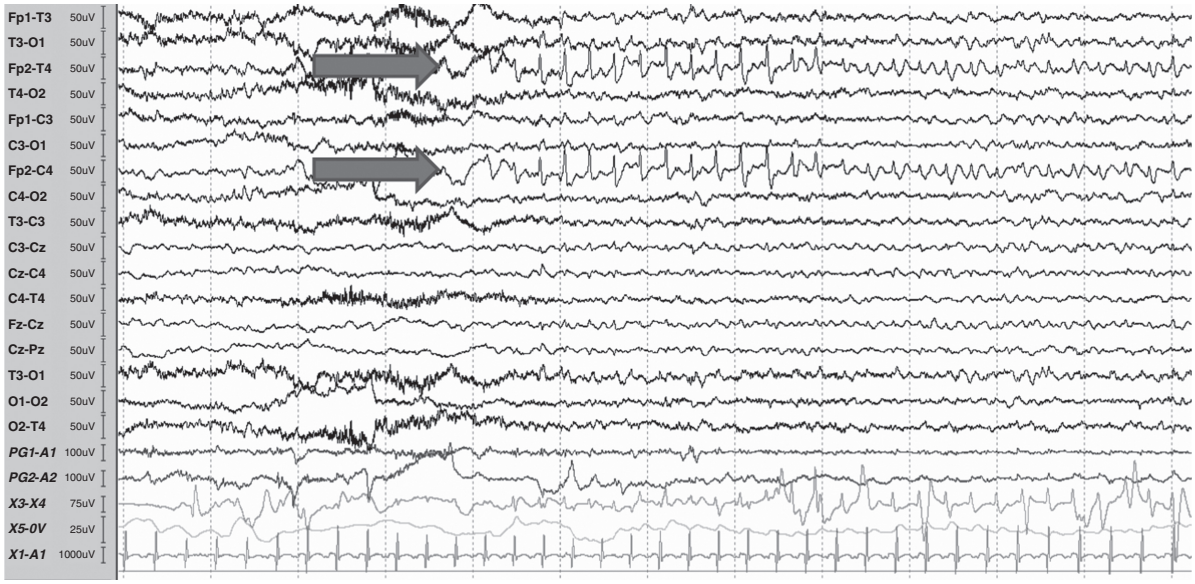


Figure 17.8 Example of patting artifact. The arrows indicate rhythmic, sharply contoured activity in the EEG that could be mistaken for seizure. Review of the accompanying video, however, revealed that this was an artifact due to rhythmic patting of the baby. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

seizure. Other clues include the presence of artifact in the ECG and noncerebral channels and sometimes abrupt onset and offset. In neonates with low-amplitude brain activity, an ECG artifact may also be mistaken for seizure (Figure 17.9). The ECG signal can be picked up by scalp electrodes, especially if brain activity is suppressed and does not interfere with the ECG. There are numerous other artifacts that may be seen on EEG; an EEG atlas can be helpful for identifying these patterns [18,19].

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Figure 17.9 Example of ECG artifact. Very sharp deflections are seen rhythmically in multiple channels of the EEG, but comparison with the ECG channel at the bottom of the image (A1–X1) reveals that these are all time locked to the ECG. This confirms they are ECG artifacts and not reflective of brain activity.

Amplitude-Integrated EEG (aEEG) Use in the Newborn

Introduction to aEEG

Amplitude-integrated EEG (aEEG) is a bedside brain-monitoring tool whose use is becoming more prevalent in the intensive care nursery setting. aEEG monitoring devices display both a limited-channel EEG recording and a compressed aEEG trace that allows evaluation of the brain's background activity, displays changes in the background activity over time, and facilitates screening for seizures. aEEG background pattern classification nomenclature is similar to the nomenclature used in EEG interpretation, facilitating communication between neonatologists, neurologists, and neurophysiologists. Evolution of the aEEG background pattern in term neonates with HIE conveys prognostic information, and in preterm neonates, evolution of the background activity over time corresponds well with evolving brain maturity. aEEG is also frequently used as a screening tool for the diagnosis of seizures because it is easy to apply and to interpret; however, it does have some limitations. While it is not the "gold standard" test, seizures can be diagnosed by aEEG. Seizure diagnosis is facilitated by evaluation of both the compressed aEEG trace and the raw EEG trace and review by an experienced reader.

History of aEEG

aEEG was first developed as a tool to assess the depth of anesthesia during surgery, providing a real-time assessment of brain activity during exposure to anesthetic agents. It was also used to monitor brain activity following adult cardiac arrest. Limited-channel EEG was then adapted to study brain activity in full-term neonates with encephalopathy. The first aEEG background classification system was developed by Helstrom-Westas and colleagues. The Helstrom-Westas system is based on pattern recognition, incorporates voltage criteria, and uses conventional EEG terminology [20]. The second most commonly referred to system was described by al Naqueeb [21] and is based on assessment of voltages (Figure 17.10). The use of aEEG in neonates has been studied primarily in two distinct populations, infants with concern for HIE and neonates who are born premature. Reports on the use of bedside aEEG monitoring first appeared in the literature in the 1980s, with several seminal publications regarding the ability of the background pattern observed on aEEG to serve as a predictor of outcome in neonates with HIE [22,23], as well as the ability of aEEG to identify seizures that were clinically silent in this same population [24]. Over the past 20 years, there have been numerous studies of aEEG in various neonatal patient

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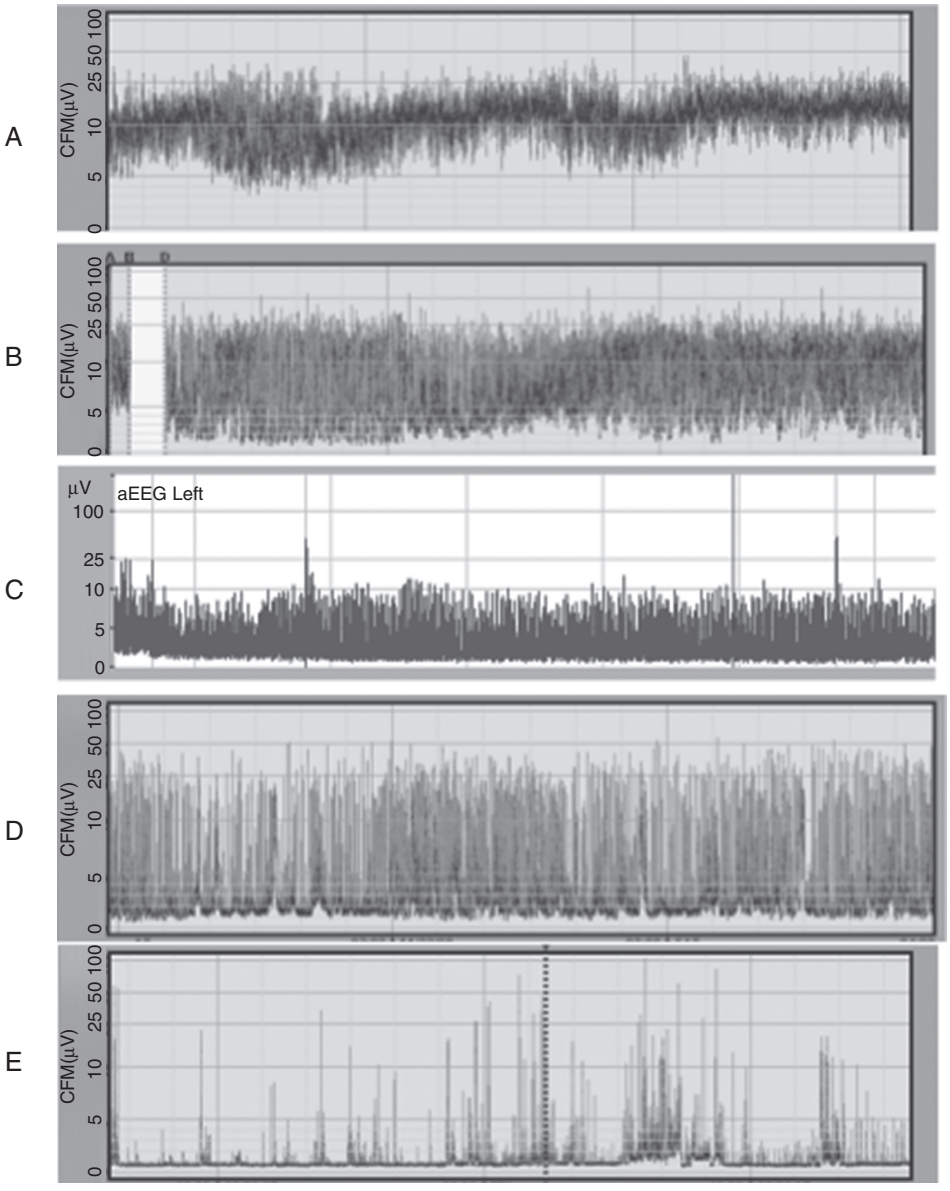


Figure 17.10 Pattern recognition/voltage classification comparison.

populations. There is also increased awareness of the impact of prematurity and critical illness on the vulnerable neonatal brain. This has led to increased recognition of the importance of brain monitoring and the development of neurocritical care for newborns [25]. As a result, aEEG is increasingly being used to monitor brain activity and to screen for seizures or evidence of brain injury in critically ill newborns.

Comparing EEG and aEEG

aEEG has several advantages over conventional EEG, but it does not replace conventional video-EEG as the "gold standard" for seizure diagnosis or for evaluation of the EEG background brain activity. Due to the limited number of channels that are recorded (usually left and right parietal and/or central leads), aEEG is easy to apply without the need for an EEG technician

(Figure 17.11). Favorable characteristics of aEEG include the following: aEEG is often available in clinical settings where full conventional EEG is not readily available; aEEG lead application is easy to learn and is not a time-consuming procedure; aEEG can be used to monitor for long periods of time without burdening neurophysiologists; aEEG recording devices are easy to use and have a small bedside footprint; aEEG can be incorporated into the software of conventional EEG devices, allowing for simultaneous recording and display of the aEEG compressed trace as well as the full video-EEG; aEEG is easy to interpret with a pattern-based classification system that parallels the classification of conventional EEG [26] but does not require extensive training in neurophysiology; and finally, the prognostic ability of aEEG may be superior to more subjective evaluations such as the neonatal neurologic examination. aEEG does have important limitations, especially when it is used to diagnose seizures. Due to the manner in which the signal is recorded and how the compressed aEEG trace is created, some seizures can be missed. First, aEEG only records EEG signal from a limited number of channels/regions of the brain. Seizures that arise in areas away from the recording leads may not be captured and therefore can be missed. In addition, seizures that are brief (e.g., <30 seconds) or low amplitude may be difficult to identify on the compressed trace. Using only the compressed aEEG trace to identify seizures results in low sensitivity and specificity for seizure recognition [27], so both the compressed trace and the raw trace should be evaluated.

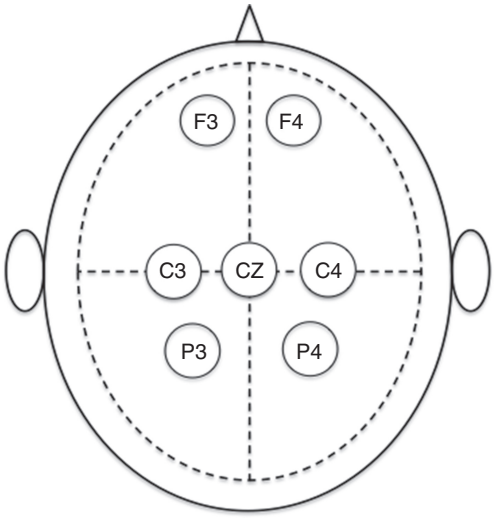


Figure 17.11 aEEG lead placement.

Technical Considerations

General Description of aEEG

The aEEG signal is traditionally recorded from either biparietal (P_3/P_4) and/or bicentral (C_3/C_4) EEG leads, although with digitalization it can be recorded from any pair of leads used in the International EEG 10–20 Classification System. With advancement of aEEG technologies, right, left, and cross-cerebral channels can be recorded. In order to derive the compressed aEEG trace, approximately 15 seconds of EEG signal is filtered, rectified, smoothed, and displayed in a semilogarithmic fashion. The minimum and maximum amplitudes are plotted at a paper speed of 6 cm/h on a semilogarithmic scale. This process is repeated every 15 seconds and results in a band of processed EEG activity, its width reflecting the minimum and maximum EEG amplitudes that are observed over time (Figure 17.12). The displayed

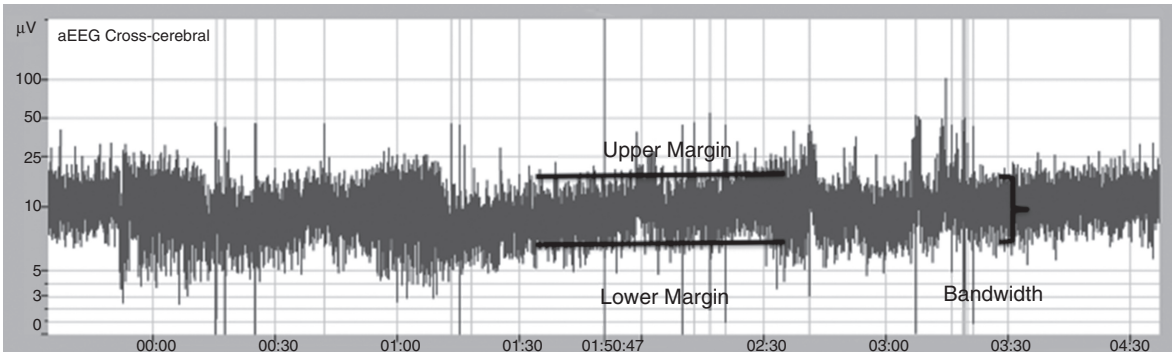


Figure 17.12 aEEG trace with bandwidth and minimum and maximum amplitudes highlighted.

amplitude is linear from 0–10 μV and logarithmic from 10–100 μV, which highlights changes in the low-voltage activity [20].

Electrode Application Techniques

Various types of electrodes can be used, including hydrogel and subdermal needle electrodes, which are sold specifically for aEEG devices, and conventional EEG electrodes in the form of disks and cups. Electrode choice is user and unit dependent. Each has its own set of advantages and disadvantages. Appropriate electrode placement is critical because the interelectrode distance has an impact on the appearance of the compressed trace. It is important that the electrodes themselves do not come into contact with each other. At the time of application, the impedance of each lead needs to be checked, and the leads should be reapplied if the impedance is too high.

Event Marking

In the intensive care unit, events such as apnea or movements that are suspicious for seizure activity, as well as the administration of anticonvulsant medications, can be marked on the recording to facilitate interpretation. Marking of events or procedures that could be confused with seizures is important to prevent inappropriate treatment of nonseizure events with anticonvulsant medications. These events include patting or rocking of the baby, feeding or sucking movements, high-frequency ventilation (HFOV), and hiccups. Administration of medications that may alter the background such as anticonvulsants, benzodiazepines, and opioids should also be documented using event marking. It is especially important to document the administration of the anticonvulsants because this will assist in evaluating the response to treatment and to determine whether further treatment is needed.

Interpretation by Neonatal Clinicians

Various providers in the neonatal intensive care unit (NICU) can reliably interpret the aEEG trace. aEEG is a bedside monitoring tool that provides real-time continuous information about brain activity and therefore is similar to other monitoring devices commonly used in the intensive care setting, such as heart rate, blood pressure, and oxygen saturation monitoring. It is important that bedside nurses have an understanding of aEEG because they are continuously present at the bedside. Nurses can be trained to apply the leads, to initiate aEEG monitoring, and to recognize and document the background pattern and areas of the aEEG trace that might be concerning for seizure activity. Nurses can also notify physicians and other practitioners regarding acute changes in the aEEG trace. In combination with neurologic examinations, aEEG findings can be documented in the medical record and provide a longitudinal record of the patient's neurologic health. In the setting of seizures, the response to medications can be identified on the aEEG, facilitating appropriate management of the patient. Seizures without overt clinical manifestations, known as *subclinical seizures*, are common in sick newborns and would remain undiagnosed without aEEG or EEG monitoring. Abnormal movements suspicious for seizure activity are common in sick newborns; however, they are often not found to have electrographic correlates. The American Clinical Neurophysiology Society recently published guidelines for brain monitoring of newborns in whom there is a concern for seizures, those deemed to be at risk of developing seizures, and those at risk of acquiring neurologic injury [2]. aEEG monitoring applied to at-risk patients can be helpful in diagnosing electrographic seizures or status epilepticus; each can occur without obvious clinical manifestations. Electroclinical dissociation occurs when seizures that initially had a clinical manifestation become clinically silent following treatment with an anticonvulsant medication. aEEG can detect these events and therefore can facilitate appropriate treatment of ongoing electrographic seizures.

aEEG Devices Used

Various aEEG recording devices are approved by the Food and Drug Administration (FDA) and available commercially. Stand-alone devices include the CNS EEG Monitor (Moberg ICU Solutions, Ambler, PA) and three other devices from Natus (San Carlos, CA): the Olympic Brainz Monitor, the Brainz BRM3 Monitor, and the Olympic CFM 6000 Monitor. As an alternative to stand-alone devices, aEEG software can be added to various conventional EEG platforms and allows for simultaneous recording and display of aEEG and complete video-EEG.

aEEG Classification Systems and Measures in Term Neonates

There are two commonly used classification systems that describe aEEG background activity. Hellstrom-Westas and al Naqeeb developed two separate but

similar classification systems. The al Naqueeb system uses voltage-based criteria and is divided into the following categories: normal amplitude (upper margin > 10 μV, lower margin > 5 μV), moderately abnormal amplitude (upper margin > 10–25 μV, lower margin ≤ 5 μV), and suppressed amplitude (also referred to as severely abnormal amplitude) (upper margin < 10 μV, lower margin < 5 μV) [21]. The Hellstrom-Westas classification system is both pattern and voltage based and uses terminology similar to that used to describe conventional EEG. Continuous normal voltage with sleep-wake cycling (SWC) is the most normal pattern that can be observed. In continuous normal voltage there are periods of continuous EEG activity followed by periods of discontinuous EEG activity, resulting in alternating sections of narrow and then broad bandwidth on the compressed aEEG trace. The lower margin (minimum amplitude) of the compressed trace is greater than 5–10 μV, and the upper margin (maximum amplitude) is 10–25 μV. Sleep-wake cycling in the compressed aEEG trace is demonstrated by smooth sinusoidal variations, mostly in the lower margin. The broadest part of the bandwidth reflects the discontinuous activity that occurs during quiet sleep in term newborns. Discontinuous normal voltage describes a decrease in the minimum amplitude to less than 5 μV, although there is still some variation in the minimum amplitude and the maximum amplitude is greater than 10 μV. SWC is typically absent, resulting in broad bandwidth on the compressed aEEG trace. Continuous low voltage describes a continuous pattern where both the maximum and minimum amplitudes are decreased at or around 5 μV. Burst suppression can be described by a loss of variation in the minimum amplitudes as well as decreased amplitude resulting in a flatting of the lower margin to between 0 and 2 μV with intermittent bursts of high-amplitude activity (>25 μV). Flat trace describes the pattern observed when little or no cortical electrical activity is detected, resulting in a flat lower margin at 0–2 μV and no bursts of activity. The background classification systems are demonstrated in Figure 17.10.

Medication and Artifacts

Effect of Sedatives, Analgesics, and Anticonvulsants

Medications such as sedatives, analgesics, and anticonvulsants may have an impact on the aEEG background pattern. Treatment with anticonvulsants and benzodiazipines such as phenobarbital, phenytoin, and lorazepam may result in a reduction in amplitude and may alter sleep-wake cycling [28]. The degree of impact on the background brain activity varies from patient to patient and may be related to the degree of underlying brain dysfunction as well as to the dose of medication administered. General anesthetics are also known to reduce voltages and thus affect the background pattern. Opiates such as morphine may also affect the background activity and may be dose dependent [29]. Administration of surfactant has also been reported to affect the background pattern, although the mechanism of action is not understood [30].

Artifacts

There are numerous sources of artifact that may affect an aEEG recording. Some artifacts are electrical in nature, and others result from physical movement. Electrical artifacts include high-frequency oscillating ventilation (HFOV), ECG, EMG, and other electrical interference from nearby medical equipment. Physical repetitive movements such as hiccups, patting, rocking, and sucking on a bottle or pacifier may be transmitted and produce changes in the aEEG trace that can be confused with seizure activity. Overhydration of hydrogel electrodes or electrodes that are too close or that are in contact may also produce artifacts.

aEEG in Term Infants

Prediction of Outcome

Our ability as clinicians to accurately identify neonates with certain poor or devastating prognoses is limited by the types of tools that are currently available and the amount of subjective interpretation required. Clinical history, neurologic examination, serum biomarkers, neurophysiology (aEEG or EEG), near-infrared spectroscopy (NIRS), and brain imaging (ultrasound [US], computed tomography [CT], and magnetic resonance imaging [MRI]) have all been studied as predictors of severe neurologic injury and poor outcome, although none has a high degree of accuracy. Amplitude-integrated EEG (aEEG) and conventional EEG seem to be the best objective tools to identify newborns at the highest risk for abnormal outcome [31]. Change in the aEEG/EEG background over the first days to weeks after a perinatal insult carries important prognostic information that may be more objective and less subjective than the

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neurologic examination. Both aEEG and conventional EEG allow for continuous real-time assessment of brain background activity. aEEG can be used in place of EEG when long periods of continuous monitoring are being performed without causing a significant burden on neurophysiologists. The majority of work regarding prognostic abilities of aEEG has been performed in term newborns with HIE. There are several studies that evaluate aEEG and its association with neurodevelopmental outcome in non-hypothermia-treated and hypothermia-treated neonates with HIE. Thoresen et al. performed one of the best studies to date of aEEG background during hypothermia treatment as a predictor of composite outcome of death or disability at 18 months of age [32]. The time to regain a normal aEEG trace during hypothermia and failure to develop sleep-wake cycling in neonates with HIE are now established important predictors of poor outcome (death or disability). In neonates treated with hypothermia, the positive predictive value (PPV) of an abnormal trace (BS, CLV, FT) at 3–6 hours after birth was low at 0.59. Conversely, at the same time point in non-hypothermia-treated neonates the PPV of an abnormal trace was 0.84. The PPV in hypothermia-treated patients increased steadily over time and at 24–36 hours was 0.92. At 60 hours the PPV was 1, the same as in normothermic patients (Figure 17.13). Failure to achieve sleep-wake cycling during the recording period, usually the first 96 hours after birth, was always associated with a poor prognosis [32].

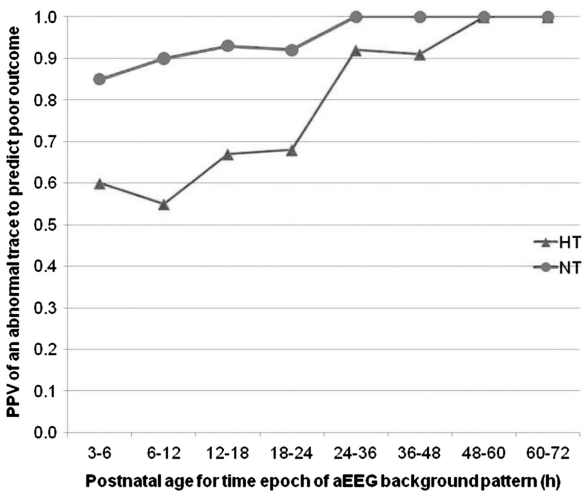


Figure 17.13 PPV of an abnormal trace (BS, LV, or FT) to predict poor outcome (death/disability) in hypothermia-treated or normothermia-treated infants at age epochs as indicated on the *x*-axis. (Reproduced with permission from Thoresen et al. [32].)

Use as an Entry Criterion for Hypothermia Trials

The presence of an abnormal aEEG background (burst suppression [BS], continuous low voltage [CLV], flat trace [FT]) or the presence of electrographic seizures within 6 hours of birth was used as an inclusion criterion in both the Cool-Cap [16] and the TOBY [34] randomized trials of therapeutic hypothermia and was recorded in some patients of the NICHD Neonatal Research Network whole-body hypothermia trial but not used as inclusion an criterion. aEEG was used in these trials as a method to improve the specificity of patient selection for the trial as well as a way to later stratify the analysis by moderate or severe encephalopathy. In clinical practice, due to the desire to rapidly identify and transfer patients who may be eligible for therapeutic hypothermia, aEEG is not routinely used in the United States as an eligibility criterion for therapeutic hypothermia.

Influence of Hypothermia on aEEG

Hypothermia treatment delays the time at which aEEG background abnormalities are best predictive of outcome. Prior to hypothermia therapy, an abnormal background pattern present at 3–6 hours after birth was highly predictive of a poor outcome [35]. In the setting of hypothermia treatment, the presence of an abnormal background, especially early in the course of treatment, is not as important for prognostication as is the recovery from an abnormal to a normal background pattern during treatment. Normalization of the background pattern at 48 hours is associated with a good outcome in patients treated with hypothermia [32,36] (Figure 17.14).

Use for Seizure Detection

Seizures are common in critically ill newborns and occur in 30–60% of newborns with HIE who are receiving hypothermia therapy [37–39]. Seizures on aEEG are identified by a sudden rise in the upper and lower margins of the compressed trace and can be confirmed by review of the raw EEG signal (Figure 17.15). By definition, seizures need to be greater than 10 seconds in duration and demonstrate evolution in frequency, morphology, and spatial distribution [3]. Seizures on aEEG are easily identified, especially if there are repetitive events separated by some return to the background activity pattern. Status epilepticus

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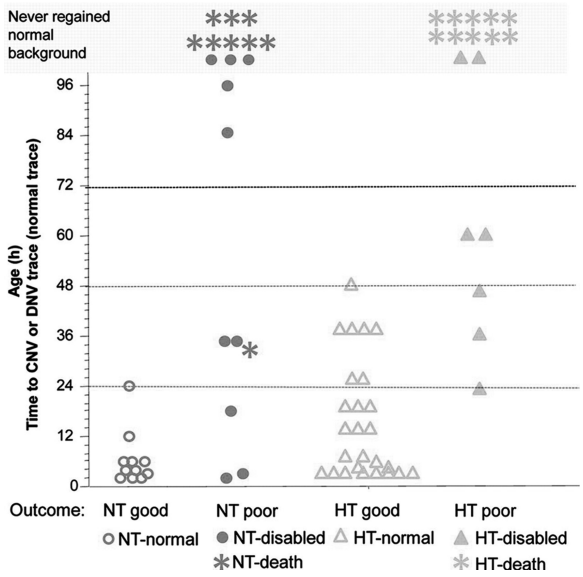


Figure 17.14 Time to regain a normal aEEG trace is shown on the *y*-axis, and infants who never regained a normal trace within the recording period are plotted on top of the figure. Symbols that define outcome are listed under the *x*-axis. (Reproduced with permission from Thoresen et al. [32].)

can also be identified on aEEG and is most commonly identified by a saw-toothed pattern of elevations of the upper and lower margins (Figure 17.16). Seizure detection is facilitated by simultaneous evaluation of both the compressed aEEG trace and the raw EEG trace. Sensitivity and specificity for seizure detection improve with reader experience and evaluation of both the compressed trace and raw EEG trace. In a recent meta-analysis, sensitivity and specificity were as high as 80–100% in experienced users [40].

Use of aEEG with Other Diagnoses

aEEG is also frequently applied as a monitoring tool for seizures or for evaluation of background activity in neonates with diagnoses that increase their risk of neurologic dysfunction. In particular, aEEG has been used to monitor newborns with inborn errors of metabolism [41], hypernatremia or hyponatremia [42], CNS infections due to viruses or bacteria [43,44], brain malformations (including arteriovenous malformations and periventricular leukomalacia) [45], and stroke.

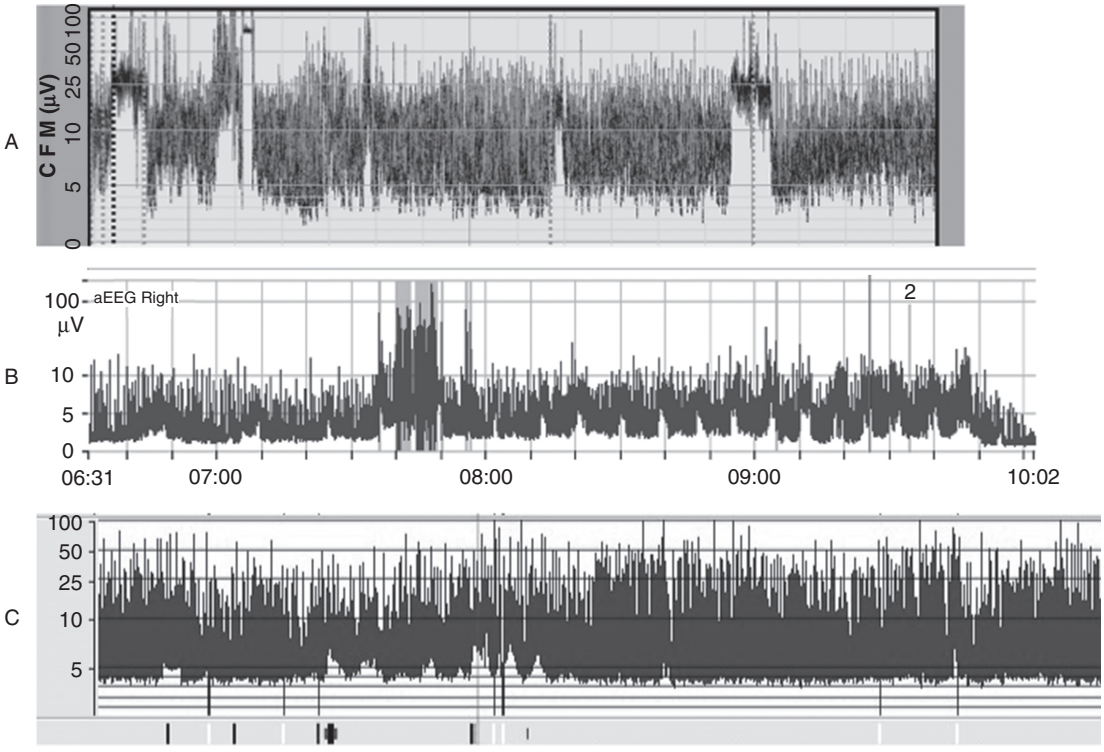


Figure 17.15 Seizures on aEEG.

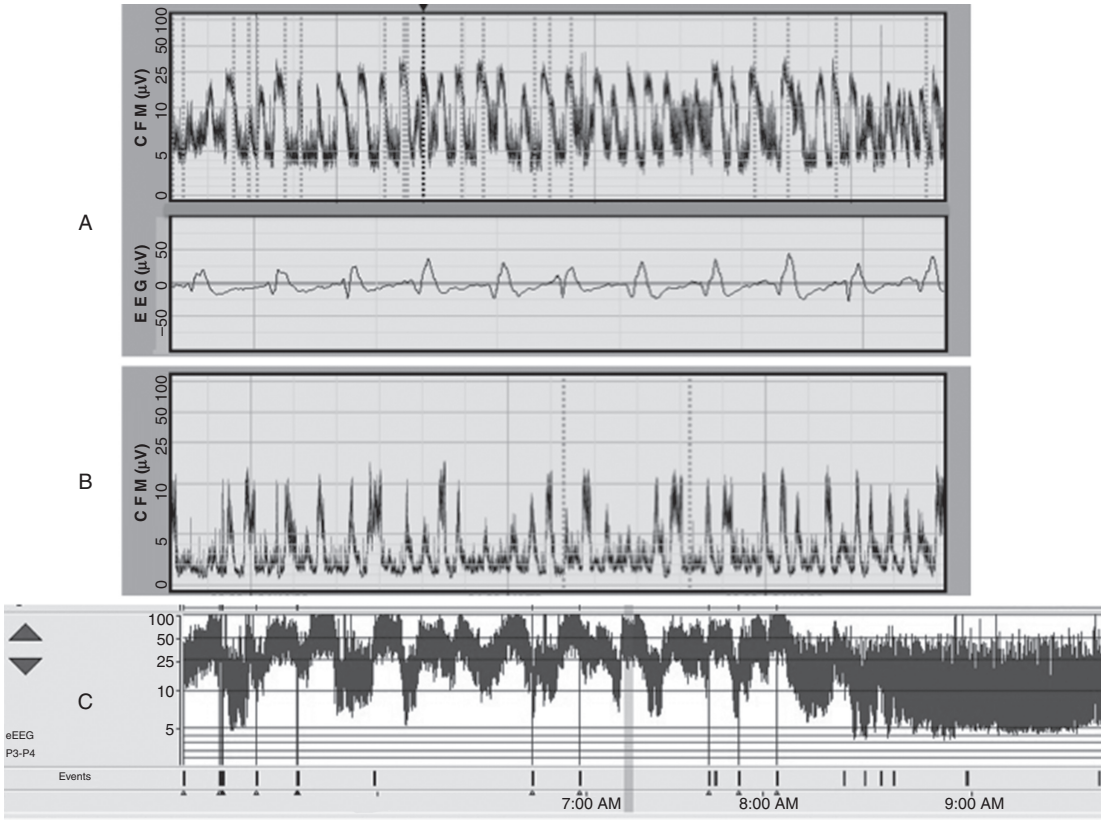


Figure 17.16 Status epilepticus.

aEEG in Preterm Infants

Advances in neonatal intensive care over the last several decades have resulted in improved survival rates for preterm infants; however, children born at extremely low gestational ages are at high risk for neurodevelopmental impairments [46,47]. A primary goal of neonatal research is the prevention of neurologic injury and subsequent disability. aEEG has been increasingly used as a method to assist in the identification of risk factors and individual infants at risk for adverse outcomes. Assessment of risk has been undertaken using clinical risk scores, neuroimaging, and assessments of brain function. Because aEEG can readily assess brain function, its utility in the prediction of outcome in premature infants has been of significant interest. aEEG avoids some of the problems of conventional EEG with its generation of a time-compressed tracing, ease of application and interpretation, and reduced interference with bedside intensive care. aEEG has shown good agreement with conventional EEG in term infants, but no similar investigation has been performed in preterm infants [26,48].

Normal Values in Healthy Preterm Infants

Several studies have provided normative data on aEEG in preterm infants at different gestational and postmenstrual ages. The normal background of the extremely preterm infant is discontinuous, characterized by periods with high-voltage activity termed *bursts* separated by periods of low-amplitude termed the *interburst interval* (IBI). The duration of the bursts increases with increasing gestational age, whereas the interburst interval decreases. Olischar et al. described the aEEG patterns seen in 75 preterm infants at between 23 and 29 weeks who were clinically stable and neurologically normal [49]. aEEG recordings were performed during the first 2 weeks of life. The authors found that continuous activity increased while discontinuous activity decreased with advancing gestational age. Cyclic changes in aEEG resembling early sleep-wake cycles could be seen in all

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infants. In a study of EEG in neurologically normal preterm infants born between 26 and 28 weeks' gestation, Selton et al. found that bursts lasted up to 3 minutes and the IBI was less than 46 seconds [50]. These authors concluded that these measures were useful in determining the normalcy of a tracing. Several other EEG and aEEG studies in stable preterm infants have been performed with similar findings [51]. Weekly recordings in stable preterm newborns without neurologic injury have shown that both gestational age (GA) and postnatal age (PNA) influence the maturation of the aEEG [52,53]. A higher odds ratio (OR) for PMA versus GA on the occurrence of a continuous pattern suggests that extrauterine life may accelerate aEEG maturation [53].

Cerebral Maturation

There has not been uniform agreement on how best to analyze the evolving aEEG pattern in preterm infants. Visual pattern recognition is most commonly used in term infants, but it is not suitable for comparisons between tracings, either from different infants or from the same infant at different postconceptual ages. Burdjalov et al. developed a scoring system for interpretation of aEEG tracings to objectively assess maturation at increasing gestational and postnatal ages [54] (Figure 17.17 and Table 17.2). The scoring system includes measures of continuity, presence of cyclic changes, degree of voltage amplitude depression, and bandwidth. Each variable is scored and summed to yield a total score for each recording ranging from 0 to a maximum of 13. In this study, 30 term and preterm infants were monitored with aEEG at 12–24 hours of age, 48–72 hours, and then weekly or biweekly until hospital discharge. A progressive increase in the overall score, as well as the individual component scores, was documented. The cycling score appeared to have the highest correlation with postconceptual age and was felt to be the single best sign of cerebral maturity. The Burdjalov scoring system has been used widely in the literature to assess aEEG maturation in preterm infants.

Sleep-wake Cycling or Cyclicity

Sleep-wake states cannot be assessed using aEEG because this requires evaluation of rapid eye movements, respiration, cardiac activity, and movement. Sleep-wake cycles (SWCs) can be seen on the aEEG as a sinusoidal pattern with varying bandwidth and continuity. Quiet sleep has a more discontinuous pattern,

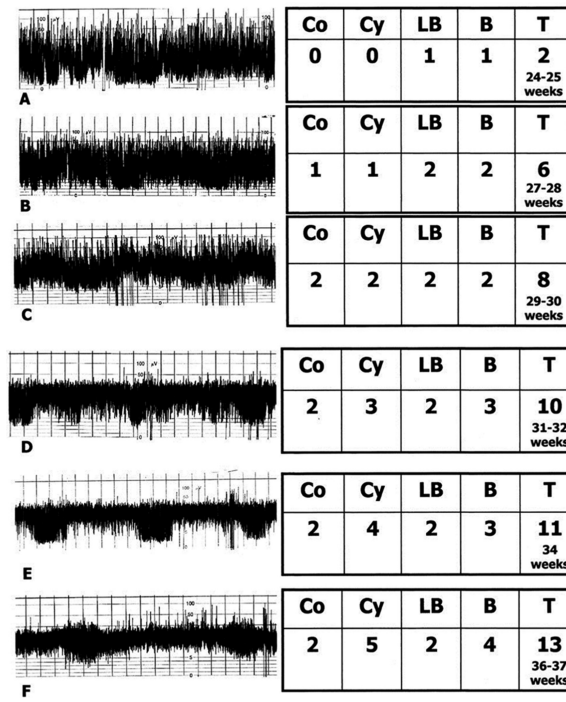


Figure 17.17 The left side of the figure demonstrates a progressive series of CFM monitor recordings; the right side shows the component score values for the respective studies. There is a maturation of the tracings from A through F in these recordings. Postconceptional age ranges are indicated. Co, continuity of the recording; Cy, presence of cycling; LB, lower border amplitude score; B, bandwidth; T, total score. (Reproduced with permission from Burdjalov et al. [54].)

whereas active sleep or wakefulness has a more continuous pattern (Table 17.2). The average duration of quiet sleep is approximately 20 minutes. SWCs are seen in preterm infants, but they are not as well defined and appear as sinusoidal changes in the lower margin in a discontinuous tracing. The emergence of SWCs is thought to provide a sensitive indicator of integrity and maturity of the CNS and may be predictive of long-term outcome. The cyclic variations in background activity may represent switches between thalamocortical and neocortical pattern generators. Kuhle et al. studied 38 infants without neurologic injury with mean gestational age (GA) of 27 weeks [55]. Cyclic variations in the EEG tracing were seen at a mean GA of 28 weeks and median postnatal age of 6 days. The majority had SWCs within the first week of life, and early SWCs were seen in preterm infants as young as 24 weeks. An early study by Hellström-Westas et al. found that the presence of either continuous background activity or

Table 17.2 Burdjalov Scoring System.

Score	Continuity	Cycling	Amplitude of lower border	Bandwdth span and amplitude of lower border
0	Discontinuous	None	Severely depressed (<3 μV)	Very depressed: low span (≤15 μV) and low voltage (5 μV)
1	Somewhat continuous	Waves first appear	Somewhat depressed (3–5 μV)	Very immature: high span (>20 μV) or moderate span (15–20 μV) and low voltage (5 μV)
2	Continuous	Not definite, somewhat cycling	Elevated (>5 μV)	Immature: high span (>20 μV) and high voltage (>5 μV)
3		Definite cycling but interrupted		Maturing: moderate span (15–20 μV) and high voltage (>5 μV)
4		Definite cycling, noninterrupted		Mature: low span (≤15 μV) and high voltage (>5 μV)
5		Regular and mature cycling		

Source: Reproduced with permission from Burdjalov et al. [54].

SWCs in the first week of life predicted a good outcome at 2 years of age [56]. Absent cyclicity within the first 24 hours was found to be associated with a poor outcome in a small study of 12 preterm infants [45].

Use with Intraventricular Hemorrhage, Posthemorrhagic Hydrocephalus, and Periventricular Leukomalacia

Intraventricular hemorrhage (IVH) is a common cause of long-term neurologic morbidity in preterm infants. Similar to the acute effects of HIE on the aEEG in the term infant, in preterm infants with IVH or periventricular leukomalacia (PVL), the electrocortical background activity is affected during the acute stage of illness. When a severe IVH is diagnosed on ultrasound, it is difficult to predict outcome based on the size of the bleed. Some infants will develop normally, and others will survive with severe handicaps. Studies have shown that there is a correlation between the extent of neurologic injury and the degree of depression seen on both EEG and aEEG. A older study by Aso et al. found that EEG background was more closely correlated with postmortem neurologic injury than the grade of hemorrhage on head ultrasound [57]. Hellström-Westas et al. studied the aEEG tracings from the first postnatal week of 64 preterm infants with grade III or IV hemorrhage [56]. Outcome was classified as death or survival with either poor or fair outcome. aEEG background was discontinuous in the majority of infants. Infants with continuous activity at 72–96 hours of age or sleep-wake cycling by end of the first week had better outcomes. Significant differences in the number of maximum bursts per hour (maxB) were documented at all time periods up to 96 hours. The authors concluded that maxB < 130 was predictive of death or survival with poor outcome. This cutoff was chosen because it had high specificity but a lower sensitivity for identifying high-risk infants. Outcome could be accurately predicted in 68% at 0–24 hours and 78% at 24–48 hours. Olischar et al. performed a study in 56 preterm infants at less than 30 weeks with grades I–IV hemorrhage during the first 2 weeks of life and compared the tracings with those of healthy preterm infants without IVH [58]. Discontinuous activity increased with higher grades of IVH versus control infants. Suspected seizure activity was common, occurring in up to 75% of infants at between 23 and 26 weeks with grade III or IV hemorrhage. One limitation of this study was that the raw EEG was not yet available to confirm seizure activity. Sleep-wake cycling was seen in fewer infants with larger hemorrhages versus control infants. In a recent study by Chalak et al., 30 newborns were monitored with aEEG during surfactant administration and tracheal suctioning during the first 48 hours of life [59]. The authors found that infants who developed IVH had lower upper and lower margin amplitude

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measures, and the four infants with severe IVH all developed a burst suppression pattern.

Approximately 25% of IVH is accompanied by posthemorrhagic hydrocephalus (PHH) that may resolve spontaneously or persist. Animal studies suggest that ventricular distension with PHH causes secondary brain injury due to periventricular hypoperfusion and may be prevented by serial lumbar punctures, temporary ventricular drainage, or permanent ventricular shunting. Most centers use cranial ultrasound together with Doppler and clinical signs to assist in the timing of intervention. In a small case series, abrupt aEEG changes were seen in two patients with PHH [60]. Increased discontinuity with loss of sleep-wake cycling was seen in one infant followed over 6–12 hours by clinical signs of increased intracranial pressure. Shunting was accompanied by the return of normal aEEG activity. The second infant had the abrupt onset of isoelectric tracing followed by seizure activity. Head ultrasound has been used to assess ventricular enlargement along with clinical signs and is generally used to guide decision making regarding intervention. Changes in aEEG may be a more sensitive indicator of the need for intervention in preterm infants with PHH. In two case series of preterm infants with PHH, aEEG was found to be abnormal, whereas concurrent clinical signs and head ultrasound findings were stable [61,62]. The aEEG tracings returned to normal following cerebrospinal fluid (CSF) drainage. The authors suggest that aEEG should be used in the assessment and management of PHH because aEEG abnormalities precede both clinical signs and ultrasound measurements indicating the need for neurosurgical intervention. A multicenter retrospective study by de Vries et al. compared infants with PHH receiving late intervention with those receiving early intervention and found that infants receiving late intervention more frequently needed a ventriculoperitoneal (VP) shunt (62% versus 16%, odds ratio [OR] 0.22, 95% confidence interval [CI] 0.08–0.62) [63]. Early intervention was defined as intervention prior to attaining a ventricular width of more than 4 mm above the 97th percentile for age. Moderate to severe handicap was seen more frequently in the late intervention group, but this difference was not statistically significant.

White matter injury in premature infants is responsible for adverse outcomes such as cerebral palsy and mental retardation. The use of aEEG in premature infants with IVH has received considerable attention, whereas its use in preterm infants with white matter injury has been less frequently studied. Song et al. examined the ability of aEEG in the first 72 hours of life to predict white matter injury and poor neurodevelopmental outcome at 18 months' corrected age in a cohort of 63 infants at 32 or fewer weeks of gestation [64]. Sensitivity, specificity and positive and negative predictive power of aEEG for white matter injury were 94, 41, 81, and 70%, respectively. aEEG was classified using the al Naqeeb amplitude criteria. Furthermore, the degree of abnormality of the aEEG showed a significant correlation with white matter injury and neurodevelopmental prognosis. In a subsequent study, Song et al. studied the use of early aEEG in the first 72 hours of life to predict brain injury and long-term outcome compared with brain imaging techniques including head ultrasound and MRI [65]. In this analysis, the aEEGs were assessed using the scoring system described by Burdjalov et al. Severe abnormalities using either aEEG, head US, or MRI were correlated with poor outcome at 18 months, but severe EEG abnormalities in the first 72 hours of life were positively correlated with white matter injury but not with IVH. The specificity of aEEG to predict poor outcome was similar to that of head US but lower than MRI, while the sensitivity of aEEG was highest of the three techniques. The predictive abilities of aEEG and MRI were the same as for aEEG, MRI, and head US with a sensitivity, specificity, and positive and negative predictive power of 52, 96, 79, and 88%, respectively. The authors concluded that aEEG has potential use as an early marker of adverse outcome in preterm infants.

Prediction of Outcome in Preterm Infants

Neurodevelopmental impairment is prevalent after preterm birth, and the etiology is assumed to be multifactorial, including acute injury due to IVH occurring in the first few days of life as well as white matter damage and infection that may develop later. Methods to identify brain injury are urgently needed to inform medical care and prognosis as well as to select infants for neuroprotective therapies. Background pattern and sleep-wake cycling have proven to be accurate early predictors of outcome in term HIE, but the utility of aEEG measures in predicting outcome in preterm infants is less clear. Wikström et al. monitored 49 preterm infants during the first 24 hours for background pattern, SWCs, seizures, IBI, and IBI percentage and assessed survivors at 2 years of

age [66]. The authors concluded that outcome can be predicted with 75–80% accuracy. The best predictors of poor outcome were burst suppression pattern, IBI > 6 seconds, and IBI percentage > 55%. Seizures were associated with IVH but not with poor outcome in this study. A large study of 143 preterm infants by Klebermass et al. also addressed this question by performing aEEG within the first 2 weeks of life and following infants at 3 years of age [67]. aEEG was assessed using scales for background activity, SWCs, and seizures. The authors concluded that aEEG predicts outcome with a specificity of 98%, a sensitivity of 61%, a PPV of 96%, and a NPV of 79% and can be used as an early prognostic tool. A study by Welch et al. assessed the correlation between the rate of brain maturation as measured by monthly serial aEEGs scored using the Burdjalov scoring system and neurodevelopmental outcome at 18–22 months of adjusted age [68]. The rate of brain maturation did not predict neurodevelopmental outcome in this cohort of 63 preterm infants. Using a short-term biomarker of outcome, aEEG maturity scores in the first week of life in a cohort of 39 preterm infants born at less than 32 weeks were found to be predictive of brain maturation, as judged by conventional MRI at term-equivalent age [69].

Use in Critically Ill Preterm Infants

While aEEG measures in the first few days have been found to be associated with short-term outcomes in extremely low-birth-weight infants, there has been limited investigation focused on the acute effects of physiologic parameters such as systemic blood flow, ligation of the patent ductus arteriosus, and hypotension on aEEG measures. Early studies suggested that low cerebral blood flow was associated with discontinuous aEEG in preterm infants and that EEG activity deteriorated with low cerebral saturations in an animal model [70,71]. A study by West et al. of 40 preterm infants using multiple regression analysis found that echocardiographic measures of right ventricular output at 12 hours were related to median EEG amplitude at 24 hours and that diastolic blood pressure at 24 hours was related to simultaneous EEG continuity [72]. The data suggest that low cardiac output and hypotension have both acute and prolonged impacts on EEG activity, but one cannot conclude that a causal relationship exists. A similar study by Shah et al. enrolled 92 preterm infants at fewer than 29 weeks of gestation and concluded that superior vena cava (SVC) flow at 12 hours was significantly associated with aEEG amplitude after adjustment for GA and severity of illness [73]. Infants receiving inotropes even with normalized blood pressure had significantly lower aEEG amplitude and continuity.

Hemodynamically significant patent ductus arteriosus (PDA) is associated with increased morbidity and mortality in preterm infants. The left-to-right shunt causes a ductal steal phenomenon and adversely affects both perfusion and oxygenation to various organs. Preterm infants with a hemodynamically significant PDA have lower cerebral saturations and a higher risk for both IVH and white matter injury [74–76]. An analysis of data from the Trial of Indomethacin Prophylaxis (TIPP) determined that ligation of the PDA is associated with increased risk of neurosensory impairment at 18 months [77]. Possible explanations are that infants undergoing surgery are sicker and that intraoperative or perioperative events including perioperative instability or anesthesia may contribute to poor outcome. Lemmers et al. studied 20 preterm infants undergoing PDA ligation using near-infrared spectroscopy (NIRS) and aEEG [78]. Median cerebral saturation ($rScO_2$) was 53% and dropped to 46% prior to placement of the clip. A subset of infants developed hypotension and a further decline in $rScO_2$ accompanied by lower aEEG amplitudes. The effect on aEEG amplitude was most dramatic in infants with the lowest $rScO_2$ values. In another case series of infants undergoing PDA ligation, a decline in the lower margin of the aEEG trace and degree of continuity was documented [79]. There was no relationship of changes in the aEEG to changes in cardiac output. The authors could not exclude the possibility that the aEEG suppression was related to the anesthetic and analgesic drugs used because there is growing evidence that anesthetic agents may be neurotoxic to the developing brain.

Use in Sepsis and Meningitis

Ter Horst et al. studied the longitudinal course and prognostic value of aEEG in newborns with sepsis or meningitis [43]. All infants with persistence of a continuous low-voltage or flat trace had abnormal outcome at 24 months. Seizure activity was seen more frequently in infants with poor outcomes ($p < 0.01$), whereas SWCs were more frequent in infants with good outcomes ($p < 0.05$). In another study of preterm

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infants with sepsis, burst suppression was seen in 57% of recordings versus 22% of recordings in patients without sepsis [80]. Sepsis was not found to affect the subsequent rate of brain maturation as assessed using the Burdjalov scoring method.

Conclusion

EEG and aEEG are valuable objective tools for assessing neonatal brain function. Conventional video-EEG is the "gold standard" for seizure detection, but aEEG may be used as a screening device as well as to diagnose seizures in settings where conventional EEG may not be available. Both modalities provide the ability to perform continuous monitoring and thus enable users to objectively evaluate the impact of prematurity and critical illness on the vulnerable neonatal brain, as well as to provide diagnostic and prognostic information that may facilitate management and decision making. Brain monitoring is crucially important to accurately diagnose seizures in neonates and thus ensure appropriate treatment of seizures. Without brain monitoring, neonates with paroxysmal movements that are not seizures may be inappropriately treated with anticonvulsant medications and critically ill patients with clinically silent seizures may not receive treatment.

References

1. Guideline II: Minimum technical standards for pediatric electroencephalography, April 2016. Available at www.acns.org/practice/guidelines.
2. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol* 2011; **28**(6): 611–7.
3. Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. *J Clin Neurophysiol* 2013; **30**(2): 161–73.
4. Neurodiagnostic Society. Skin safety during EEG procedures, April 2016. Available at www.aset.org/i4a/pages/index.cfm?pageid=4134.
5. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; **52**: 3–6.
6. World Health Organization (WHO). Guidelines on neonatal seizures, WHO Guidelines Approved by the Guidelines Review Committee, 2011. Available at www.ncbi.nlm.nih.gov/books/NBK304092/.
7. Murray DM, Boylan GB, Ali I, et al. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**(3): F187–91.
8. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. *Epilepsia* 1988; **29**(3): 256–61.
9. Glass HC, Wusthoff CJ, Shellhaas RA, et al. Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. *Neurology* 2014; **82**(14): 1239–44.
10. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. Electrographic seizures during therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Child Neurol.* 2011; **26**(6): 724–8.
11. Committee on Fetus and Newborn, Papile L-A, Baley JE, et al. Hypothermia and neonatal encephalopathy. *Pediatrics* 2014; **133**(6): 1146–50.
12. Scher MS, Alvin J, Gaus L, et al. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol* 2003; **28**(4): 277–80.
13. Tsuchida TN. EEG background patterns and prognostication of neonatal encephalopathy in the era of hypothermia. *J Clin Neurophysiol* 2013; **30**(2): 122–5.
14. Bye AM, Lee D, Naidoo D, Flanagan D. The effects of morphine and midazolam on EEGs in neonates. *J Clin Neurosci* 1997; **4**(2): 173–5.
15. Young GB, da Silva OP. Effects of morphine on the electroencephalograms of neonates: a prospective, observational study. *Clin Neurophysiol* 2000; **111**(11): 1955–60.
16. Le Bihannic A, Beauvais K, Busnel A, et al. Prognostic value of EEG in very premature newborns. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**(2): F106–9.
17. Abend NS, Wusthoff CJ. Neonatal seizures and status epilepticus. *J Clin Neurophysiol* 2012; **29**(5): 441–8.
18. Hrachovy RA, Mizrahi EM. *Atlas of Neonatal Electroencephalography*, 4th edn. New York: Demos Medical, 2015.
19. Clancy R, Wusthoff C. *Brain Monitoring: Normal Neonatal EEG*. Ambler, PA: Moberg Multimedia, 2011.
20. Hellström-Westas L, Rosén I, Vries LS de, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. *NeoReviews* 2006; 7(2): e76–87.
21. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by

amplitude-integrated electroencephalography. *Pediatrics* 1999; **103**(6 Pt 1): 1263–71.

22. Bjerre I, Hellström-Westas L, Rosén I, Svenningsen N. Monitoring of cerebral function after severe asphyxia in infancy. *Arch Dis Child* 1983; **58**(12): 997–1002.
23. Hellström-Westas L, Rosén I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **72**(1): F34–8.
24. Hellström-Westas L, Rosén I, Swenningsen NW. Silent seizures in sick infants in early life: diagnosis by continuous cerebral function monitoring. *Acta Paediatr Scand* 1985; **74**(5): 741–8.
25. Bonifacio SL, Glass HC, Peloquin S, Ferriero DM. A new neurological focus in neonatal intensive care. *Nat Rev Neurol* 2011; **7**(9): 485–94.
26. Toet MC, van der Meij W, de Vries LS, et al. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. *Pediatrics*. 2002; **109**(5): 772–9.
27. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007; **120**(4): 770–7.
28. Hellström-Westas L, Rosén I. Continuous brain-function monitoring: state of the art in clinical practice. *Semin Fetal Neonatal Med* 2006; **11**(6): 503–11.
29. Norman E, Wikström S, Rosén I, et al. Premedication for intubation with morphine causes prolonged depression of electrocortical background activity in preterm infants. *Pediatr Res* 2013; **73**(1): 87–94.
30. Hellström-Westas L, Bell AH, Skov L, et al. Cerebroelectrical depression following surfactant treatment in preterm neonates. *Pediatrics* 1992; **89**(4 Pt 1): 643–7.
31. Merchant N, Azzopardi D. Early predictors of outcome in infants treated with hypothermia for hypoxic-ischaemic encephalopathy. *Dev Med Child Neurol* 2015; **57**: 8–16.
32. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* 2010; **126**(1): e131–9.
33. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**(9460): 663–70.
34. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; **361**(14): 1349–58.
35. Toet MC, Hellström-Westas L, Groenendaal F, et al. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**(1): F19–23.
36. Bonifacio SL, deVries LS, Groenendaal F. Impact of hypothermia on predictors of poor outcome: how do we decide to redirect care? *Semin Fetal Neonatal Med* 2015; **20**(2): 122–7.
37. Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. *Lancet Neurol.* 2013; **12**(12): 1170–9.
38. Nash KB, Bonifacio SL, Glass HC, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *Neurology* 2011; **76**(6): 556–62.
39. Shah DK, Wusthoff CJ, Clarke P, et al. Electrographic seizures are associated with brain injury in newborns undergoing therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**(3): F219–24.
40. Rakshasbhuvankar A, Paul S, Nagarajan L, et al. EEG for detection of neonatal seizures: a systematic review. *Seizure*. 2015; **33**: 90–8.
41. Olischar M, Shany E, Aygün C, et al. Amplitude-integrated electroencephalography in newborns with inborn errors of metabolism. *Neonatology* 2012; **102**(3): 203–11.
42. Tekgunduz KŞ, Caner I, Eras Z, et al. Prognostic value of amplitude-integrated electroencephalography in neonates with hypernatremic dehydration. *J Matern-Fetal Neonatal Med* 2014; **27**(7): 658–63.
43. ter Horst HJ, van Olffen M, Remmelts HJ, et al. The prognostic value of amplitude integrated EEG in neonatal sepsis and/or meningitis. *Acta Paediatr Oslo Nor* 2010; **99**(2): 194–200.
44. Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates. *Ann Neurol* 2008; **64**(3): 266–73.
45. Kidokoro H, Kubota T, Hayashi N, et al. Absent cyclicity on aEEG within the first 24 h is associated with brain damage in preterm infants. *Neuropediatrics* 2010; **41**(6): 241–5.
46. Wood NS, Costeloe K, Gibson AT, et al. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**(2): F134–40.
47. Hintz SR, Kendrick DE, Wilson-Costello DE, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. *Pediatrics* 2011; **127**(1): 62–70.

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48. Hellström-Westas L. Comparison between tape-recorded and amplitude-integrated EEG monitoring in sick newborn infants. *Acta Paediatr Oslo Nor* 1992; **81**(10): 812–9.
49. Olischar M, Klebermass K, Kuhle S, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks' gestational age. *Pediatrics* 2004; **113**(1 Pt 1):e61–6.
50. Selton D, Andre M, Hascoët JM. Normal EEG in very premature infants: reference criteria. *Clin Neurophysiol* 2000; **111**(12): 2116–24.
51. Hayakawa M, Okumura A, Hayakawa F, et al. Background electroencephalographic (EEG) activities of very preterm infants born at less than 27 weeks gestation: a study on the degree of continuity. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**(3): F163–7.
52. Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. *J Perinatol* 2005; **25**(6): 391–6.
53. Klebermass K, Kuhle S, Olischar M, et al. Intra- and extrauterine maturation of amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks of gestation. *Biol Neonate* 2006; **89**(2): 120–5.
54. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics* 2003; **112**(4): 855–61.
55. Kuhle S, Klebermass K, Olischar M, et al. Sleep-wake cycles in preterm infants below 30 weeks of gestational age: preliminary results of a prospective amplitude-integrated EEG study. *Wien Klin Wochenschr*. 2001; **113**(7–8): 219–23.
56. Hellström-Westas L, Klette H, Thorngren-Jerneck K, Rosén I. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. *Neuropediatrics* 2001; **32**(6): 319–24.
57. Aso K, Abdab-Barmada M, Scher MS. EEG and the neuropathology in premature neonates with intraventricular hemorrhage. *J Clin Neurophysiol* 1993; **10**(3): 304–13.
58. Olischar M, Klebermass K, Waldhoer T, et al. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr Oslo Nor* 2007; **96**(12): 1743–50.
59. Chalak LF, Sikes NC, Mason MJ, Kaiser JR. Low-voltage aEEG as predictor of intracranial hemorrhage in preterm infants. *Pediatr Neurol* 2011; **44**(5): 364–9.
60. Olischar M, Klebermass K, Kuhle S, et al. Progressive posthemorrhagic hydrocephalus leads to changes of amplitude-integrated EEG activity in preterm infants. *Childs Nerv Syst* 2004; **20**(1): 41–5.
61. Olischar M, Klebermass K, Hengl B, et al. Cerebrospinal fluid drainage in posthaemorrhagic ventricular dilatation leads to improvement in amplitude-integrated electroencephalographic activity. *Acta Paediatr Oslo Nor* 2009; **98**(6): 1002–9.
62. Klebermass-Schrehof K, Rona Z, Waldhör T, et al. Can neurophysiological assessment improve timing of intervention in posthaemorrhagic ventricular dilatation? *Arch Dis Child Fetal Neonatal Ed* 2013; **98**(4): F291–7.
63. de Vries LS, Liem KD, van Dijk K, et al. Early versus late treatment of posthaemorrhagic ventricular dilatation: results of a retrospective study from five neonatal intensive care units in the Netherlands. *Acta Paediatr Oslo Nor* 2002; **91**(2): 212–7.
64. Song J, Zhu C, Xu F, et al. Predictive value of early amplitude-integrated electroencephalography for later diagnosed cerebral white matter damage in preterm infants. *Neuropediatrics* 2014; **45**(5): 314–20.
65. Song J, Xu F, Wang L, et al. Early amplitude-integrated electroencephalography predicts brain injury and neurological outcome in very preterm infants. *Sci Rep* 2015; **5**: 13810.
66. Wikström S, Pupp IH, Rosén I, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. *Acta Paediatr Oslo Nor* 2012; **101**(7): 719–26.
67. Klebermass K, Olischar M, Waldhoer T, et al. Amplitude-integrated EEG pattern predicts further outcome in preterm infants. *Pediatr Res* 2011; **70**(1): 102–8.
68. Welch C, Helderman J, Williamson E, O'Shea TM. Brain wave maturation and neurodevelopmental outcome in extremely low gestational age neonates. *J Perinatol* 2013; **33**(11): 867–71.
69. Natalucci G, Leuchter RH-V, Bucher HU, et al. Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants. *Pediatr Res* 2013; **74**(1): 68–74.
70. Greisen G, Pryds O. Low CBF, discontinuous EEG activity, and periventricular brain injury in ill, preterm neonates. *Brain Dev* 1989; **11**(3): 164–8.
71. Van Os S, Klaessens J, Hopman J, et al. Preservation of electrocortical brain activity during hypoxemia in preterm lambs. *Exp Brain Res* 2003; **151**(1): 54–9.
72. West CR, Groves AM, Williams CE, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. *Pediatr Res* 2006; **59**(4 Pt 1): 610–5.

73. Shah D, Paradisis M, Bowen JR. Relationship between systemic blood flow, blood pressure, inotropes, and aEEG in the first 48 h of life in extremely preterm infants. *Pediatr Res* 2013; **74**(3): 314–20.

74. Lemmers PMA, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. *Pediatrics* 2008; **121**(1): 142–7.

75. Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996; **75**(3): F183–6.

76. Miller SP, Mayer EE, Clyman RI, et al. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. *Pediatrics* 2006; **117**(5): 1626–31.

77. Kabra NS, Schmidt B, Roberts RS, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007; **150**(3): 229–34, 234.e1.

78. Lemmers PMA, Molenschot MC, Evens J, et al. Is cerebral oxygen supply compromised in preterm infants undergoing surgical closure for patent ductus arteriosus? *Arch Dis Child Fetal Neonatal Ed* 2010; **95**(6): F429–34.

79. Leslie ATFS, Jain A, El-Khuffash A, et al. Evaluation of cerebral electrical activity and cardiac output after patent ductus arteriosus ligation in preterm infants. *J Perinatol* 2013; **33**(11): 861–6.

80. Helderman JB, Welch CD, Leng X, O'Shea TM. Sepsis-associated electroencephalographic changes in extremely low gestational age neonates. *Early Hum Dev* 2010; **86**(8): 509–13.

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Chapter 18

Neuroimaging in the Evaluation of Pattern and Timing of Fetal and Neonatal Brain Abnormalities

Patrick D. Barnes

Introduction

In this updated chapter, current and advanced neuroimaging technologies are discussed, along with the basic principles of imaging diagnosis and guidelines for use in fetal, perinatal, and neonatal brain abnormalities [1,2]. This includes pattern of injury and timing issues, with special emphasis on neurovascular disease and the differential diagnosis. In the causative differentiation of static encephalopathies (e.g., cerebral palsy [CP]) from progressive encephalopathies, specific categories and timing are addressed. These include developmental abnormalities, trauma, neurovascular disease, infections and inflammatory processes, and metabolic disorders. Although a rare but important cause of progressive perinatal encephalopathy, neoplastic processes are not considered in detail here. Molecular and genetic technologies continue to advance toward eventual clinical application.

Neuroimaging Technologies and General Utilization

Imaging modalities may be classified as structural or functional [1–12]. *Structural imaging modalities* provide spatial resolution based primarily on anatomic or morphologic data. *Functional imaging modalities* provide spatial resolution based on physiologic, chemical, or metabolic data. Some modalities may actually be considered to provide both structural and functional information.

Ultrasonography (US) is primarily a structural imaging modality with some functional capabilities (e.g., Doppler: Figure 18.1a,b) [1–8,13–26]. It is readily accessible, portable, fast, real time, and multiplanar. It is less expensive than other cross-sectional modalities and relatively noninvasive (nonionizing radiation). It requires no contrast agent and infrequently needs patient sedation. The resolving power of US is based on variations in acoustic reflectance of tissues. Its diagnostic effectiveness, however, continues depend on the skill and experience of the operator and interpreter, and there are issues regarding interobserver reliability and accuracy [1–8,13–26]. In addition, US requires a window or path unimpeded by bone or air for cranial and spinal imaging. The most common uses of US are (1) fetal and neonatal screening, (2) screening of the infant who cannot be examined in the radiology department (e.g., premature neonate with intracranial hemorrhage, those with extracorporeal membrane oxygenation [ECMO], and intraoperative neonates), (3) when important adjunctive information is quickly needed (e.g., cystic versus solid, vascularity, vascular flow [Doppler: Figure 18.1a,b], or increased intracranial pressure), and (4) for real-time guidance and monitoring of invasive diagnostic or therapeutic surgical and interventional procedures [1–8,13].

In recent years, advanced US techniques have been introduced into clinical practice [1–8,13]. The development of high-resolution transducers, improvements in color Doppler signal processing, and new scanning techniques have significantly improved our ability to visualize structural, vascular, and cerebrospinal fluid (CSF) abnormalities in the neonatal brain. Examples are the mastoid view to better visualize the posterior fossa, power Doppler and transcranial Doppler (TCD) to evaluate intracranial hemodynamics (e.g., resistive indices [RIs]: Figure 18.1a,b), and the graded fontanel compression Doppler technique to evaluate hydrocephalus. Another advance in US technology that has yet to be translated is the development of vascular US contrast agents to amplify reflected sound waves. Potential applications include the detection of slow flow and the assessment of organ perfusion. Computerized analysis of textural features is another development that has promised increased sensitivity and specificity but has not been translated to clinical practice [13].

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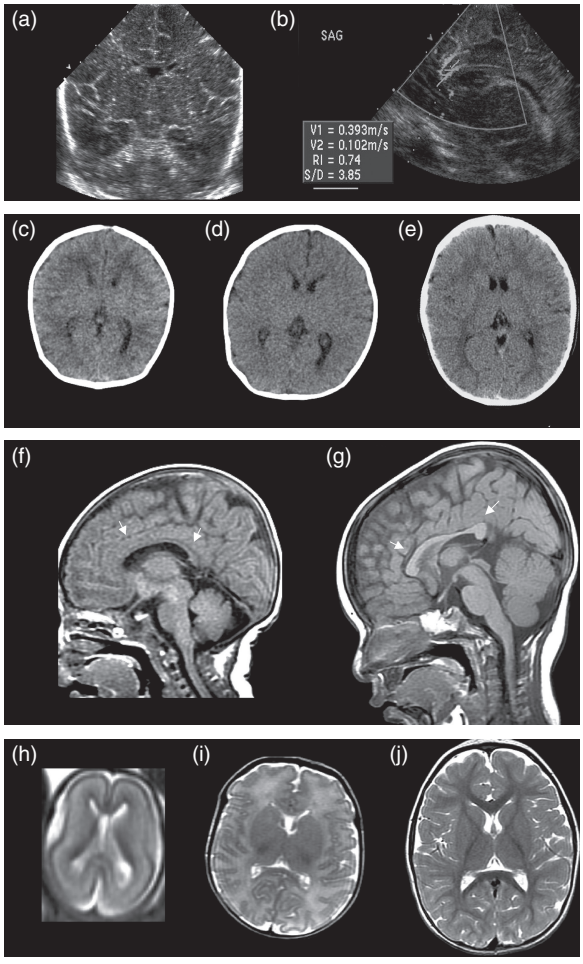


Figure 18.1 Normal infant and child brain. Ultrasound (US) images of term neonate: (a) coronal US; (b) sagittal US + Doppler with resistive indices (RIs). Computed tomographic (CT) images of (c) term neonate, (d) 2-month-old infant, and (e) 2-year-old child show progress of maturation, including myelination. Sagittal T1 magnetic resonance images (MRIs) of (f) term neonate and (g) 1-year-old infant show progress in brain growth, myelination of the corpus callosum (arrows), and pituitary maturation. T2 MRIs of (h) 20-week fetus, (i) term neonate, and (j) 2-year-old child show progress in maturation, i.e., decreasing water content and increasing myelination and cortication. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

Computed tomography (CT) is also primarily a structural imaging modality that has some functional capabilities (e.g., CT angiography) [1–8]. Although using ionizing radiation, current-generation multidetector CT (MDCT) effectively collimates and restricts the x-ray exposure to the immediate volume of interest, particularly when using the ALARA standard for pediatric patients, which adjusts radiation dose relative to age, size, and anatomic region [27]. Direct imaging is usually restricted to the axial plane (Figure 18.1c–e). Reformatting from axial sections to other planes (e.g., coronal or sagittal) is now the MDCT standard. Projection scout images may provide information similar to plain films but with less spatial resolution. CT of the pediatric CNS is usually done using either the conventional or the helical/spiral technique. CT requires sedation in infants and young children more often than does US but less often than MRI. The more rapid MDCT technology, however, has allowed a significant reduction in the need for sedation or anesthesia. The neonate or very young infant, for example, may be examined bundled while asleep after a feeding or during a nap. CT occasionally needs intravenous iodinated contrast enhancement, but CSF contrast opacification is rarely needed. High-resolution bone and soft-tissue algorithms are important for demonstrating fine anatomy (e.g., skull base). Advances in computer display technology include image fusion, two-dimensional reformatting, three-dimensional volumetric and reconstruction methods, segmentation, and surface-rendering techniques. These high-resolution display techniques are used for CT angiography and venography, craniofacial and spinal imaging for surgical planning, and stereotactic image guidance of radiotherapy and interventional and neurosurgical procedures.

The role of CT has been further redefined in the context of accessible and reliable US and MRI [1–12,15,28,29]. US is the procedure of choice for primary imaging or screening of the brain and spinal neuraxis in neonates and young infants. When US does not satisfy the clinical inquiry or an acoustic window is not available, then CT becomes the primary modality for brain imaging in children, especially in acute or emergent presentations. This is especially important for acute neurologic presentations. In these situations, CT is used primarily to screen for acute or subacute hemorrhage, focal or diffuse edema, herniation, fractures, hydrocephalus, tumor mass, or abnormal collections (e.g., blood, pus, air, CSF, etc.). Other primary indications for CT include the evaluation of bony or airspace abnormalities of the skull base, cranial vault, orbit, paranasal sinuses, facial bones, and temporal bone. Additionally, CT is the definitive procedure for detection and confirmation of calcification. It is also important in the bony evaluation of a localized spinal column abnormality (e.g., trauma). Contraindications to CT in childhood are unusual, particularly with the proper application of radiation protection (ALARA standard), the appropriate use of nonionic contrast

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agents, the proper administration of sedation or anesthesia, and the use of vital monitoring.

When CT is used, intravenous enhancement for blood pool effect (e.g., CT angiography) or blood-brain barrier disruption is additionally recommended for the evaluation of suspected or known vascular malformation, neoplasm, abscess, or empyema [1–4,28,29]. Enhanced CT may help to evaluate a mass or hemorrhage of unknown etiology and identify the membrane of a chronic subdural collection. By identifying the cortical veins, enhanced CT may distinguish prominent low-density subarachnoid collections (e.g., benign extracerebral collections or benign external hydrocephalus of infancy) from low-density subdural collections (e.g., chronic subdural hematomas or hygromas). It also may help to differentiate infarction from neoplasm or abscess, serve as an indicator of disease activity, for example, in degenerative or inflammatory disease and vasculitis, and provide a high-yield guide for stereotactic or open biopsy. Ventricular or subarachnoid CSF contrast opacification may further assist in evaluating or confirming CSF compartment lesions or communication (e.g., arachnoid cyst or ventricular encystment). As a rule, MRI is the preferred alternative to contrast-enhanced CT in the circumstances just enumerated.

Nuclear medicine (NM) is primarily a functional imaging technology [1–8]. NM involves imaging of the biologic distributions of administered radioactive pharmaceuticals. Whereas positron-emission tomography (PET) has the unique ability to provide specific metabolic tracers (e.g., oxygen use and glucose metabolism), the wider availability, relative simplicity, and rapid technical advancement of single-photon-emission computed tomography (SPECT) allows more practical functional assessment of the pediatric CNS. Clinical and investigative applications have included the assessment of brain development and maturation, focus localization in refractory childhood epilepsy (e.g., ictal perfusion SPECT, interictal PET), assessment of tumor progression versus treatment effects in childhood CNS neoplasia (perfusion and thallium SPECT, ^{18}FDG-PET), the evaluation of occlusive cerebrovascular disease for surgical revascularization (e.g., perfusion SPECT), the diagnosis of brain death (perfusion SPECT), the use of brain activation techniques (e.g., perfusion SPECT, PET) in the elucidation of childhood cognitive disorders, the assessment of CSF kinetics (e.g., in hydrocephalus, CSF leaks), and spinal column screening (skeletal SPECT) [1–8].

Magnetic resonance imaging (MR, MRI) is both a structural and a functional imaging modality [1–12]. MRI uses magnetic fields and radio waves. It is one of the less invasive or relatively noninvasive imaging technologies (Figure 18.1f–j). Furthermore, the MRI signal is exponentially derived from multiple parameters (e.g., T1, T2, proton density, T2*, proton flow, proton relaxation enhancement, chemical shift, magnetization transfer, and molecular diffusion). MRI also employs many more basic imaging techniques than other modalities (e.g., spin-echo, inversion-recovery, gradient-echo, and chemical-shift imaging methods). Advancing MRI capabilities have further improved its sensitivity, specificity, and efficiency [1–12,30]. These include the fluid attenuation inversion recovery technique (FLAIR), fat-suppression short TI inversion recovery imaging (STIR), and magnetization transfer imaging (MTI) for increased structural resolution. Fast and ultrafast MRI techniques (fast spin-echo, fast gradient-echo, echo-planar imaging, parallel imaging) have also been developed to reduce imaging times, improve structural resolution, and provide functional resolution (e.g., fetal imaging). Important applications include MR vascular imaging (MR angiography and venography [MRA]) and perfusion MRI (PMRI), diffusion-weighted imaging (DWI), CSF flow and brain/cord motion imaging, brain activation techniques, and MR spectroscopy (MRS). Fast and ultrafast imaging techniques are also being used for fetal/obstetric imaging [31–36], morphometrics, treatment planning, and real-time MRI-guided surgical and interventional procedures.

The role of MRI in imaging of the developing CNS is defined by its superior sensitivity and specificity in a number of areas compared with US and CT [1–12,15,19–24,26,28–36]. MRI has also obviated or redefined the roles of invasive procedures (e.g., myelography, ventriculography, cisternography, and angiography). MRI provides multiplanar imaging with equivalent resolution in all planes without repositioning the patient. Bone does not interfere with soft-tissue resolution, although metallic objects often produce signal void or field distortion artifacts. Some ferromagnetic or electronic devices (e.g., ferrous aneurysm clips and pacemakers) pose a hazard, and MRI is usually contraindicated in these cases. MRI usually requires longer examination times than does US and CT, and patient sedation or anesthesia is often required in infants and younger children because image quality is easily compromised by motion. However, MRI may be

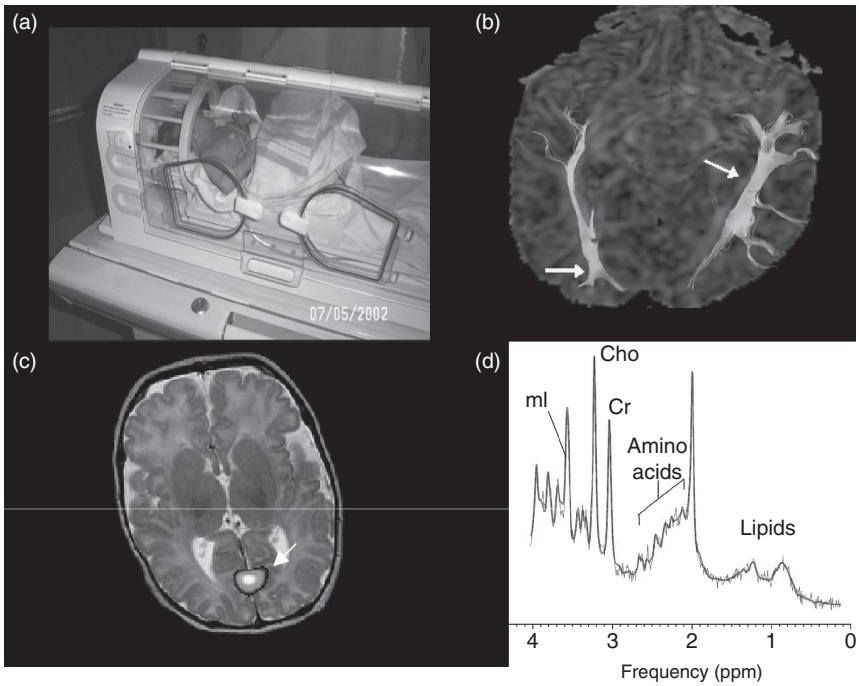


Figure 18.2 Advanced MRI techniques: (a) MR-compatible incubator; (b) DTI white matter tractography (arrows); (c) fMRI (primary visual cortex activation: arrow); (d) MR spectroscopy (see text). (Courtesy of Ashok Panigrahy, MD, Children's Hospital of Pittsburgh – UPMC [12].) (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

done successfully in a large percentage of stable neonates and young infants using the "bundle and feed" technique. MRI may not be as readily accessible to critically ill pediatric patients as US or CT, and it may not be feasible in emergencies or for intensive care cases unless magnet-compatible vital monitoring and support are available. This is particularly important for unstable neonates (e.g., using an MRI-compatible incubator) [12] (Figure 18.2a).

MRI demonstrates superior sensitivity and specificity in a number of circumstances, particularly with the addition of new structural and functional techniques such as FLAIR, STIR, MTI, DWI, PMRI, and MRS [1–12,15,19–24,26,28–36]. The *FLAIR* sequence attenuates the signal from flowing water (i.e., CSF) and increases the conspicuity of non-fluid-water-containing lesions lying in close approximation to the CSF-filled subarachnoid and ventricular spaces. The *STIR* technique suppresses fat signal to provide improved conspicuity of water-containing lesions in regions where fat dominates (e.g., orbit, head and neck, spine). The *MTI* method suppresses background tissues and increases conspicuity for vascular flow enhancement (e.g., MRA) and gadolinium enhancement.

MRI is the imaging modality of choice in a number of clinical situations [1–12,15,19–24,26,28–36]. These include developmental delay (e.g., static encephalopathy versus neurodegenerative disease); unexplained seizures (especially focal), unexplained neuroendocrine disorder, or unexplained hydrocephalus; the pretreatment evaluation of neoplastic processes and the follow-up of tumor response and treatment effects; suspected infectious, postinfectious, and other inflammatory or noninflammatory encephalitides (e.g., encephalitis, postinfectious demyelination, vasculitis); migrational and other submacroscopic dysgeneses (e.g., cortical dysplasia); neurocutaneous syndromes (e.g., neurofibromatosis 1, tuberous sclerosis); intractable or refractory epilepsy; and vascular diseases, hemorrhage, and the sequelae of trauma.

MRI frequently offers greater diagnostic specificity than does CT or US for delineating vascular and hemorrhagic processes. This includes the clear depiction of vascular structures and abnormalities based on proton flow parameters and software enhancements not requiring the injection of contrast agents (e.g., MRA). *MRA and MR venography* (MRV), including with contrast blood-pool enhancement (e.g., gadolinium, feraheme), may additionally be used to differentiate arterial from venous occlusive disease [1–12,15,19–24,26,28–36]. Using gradient recalled echo (GRE) magnetic susceptibility techniques, MRI also provides more specific identification and staging of hemorrhage and thrombosis based on the evolution

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of red blood cell and hemoglobin breakdown. MRI is often reserved for more definitive evaluation of hemorrhage and as an indicator or guide for angiography in a number of special situations. MRI may be used to evaluate an atypical or unexplained intracranial hemorrhage by distinguishing hemorrhagic infarction from hematoma and by distinguishing among the types of vascular malformations (e.g., cavernous versus arteriovenous malformations). MRA may obviate the need in some cases of vascular malformation for conventional angiography in the follow-up of surgery, interventional treatment, or radiosurgery.

In the evaluation of intracranial vascular anomalies (e.g., vascular malformation and aneurysm), MRI may identify otherwise unsuspected prior hemorrhage (i.e., hemosiderin) [1–12,15,19–24,26,28–36]. When CT demonstrates a nonspecific focal high density (calcification versus hemorrhage), MRI may provide further specificity, for example, by distinguishing an occult vascular malformation (e.g., cavernous malformation) from a neoplasm (e.g., glioma). It may further assist US or CT in differentiating benign infantile collections (i.e., external hydrocephalus) from subdural hematomas [28,29]. MRI often also provides definitive evaluation of muscular and cutaneous vascular anomalies (i.e., hemangiomas and vascular malformations) that arise in parameningeal locations (e.g., head and neck, paraspinal) and extend to involve the CNS directly or are associated with other CNS vascular or non-vascular abnormalities.

MR spectroscopy (MRS) offers a non-invasive in vivo approach to biochemical analysis [1–12,37–40] (Fig. 18.2d). Furthermore, MRS provides additional quantitative information regarding cellular metabolites, since signal intensity is linearly related to steady-state metabolite concentration. MRS can detect cellular biochemical changes prior to the detection of morphological changes by MRI or other imaging modalities. MRS may therefore provide further insight into both follow-up assessment and prognosis. With recent advances in instrumentation and methodology, and using the high inherent sensitivity of hydrogen 1, single-voxel and multivoxel proton MRS is now carried out with relatively short acquisition times to detect low-concentration metabolites in healthy and diseased tissues. Phosphorus-31 spectroscopy has also been developed for pediatric use. Currently, MRS has been used primarily in the assessment of brain development and maturation (Figure 18.3), perinatal brain injury,

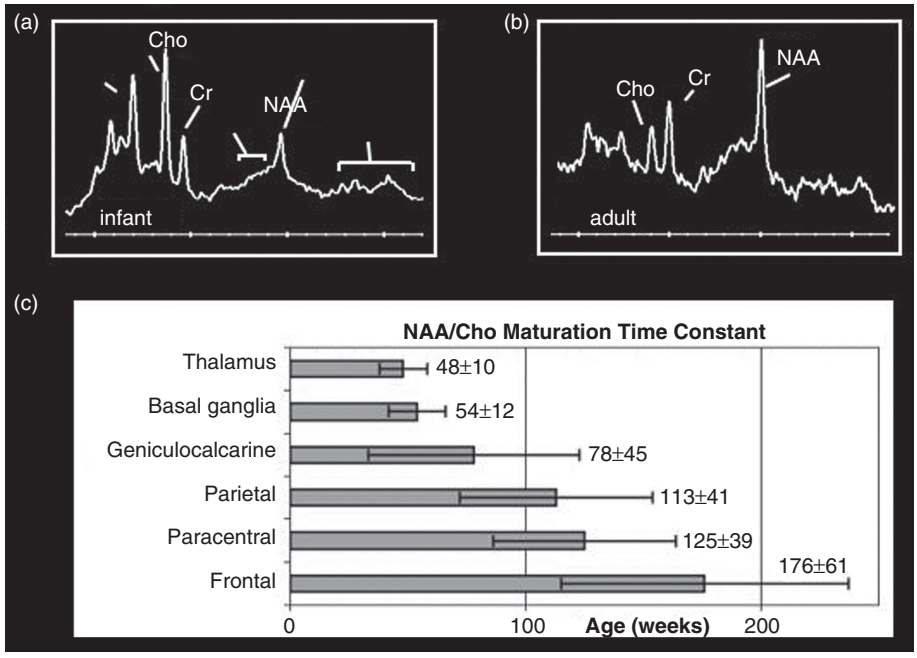


Figure 18.3 ^{1}H MR spectroscopy of the developing brain with (a) infant spectra, (b) adult spectra, and (c) maturation time constants for brain regions. (From Dermon J, Barnes PD, Spielman D. Spatiotemporal mapping of cerebral maturation in childhood using 2D MR spectroscopic imaging. American Society of Neuroradiology, 2002.)

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childhood CNS neoplasia versus treatment effects, and metabolic and neurodegenerative disorders [39,40].

Perfusion MRI (PMRI) has been developed to evaluate cerebral perfusion dynamics through the application of a dynamic contrast-enhanced T2*-weighted MRI technique [1–4,8,12,31,41]. This technique has been used to qualitate and quantitate normal and abnormal cerebrovascular dynamics of the developing brain by analyzing hemodynamic parameters including relative cerebral blood volume, relative cerebral blood flow, and mean transit time, all as complementary to conventional MR imaging. Non-contrast-enhanced methods of PMRI have also been developed (e.g., flow-activated inversion recovery [FAIR], arterial spin labeling [ASL], blood oxygen level determination [BOLD]) [41]. Current and advanced applications of these perfusion techniques include the evaluation of ischemic cerebrovascular disease (e.g., hypoxia-ischemia, moyamoya, and sickle cell disease), the differentiation of tumor progression from treatment effects, and brain activation imaging [1–4,8,12,31,41]. One of the most active areas of research is the localization of brain activity, an area previously dominated by NM including SPECT and PET.

Functional MRI (fMRI) is the terminology often applied to brain activation imaging in which local or regional changes in cerebral blood flow are displayed that accompany stimulation or activation of sensory (e.g., visual, auditory, and somatosensory), motor, or cognitive centers [1–4,12]. fMRI is providing important information regarding the spatial distribution of sensory, motor, and cognitive function and functional impairment (Figure 18.2c). Also, it may serve as a guide for safer and more effective interventions, including microneurosurgery or conformal radiotherapy, for example, in the ablation of tumors, vascular malformations, and seizure foci. More recently, fMRI is being used to evaluate brain development and maturation in neonates and young infants, including the effects of injury and postinjury repair and recovery [12].

Using echo-planar or line-scan spin-echo techniques, *diffusion-weighted imaging* (DWI) provides information based on differences in the rate of diffusion of water molecules, and it is especially sensitive to cellular changes [1–12,30,40,42–53]. The rate of diffusion, or apparent diffusion coefficient (ADC), is higher for free or pure water than for macromolecular bound water. The ADC varies according to the microstructural or physiologic state of a tissue. Fractional anisotropy (FA) is a vector measurement of the directionality of diffusion using *diffusion tensor imaging* (DTI) methods and also varies with the microstructural environment, both developmentally and pathologically [53] (Figure 18.2b). This method is especially helpful in assessing axonal development and injury, including myelination and synaptogenesis (connectivity). Current clinical applications of DWI and DTI include the assessment of brain maturation, the evaluation of acute injury, and the analysis of the sequelae of injury (Figure 18.4). A particularly important application of DWI is in the early detection of diffuse and focal ischemic injury. The ADC of water is reduced within minutes of an ischemic insult and progressively so within the first hour. High-intensity abnormalities are demonstrated on DWI, along with low-intensity abnormalities on calculated ADC images, at a time when conventional MRI is negative, and this likely reflects cellular injury (e.g., necrosis) with primary or secondary energy failure. Further investigations are under way regarding the roles of DWI, PMRI, and MRS in the early diagnosis and treatment of potentially reversible ischemic injury.

Motion-sensitive MRI techniques are used not only to evaluate vascular flow (e.g., MRA) and perfusion but also to demonstrate the effect of pulsatile cardiovascular flow on other fluid tissues (e.g., CSF) and on nonfluid tissues such as the brain and spinal cord. Using cardiac or pulse gating, these MRI techniques



Figure 18.4 DTI with FA map in a preterm neonate as a quantitative display of white matter development (arrows) of the internal capsule and corpus callosum [12].

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may be used to evaluate, preoperatively and postoperatively, abnormalities of CSF dynamics (e.g., hydrocephalus and hydrosyringomyelia), as well as abnormalities of brain motion (e.g., Chiari malformation) and spinal cord motion (e.g., tethered cord syndrome) [1–4]. A number of nongated MRI techniques (e.g., propeller imaging) are also being used to reduce motion artifacts and improve image quality.

Guidelines and Principles of Imaging Diagnosis

Developmental Abnormalities

Congenital abnormalities of the CNS may be developmental or acquired in origin and may result from defective formation, postformational destruction, or disordered maturation [1,2,4,5,54]. These are probably best classified according to gestational timing (Table 18.1) and include disorders of dorsal and ventral neural tube formation; disorders of neuronal, glial, and mesenchymal formation; neuroclastic processes (e.g., encephaloclastic and myeloclastic); and disorders of maturation (e.g., myelination and cortical maturation). These are classified in six groups (I–VI) in Table 18.1. Developmental anomalies often detected by US (prenatal or postnatal) or CT are the *gross* formational macrostructural defects of categories I–IV and the *gross* neuroclastic macrostructural lesions of category V [1,2,4,5,54]. However, MRI always provides more complete delineation of these

Table 18.1 Classification of CNS Malformations by Gestational Timing

I. Disorders of dorsal neural tube development (3–4 weeks)
Anencephaly
Cephaloceles
Dermal sinus
Chiari malformations
Spinal dysraphism
Hydrosyringomyelia
II. Disorders of ventral neural tube development (5–10 weeks)
Holoprosencephalies
Agenesis septum pellucidum
Optic and olfactory hypoplasia/aplasia
Pituitary-hypothalamic hypoplasia/aplasia
Cerebellar hypoplasia/aplasia
Dandy Walker spectrum
Craniosynostosis
III. Disorders of migration and cortical organization (2–5 months)
Schizencephaly
Neuronal heterotopia
Agyria/pachygyria
Lissencephaly
Polymicrogyria
Agenesis corpus callosum
IV. Disorders of neuronal, glial, and mesenchymal proliferation, differentiation, and histiogenesis (2–6 months)
Micrencephaly
Megalencephaly
Hemimegalencephaly
Aqueductal anomalies
Colpocephaly
Cortical dysplasias
Neurocutaneous syndromes
Vascular anomalies
Malformative tumors
Arachnoid cysts
V. Encephaloclastic processes (>5–6 months)
Hydranencephaly
Porencephaly
Multicystic encephalopathy
Encephalomalacia
Leukomalacia
Hemiatrophy
Hydrocephalus
Hemorrhage
Infarction
VI. Disorders of maturation (7 months–2 years)
Hypomyelination
Delayed myelination
Dysmyelination
Demyelination
Cortical dysmaturity

Note: See references [2,4,54].

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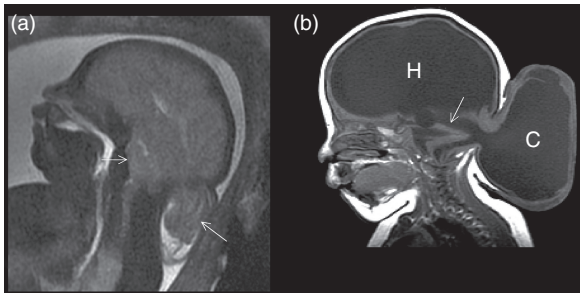


Figure 18.5 (a) Fetal sagittal T2 MRI showing cervico-occipital cephalocele (posterior arrow), Chiari III malformation (anterior arrow), agenesis of the corpus callosum, and microcephaly. (b) Neonatal sagittal T1 MRI showing occipital meningoencephalocele (C) with kinked brainstem (arrow) and hydrocephalus (H).

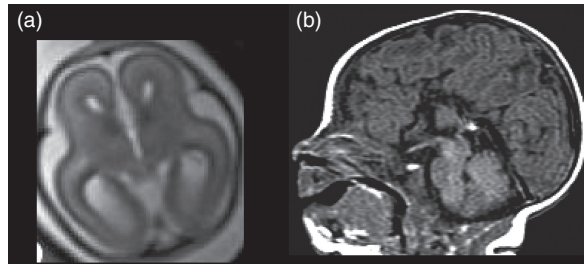


Figure 18.6 Agenesis of the corpus callosum on (a) fetal axial T2 and (b) neonatal sagittal T1 MRI (see Figure 18.1(f), (g)) [50].

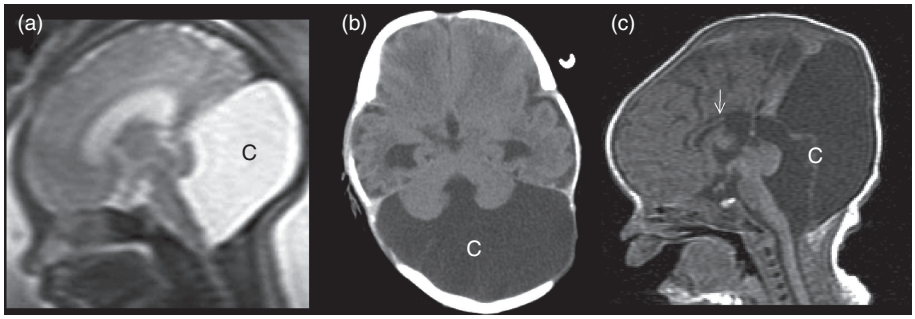


Figure 18.7 Dandy-Walker cyst (C): (a) fetal sagittal T2 MRI; (b) neonatal axial CT; (c) sagittal T1 MRI with hypogenesis of the corpus callosum (arrow).

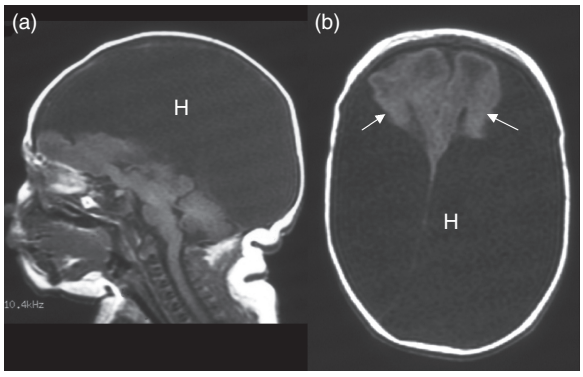


Figure 18.8 Hydranencephaly on (a) sagittal and (b) axial T1 MRI. Only a small portion of cortex is present frontally (arrows).

defects. This is especially true for abnormalities involving the ventricular system or containing CSF. These include cephaloceles (Figure 18.5), hydrocephalus, hydranencephaly, holoprosencephaly, absent septum pellucidum, hypogenesis of the corpus callosum (Figures 18.5–18.7), porencephaly, open schizencephaly, the Dandy-Walker-Blake spectrum (Figure 18.7), and arachnoid cysts. US may not clearly distinguish hydranencephaly (absent cerebral mantle) from severe hydrocephalus (attenuated cerebral mantle). This is usually clarified by CT or MRI (Figure 18.8). Other gross macrostructural anomalies often detected by US or CT include Chiari II malformation, lissencephaly, and vascular malformations such as the Galenic malformation. Any "cystic" lesion detected by US should be examined with Doppler to determine if it is vascular in nature. Neuroclastic processes are destructive lesions of the already formed CNS and may result from a variety of prenatal or perinatal insults, including hypoxia-ischemia and infection (Table 18.1). MRI often demonstrates subtle macrostructural abnormalities not revealed by US or CT (e.g., periventricular leukomalacia) [1–12,15,17,19–24,26,33].

MRI is important when the US or CT fails to satisfy the clinical investigation. MRI often provides a more complete delineation of complex macrostructural CNS anomalies for diagnosis, treatment, prognosis, and genetic counseling [1,2,4,5,33,54]. In fact, ultrafast MRI techniques are being used increasingly prenatally to evaluate for fetal CNS abnormalities in at-risk pregnancies or as detected by obstetrical US [31–36] (Figures 18.5–18.7). Furthermore, MRI is often indicated if more specific treatment is planned beyond

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simple shunting of hydrocephalus. Intraoperative guidance may be provided by real-time and Doppler US. Patients with craniosynostosis are best evaluated with three-dimensional (3D) CT. Those with multiple suture involvement, especially when it is associated with craniofacial syndromes, may require more extensive evaluation beyond 3D CT, including CT venography, MRI, and MR venography (jugular venous stenoocclusive disease with collateralization).

MRI is often required to structurally delineate the more subtle macrostructural anomalies arising as disorders of migration and cortical organization (category III: Figure 18.9) or as disorders of proliferation, differentiation, and histiogenesis (category IV: Figure 18.10) [1,2,4,5,33,54]. The perfusional and metabolic characteristics of these anomalies (e.g., focal cortical dysgenesis and hemimegalencephaly) may be investigated with SPECT and PET, respectively, in children with medically refractory partial epilepsy who are candidates for surgical ablation. For added precision, the SPECT or PET data may be fused with the MRI data to provide a higher-resolution spatial display of the functional information.

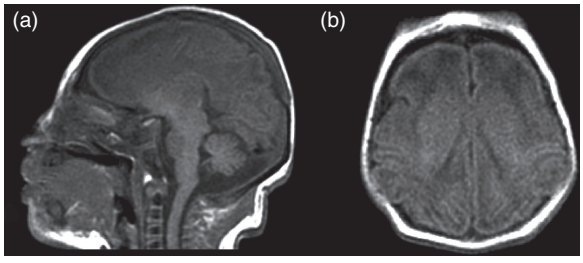


Figure 18.9 Microlissencephaly: neonatal (a) sagittal and (b) axial T1 MRI, showing microcephaly with agyric cortex.



Figure 18.10 Hemimegalencephaly: neonatal axial T2 MRI shows larger right hemisphere with unilateral ventriculomegaly and abnormal cortication.

MRS, DWI, DTI, and PMRI with fMRI are also contributing to the evaluation and treatment of these patients [4,12,30]. MRI is now the preferred modality for the screening and definitive evaluation of the dysgenetic, neoplastic, and vascular manifestations of the neurocutaneous syndromes (Figure 18.11). After initial screening with US or CT, MRI is also considered the primary technology for treatment planning and follow-up of vascular malformations and developmental tumors [1,2,4,30]. Although arachnoid cysts are often readily delineated by US or CT, MRI is usually necessary for confirmation (i.e., to exclude solid tumor) and for surgical planning. FLAIR or DWI may readily distinguish an arachnoid cyst from other lesions (e.g., dermoid-epidermoid and fibrillary astrocytoma). Maturation (i.e., myelination and cortical maturation) and disorders of maturation (category VI) may be precisely assessed only by MRI [1,2,4,5,30,33,54] (Figure 18.1f–j). The MRI findings, however, are often nonspecific regarding causation, particularly in the first year of life, because of the watery character of the immature brain. DTI and MRS may add specificity to the diagnostic evaluation of these infants [1–12,37–40] (Figures 18.2–18.4).

Neurovascular Disease

Neurovascular disease characteristically presents as an acute neurologic event (e.g., neonatal encephalopathy). However, a recently discovered but fixed deficit (e.g., hemiplegia, spastic diplegia, hypotonia) may be the first indication of a remote prenatal or perinatal neurovascular injury. Imaging assists in the clinical evaluation and differentiation of hypoxia-ischemia, hemorrhage, and occlusive vascular disease [1–12,30].

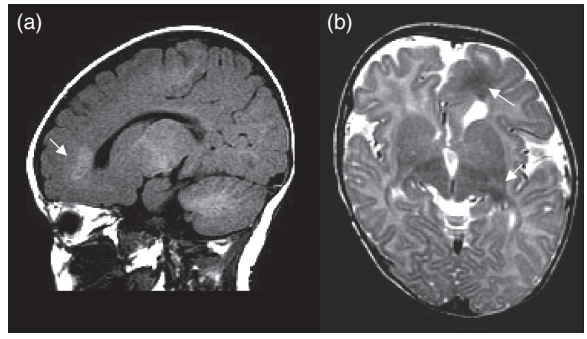


Figure 18.11 Tuberous sclerosis with periventricular and subcortical tubers (arrows) on (a) neonatal sagittal T1 and (b) axial T2 MRI.

Hypoxia-Ischemia

In general, the pattern of injury associated with hypoxic-ischemic encephalopathy (HIE) or other insults (e.g., reperfusion) varies with the severity and duration of the insult as well as with the gestational (or corrected) age (GA) of the fetus, neonate, or infant at the time of the insult or insults [1–12] (Table 18.2). Different brain structures are more vulnerable than others to the different types of HIE insults (e.g., partial prolonged, profound, combined) at different stages of brain development (e.g., formational versus postformational GA, preterm versus term versus full-term or postterm GA). Brain tissues in the arterial border zones or watersheds (intervascular boundary zones), brain tissues with high metabolic demands, mature or actively maturing tissues, and tissues with higher concentrations of neuroexcitatory amino acids are particularly vulnerable to HIE and other insults (e.g., hypoglycemia, trauma, infection, and seizures) [1–12,55–61]. Prenatal or perinatal partial prolonged HIE (e.g., one or more insults of hypoxia/hypoperfusion) may be associated with periventricular border-zone/watershed injury to the preterm fetus or neonate (e.g., 27–35 weeks' GA) [1–12,55,57,62–75]. Subtypes of white matter injury of prematurity (i.e., encephalopathy of prematurity) include the classic focal/multifocal "cystic" type of periventricular leukomalacia (PVL), the focal/multifocal "noncystic" (gliotic) form of PVL, and the diffuse white matter gliosis injury pattern (Figures 18.12–18.15). The pathogenesis may include not only hypoxia-ischemia but also other factors such as infectious or inflammatory processes (e.g., maternal infection, chorioamnionitis, funisitis, fetal inflammatory response, and cytokine-mediated injury) whether occurring in the preterm or term fetus or neonate [7,66,70]. Prenatal or perinatal partial prolonged HIE during term gestation (e.g., 37–42 weeks' GA) may produce a cortical and subcortical border-zone/watershed cerebral injury (Figures 18.16 and 18.17). A transitional partial prolonged HIE pattern (cortical/subcortical/periventricular) may be

Table 18.2 Imaging Patterns of Hypoxic-Ischemic Encephalopathy (HIE)

Hemorrhage
Germinal matrix – intraventricular hemorrhage
Choroid plexus – intraventricular hemorrhage
Subarachnoid hemorrhage
Hemorrhagic infarctions
Partial prolonged HIE
Preterm: White matter injury of prematurity (e.g., periventricular leukomalacia)
Term/full-term/post-term: Cortical/subcortical injury (borderzone, watershed, parasagittal)
Intermediate: Combined or transitional pattern
Ulegyria
Cystic encephalomalacia
Profound HIE
Thalamic and basal ganglia injury
Brainstem injury
Cerebellar vermian injury
Hippocampal injury
Cerebral white matter injury
Paracentral injury
Global injury (prolonged profound)
Combined profound and partial prolonged (or prolonged profound) HIE
Total asphyxia pattern (including cystic encephalomalacia)

Note: Depends on gestational age, chronological age, duration, and severity of the insult. See references [2–8].

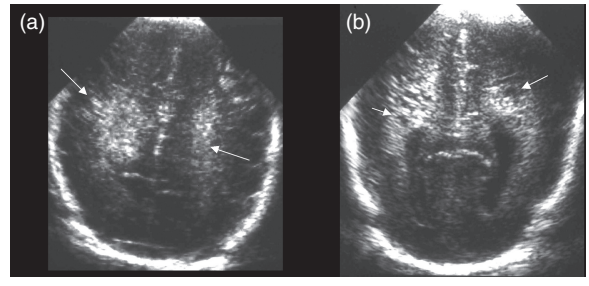


Figure 18.12 Cystic PVL: (a) US, acute edema phase (confluent increased echoes – arrows); (b) US, subacute cystic phase (hypoechoic foci with surrounding increased echoes – arrows).

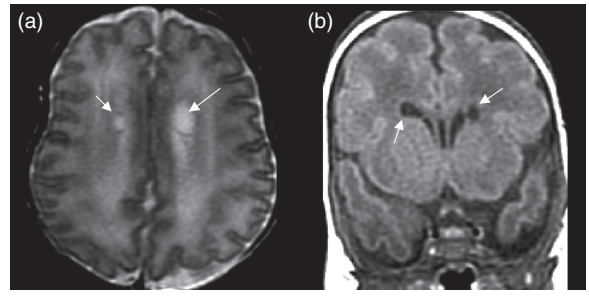


Figure 18.13 Cystic PVL: (a) axial T2 and (b) coronal FLAIR MRI, chronic cystic phase (arrows).

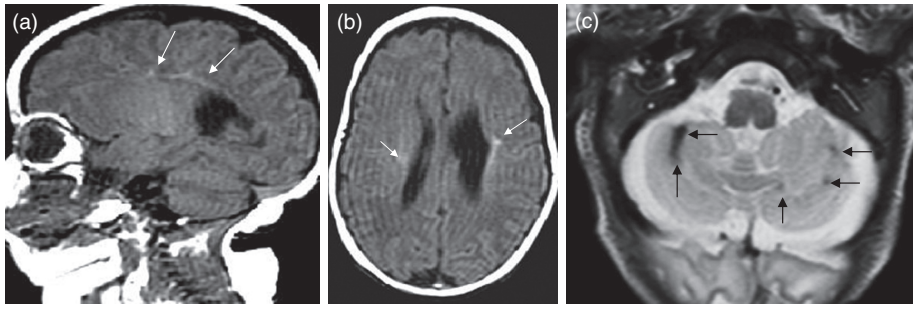


Figure 18.14 Noncystic PVL with foci of gliosis (arrows) as high intensities on (a) sagittal and (b) axial T1 MRI plus cerebellar mineralization or hemorrhages (arrows) as low intensities on (c) axial T2* GRE MRI.

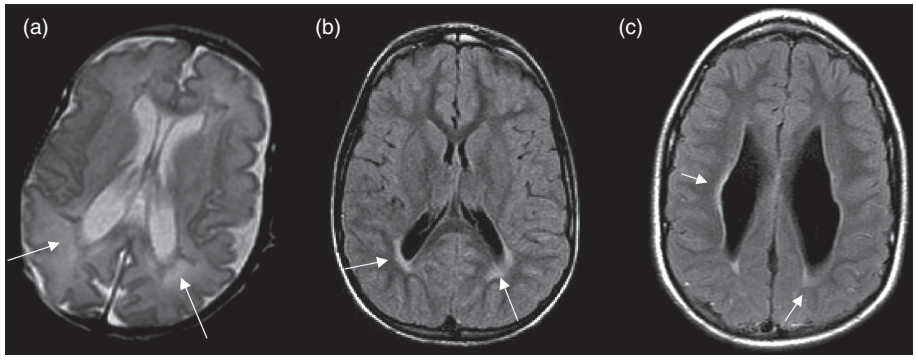


Figure 18.15 Diffuse PVL (high intensities – arrows) on (a) near-term axial T2 and (b,c) older infant axial FLAIR MRI.

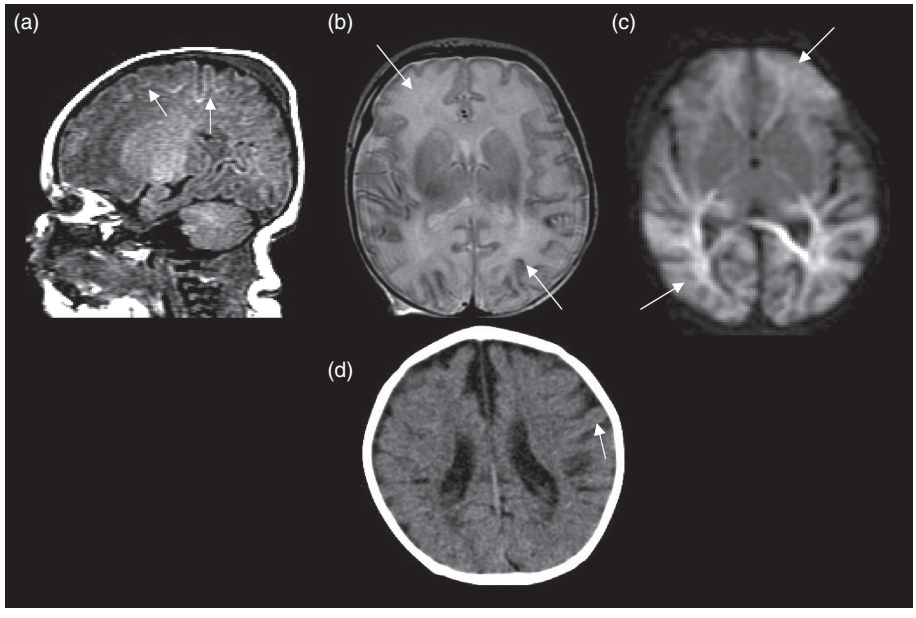


Figure 18.16 Partial prolonged HIE: acute phase with watershed injury (arrows) on (a) sagittal T1, (b) axial T2, and (c) axial DWI; (d) chronic phase with cortical atrophy and ulegyria (arrow) on axial CT.

seen in the late preterm to early midterm GA (e.g., 36–38 weeks) or with more severe injuries. Fetal or neonatal brain injury may also occur with more profound HIE insults (e.g., anoxia or circulatory arrest) and involve the thalami, basal ganglia (especially putamina), brainstem (especially midbrain), cerebellar vermis, hippocampi, paraventricular white matter, and perirolandic cortex [1–12,55,57,76–80] (Figures 18.18 and 18.19). This type of injury may also vary with GA (thalamic greater than putaminal involvement in the preterm GA; putaminal, hippocampal, and paracentral injury more common in the term GA). Combined partial prolonged plus profound HIE patterns (e.g., total asphyxia) may also occur [1–12,76–80] (Figure 18.20).

US, CT, or MRI (e.g., DWI) may demonstrate evolving edema, necrosis, or hemorrhage in the hyperacute, acute, and subacute phases [1–12] (Figures 18.12–18.20). The edema of nonhemorrhagic HIE (e.g., partial prolonged type) usually evolves over 1–7 days and often peaks between 36 and 72 hours (2–4 days by US and CT) following the insult(s) and depending on reperfusion (and other "insults"). US may show hyperechogenicity, and CT may show hypodensities with decreased gray–white matter differentiation. Complete loss of gray–white matter differentiation may correlate with peak edema [60,61]. In the early phases of the injury, the neuroimaging findings may be nonspecific as to causation. The differential diagnosis includes HIE, multifocal occlusive vascular infarction, infection, metabolic derangement (e.g., hypoglycemia, hyperbilirubinemia, and fluid-electrolyte imbalance), metabolic or connective tissue disorder, and venous thrombosis (e.g., coagulopathy) [1–12]. Associated hemorrhage

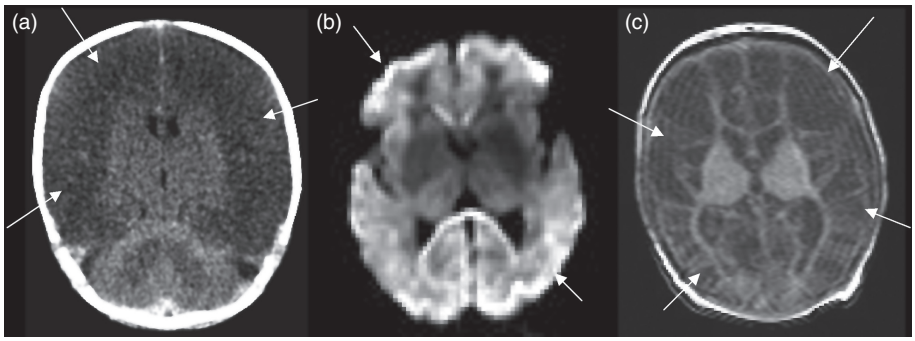


Figure 18.17 Very severe partial prolonged HIE: acute–subacute phase with (a) low-density cerebral peak edema (arrows) on axial CT and (b) high-intensity cerebral restricted diffusion (arrows) on axial DWI; (c) chronic phase with cystic encephalomalacia (arrows) on axial T1.

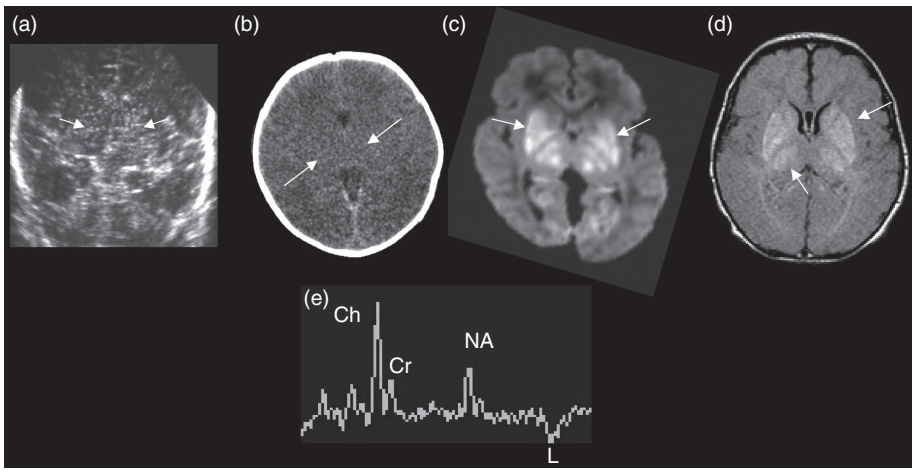


Figure 18.18 Profound HIE: acute phase with (a) bilateral basal ganglia and thalamic hyperechogenicity (arrows) on US; (b) hypodensities (arrows) on CT; high intensities (arrows) on (c) axial DWI and (d) T1/FLAIR MRI; and (e) inverted lactate doublet (L) on MRS.

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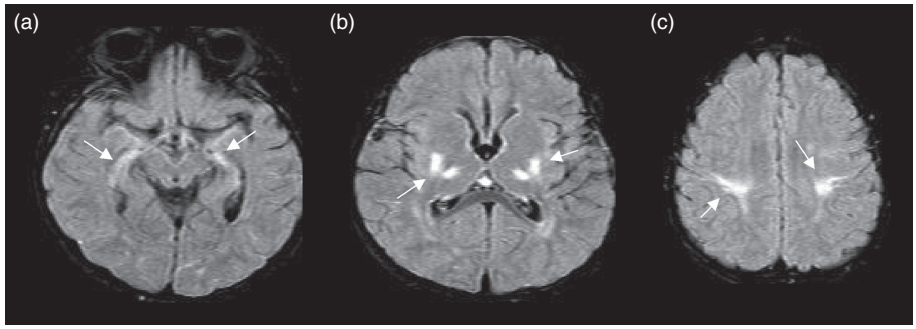


Figure 18.19 Profound HIE: chronic phase with (a–c) bilateral hippocampal, putaminal, thalamic, and paracentral high intensities (arrows) on axial FLAIR MRI.

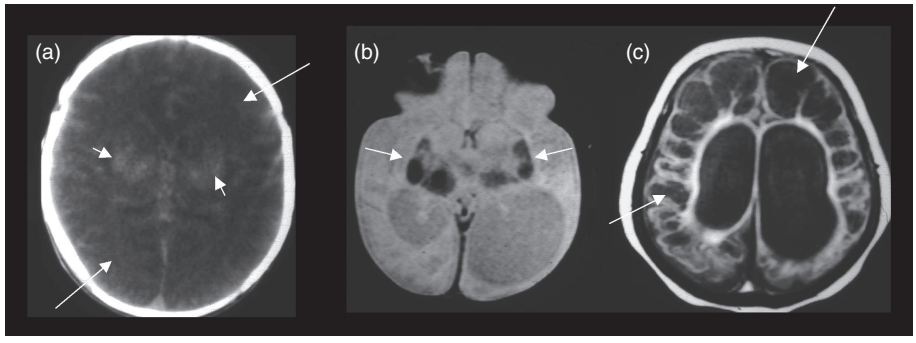


Figure 18.20 Term combined HIE: subacute phase with (a) basal ganglia and thalamic high densities (short arrows) plus cerebral low densities (long arrows) on CT; chronic phase with (b) basal ganglia and thalamic hypointense mineralization (arrows) on axial GRE plus (c) hypointense cystic encephalomalacia (arrows) on axial T1 MRI.

may be subarachnoid, germinal matrix, and intraventricular hemorrhage (e.g., preterm fetus or neonate), choroid plexus/intraventricular hemorrhage (e.g., term fetus or neonate), and cerebral or cerebellar hemorrhage (e.g., hemorrhagic infarction). Their imaging characteristics are described in the next section.

According to the evidence-based medical literature, the sensitivity and specificity of MRI depend on the techniques used and the timing of the imaging [2,4,6,7,40,45,78]. Conventional MRI may show characteristic T1 hypointensities/T2 hyperintensities (12–48 hours), followed by T1 hyperintensities (as early as 2–4 days), and then T2 hypointensities (as early as 6–7 days). These T1 and T2 changes may last for a number of weeks to a month. DWI may be abnormal before conventional MRI and show restricted diffusion with decreased ADC as increased intensity on DWI and decreased intensity on ADC maps [2,7,8,40,45]. Diffusion abnormalities may tend to evolve for up to 2–3 weeks. Knowledge of these evolving intensity features is particularly important in order to avoid misinterpretation regarding pattern of injury and timing [40]. Doppler with resistive indices (e.g., RI < 60) or MRS (e.g., elevated lactate, elevated glutamate, elevated lipids, decreased *N*-acetyl-aspartate [NAA]) may provide additional early indicators of timing and outcome [2,6,7,8,14,37,40,81]. The more subtle ischemic PVL lesions (e.g., cystic phase) may be better delineated by US (2–6 weeks after insult) than by CT or MRI, in which the density and intensity character of immature white matter often obscures the injury. However, CT and MRI often show gray matter injury better than US, and MRI demonstrates noncystic white matter injury better than US or CT [4,8,19–24,26]. Further developments of PMRI, DWI, and MRS have further improved the diagnostic sensitivity and specificity of MRI [4,8,12,30,40]. In fact, DWI has demonstrated restricted diffusion in the acute phase of PVL when US, CT, and conventional MRI are negative or nonspecific. Such advances may facilitate the early institution of neuroprotective measures (e.g., therapeutic hypothermia or cooling) to treat

potentially reversible primary injury (necrosis, apoptosis) and secondary injury (reperfusion, transneural degeneration) in HIE [82]. These advanced MRI techniques may also assist in distinguishing HIE from other causes of encephalopathy, including common metabolic derangements (e.g., hypoglycemia and hyperbilirubinemia), rarer inborn errors of metabolism, and nonmetabolic conditions (e.g., infection).

The long-term result of HIE is a static encephalopathy (i.e., CP), and imaging may demonstrate injury in the chronic phases (>14–21 days after the insult), including porencephaly, hydranencephaly, atrophy, chronic periventricular leukomalacia, cystic encephalomalacia, gliosis, and mineralization in a characteristic distribution as described earlier [1–12] (Figures 18.12–18.20). The chronic changes are best demonstrated by MRI. In general, for pattern of injury and timing purposes, two pieces of imaging evidence are optimally desired: (1) late imaging, preferably MRI, beyond 2–3 years of age when the brain is greater than 90% mature (no more water of immaturity), in order to get a final, permanent injury pattern for causative etiology and GA timing, and (2) early postnatal (and/or prenatal) imaging, preferably MRI, in order to evaluate evolution in the acute, subacute, and chronic phases so that timing as to "day range" relative to the perinatal and peripartum periods may be assessed [1–12,40].

Intracranial Hemorrhage

Intracranial hemorrhage may result from parturitional trauma, HIE, a coagulopathy (e.g., thrombocytopenia, disseminated intravascular coagulopathy [DIC], extracorporal membrane oxygenation [ECMO]), and vaso-occlusive disease (e.g., thrombophilia with venous thrombosis), or it may be idiopathic [1–12,28,29,83]. Hemorrhage may occasionally be associated with infection (e.g., herpes simplex virus 2). Vascular malformations producing intracranial hemorrhage are rare in neonates and young infants and usually not encountered until later childhood (i.e., arteriovenous malformations [AVMs], cavernous malformations, developmental venous anomalies, and telangiectasias) [1–12,28,29]. Aneurysms are exceedingly rare in children but may be developmental, associated with a syndrome (e.g., Turner syndrome), or related to trauma (e.g., dissection) or infection (i.e., mycotic aneurysm). Vein of Galen malformations are subclassified as choroidal, mural, and AVM types. They rarely hemorrhage and more commonly present in infancy with congestive heart failure, cerebral ischemia, or hydrocephalus.

US or CT remains the primary imaging choice in acute situations [1–12,29]. As mentioned earlier, there may be subarachnoid hemorrhage, germinal matrix and intraventricular hemorrhage (e.g., premature fetus or neonate), choroid plexus/intraventricular hemorrhage (e.g., term fetus or neonate), and cerebral or cerebellar hemorrhage (e.g., hemorrhagic infarction). The hemorrhage usually appears hyperechoic on US and high density on CT in the acute to subacute phases (range 3 hours–7 days) unless there is associated coagulopathy. With evolution and resolution, the hemorrhage becomes isoechoic to hypoechoic and isodense to hypodense (>7–10 days).

MRI may offer more specific characterization of the hemorrhagic component with regard to timing (Table 18.3). Acute intracranial hemorrhage, particularly subarachnoid, may be specifically diagnosed by CT or lumbar puncture for CSF analysis. Although FLAIR may identify subarachnoid hemorrhage as a

Table 18.3 MRI of Intracranial Hemorrhage and Thrombosis

Stage	Biochemical form	Site	T1 MRI	T2 MRI
Hyperacute (+edema) (<12 hours)	Fe II oxy Hb	Intact RBCs	Isointense–low i	High i
Acute (+edema) (1–3 days)	Fe II deoxy Hb	Intact RBCs	Isointense–Low i	Low i
Early subacute (+edema) (3–7 days)	Fe III met Hb	Intact RBCs	High i	Low i
Late subacute (+edema) (1–2 weeks)	Fe III met Hb	Lysed RBCs (extracellular)	High i	High i
Early chronic (+edema) (>2 weeks)	Fe III transferrin	Extracellular	High i	High i
Chronic (cavity)	Fe III ferritin and hemosiderin	Phagocytosis	Isointense–Low i	Low i

RBCs, red blood cells; +, present; –, absent; Hb, hemoglobin; Fe II, ferrous; Fe III, ferric. See references [2,4,29,84,98].

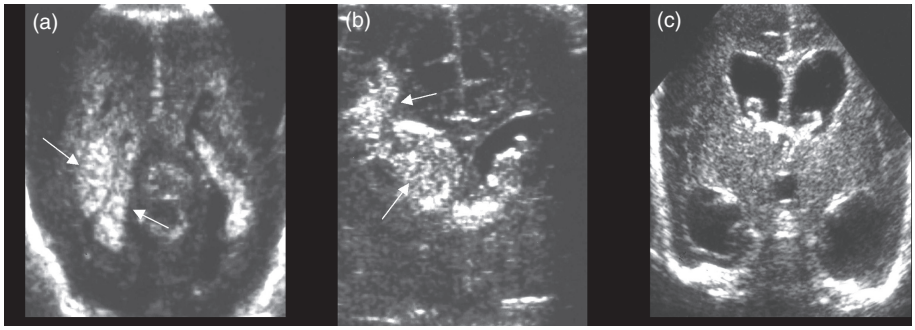


Figure 18.21 (a) Hyperechoic grade III and (b) grade IV GMH-IVH (arrows) and (c) posthemorrhagic hydrocephalus on coronal US.

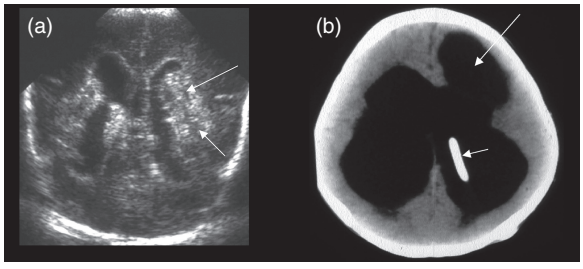


Figure 18.22 (a) Hyperechoic grade IV IVH with periventricular hemorrhagic infarction (arrows) on coronal US; (b) posthemorrhagic hydrocephalus with porencephaly (long arrow) on axial CT with shunt catheter (short arrow).

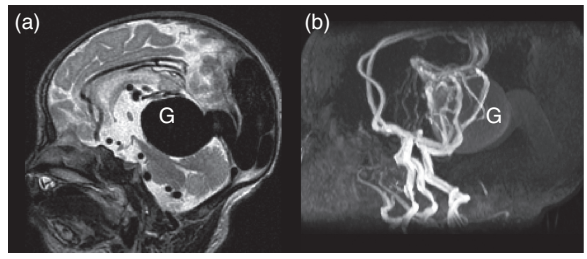


Figure 18.23 Vein of Galen (G) vascular malformation (choroidal type) on (a) sagittal T2 and (b) lateral MRA.

hyperintensity and GRE may identify acute hemorrhage in any location as a hypointensity, MRI often provides better specificity beyond the acute phases [2,4,29,84] (Table 18.3). Hemorrhagic manifestations and sequelae of HIE in premature infants readily detected by US include germinal matrix hemorrhage (GMH grades I–IV), intraventricular hemorrhage (IVH), periventricular hemorrhagic infarction (aka grade IV), and posthemorrhagic hydrocephalus [1–13,25] (Figures 18.21 and 18.22). Choroid plexus hemorrhage and hemorrhagic infarction in term infants are also easily demonstrated. Portable US may effectively delineate the potential hemorrhagic or ischemic sequelae of ECMO. Although CT has been more reliable, high-resolution US using transfontanel and transcranial approaches, including the mastoid view, may detect extracerebral hemorrhage (subdural and subarachnoid) and posterior fossa collections (cerebellar or subdural) [1–13,25]. Color Doppler US, MRA, and CTA are all able to identify and distinguish the types of Galenic malformations and provide follow-up (Figure 18.23). Angiography is more specifically directed to the definitive interventional or surgical management of these and other vascular anomalies. Real-time Doppler US provides intraprocedural guidance and monitoring. The long-term sequelae of intracranial hemorrhage are often better demonstrated by MRI than by CT (e.g., hydrocephalus, atrophy, encephalomalacia, porencephaly, calcification, and hemosiderin).

Occlusive Neurovascular Disease and Sequelae

Occlusive neurovascular disease in the fetus, newborn, and infant may be arterial or venous in origin and typically results in focal or multifocal lesions within the distribution of the occluded vessel or vessels [1–12] (Table 18.4). Arterial occlusive disease may be partial or complete and may be due to embolization, thrombosis, or stenosis. The result may be ischemic infarction or hemorrhagic infarction followed by atrophy. Arterial occlusive disease may occur as a prenatal or perinatal event (emboli of placental origin, fetal heart, or involuting fetal vessels), as a complication of infection (e.g., meningitis), with congenital heart disease, or from a hypercoagulopathy (e.g., thrombophilias and prothrombotic disorders) [85–93]. The thrombophilias may be genetic or acquired and include protein C and S deficiencies, activated protein C resistance, antiphospholipid

Table 18.4 Occlusive Neurovascular Disease in the Fetus, Neonate, and Infant

Idiopathic
Cardiac disease
Congenital
Acquired
Vascular maldevelopment
Atresia
Hypoplasia
Traumatic
Dissection
Vascular distortion
Air or fat emboli
Vasculopathy
Moyomoya
Fibromuscular dysplasia
Marfan syndrome
Takayasu arteritis
Kawasaki disease
Vasculitis
Polyarteritis nodosa
Lupus
Vasospasm
Migraine
Ergot poisoning
Subarachnoid hemorrhage
Drugs
Cocaine
Amphetamines
L-asparaginase
Oral contraceptives
Hypercoagulopathy (thrombophilias)
Protein S deficiency
Protein C deficiency
Antithrombin III deficiency
Factor V (Leiden) and prothrombin mutations
Antiphospholipid antibody (lupus, anticardiolipin)
Heparin cofactor II deficiency
Dehydration/hypernatremia
HIE/DIC
Sepsis/DIC
Polycythemia/hyperviscosity
Nephrotic syndrome
Oncologic disease
Hemolytic-uremic syndrome
Hemoglobinopathies
Sickle cell disease
Infection
Meningoencephalitis
Sepsis
Metabolic disease
Homocystinuria
Dyslipoproteinemia
Fabry disease
Mitochondrial cytopathies
Familial lipid disorders
Other
Emboli from involuting fetal vasculature
Placental vascular anastomoses (twin gestation)
Cotwin fetal death
Fetofetal transfusion
ECMO
Catheterized vessel

See references [2–5,90].

antibody (e.g., lupus and anticardiolipin), antithrombin III deficiency, factor V Leiden, prothrombin gene mutation, methylene tetrahydrofolate reductase (MTHFR), homocysteine, factors VIII/IX/XI, anemia, polycythemia, and others. These are risk factors that are often provoked by "triggers" that may include acute systemic disease (e.g., dehydration, infection, trauma, hypoxia-ischemia) and chronic systemic disease (e.g., hematologic disorders, connective tissue disorders, lupus) [90]. Other causes include trauma (e.g., dissection), arteriopathies (e.g., moyamoya), and metabolic disorders (e.g., mitochondrial cytopathies). Conditions commonly associated with cortical or dural venous sinus occlusive disease include infection, dehydration, perinatal encephalopathy, cyanotic congenital heart disease, polycythemia, other hypercoagulable states, DIC, and trauma [1–12,85–94]. Color Doppler US may be used as a noninvasive tool for initial identification and monitoring of these infants. MRI is more sensitive and specific than US or CT for ischemic infarction, hemorrhagic infarction, and venous thrombosis [2–5,7,12,30,88,90] (Figures 18.24 and 18.25).

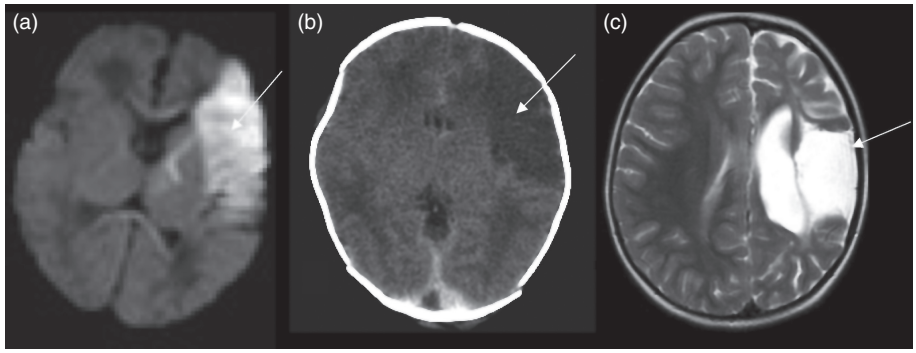


Figure 18.24 Middle cerebal arterial infarction (arrows): (a) acute phase with edema on axial DWI; (b) subacute phase on CT; (c) chronic phase on axial T2 with hemiatrophy.

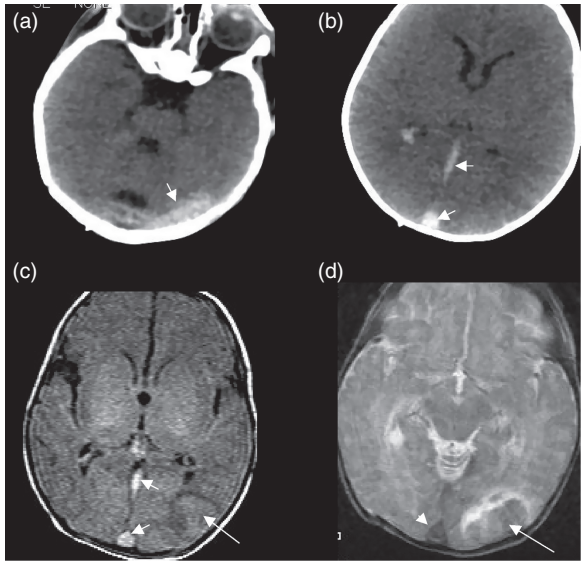


Figure 18.25 Venous thromboses (short arrows) with hemorrhages and infarctions (long arrows) on (a,b) axial CT, (c) axial T1, (d) axial GRE in infant with hypercoagulable state.

MRA or CTA may also contribute to the diagnosis of arterial or venous occlusion and clarify (or obviate) the need for cerebral angiography, particularly when anticoagulation or thrombolysis is being considered. As mentioned earlier, PMRI, DWI, and MRS are contributing to the early diagnosis and timely treatment of ischemic insults. The long-term sequelae of infarction include atrophy, encephalomalacia, gliosis, mineralization, and porencephaly. These may be better shown by MRI than by CT.

Acute myelopathy due to HIE, vascular occlusion, hemorrhage, or vascular malformation is extremely rare in the perinatal period. Spinal MRI is the definitive procedure to evaluate spinal cord infarction or

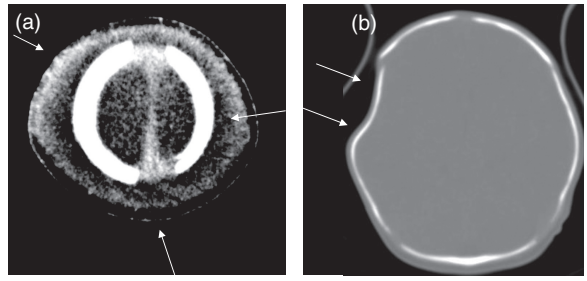


Figure 18.26 (a) Large neonatal bilateral subgaleal hematomas (arrows) on CT with soft tissue algorithm. (b) Right frontal cranial depression in another neonate (arrows) on CT with bone algorithm.

hemorrhage (see section on trauma below). Spinal angiography is necessary to evaluate for vascular malformation in anticipation of interventional or surgical therapy [2,4].

Trauma

With improvements in resolution and the use of additional views (e.g., mastoid view), US may be used as the primary modality for evaluating newborns with parturitional trauma. CT, however, is usually relied on for delineating skull and scalp injury (e.g., subgaleal hematoma: Figure 18.26), extracerebral hemorrhage (e.g., subarachnoid or subdural), posterior fossa hemorrhage, and direct (e.g., contusion, shear) versus indirect (e.g., HIE) brain injury [1–12,29,94–100]. CT is sufficiently sensitive and specific for acute hemorrhage and the complications or sequelae of fractures (e.g., depression, growing fracture, leptomeningeal cyst) (Figure 18.26). Occasionally, skull films will demonstrate a skull fracture not shown by CT. It may be difficult to distinguish fracture from sutures, synchondroses, and their variants or anomalies (e.g.,

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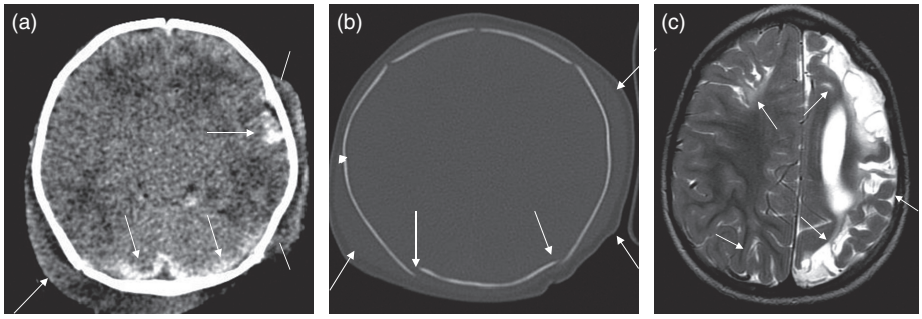


Figure 18.27 (a,b) Parturitional trauma and partial prolonged hypoxic-ischemic injury with scalp swelling, molding, and intracranial hemorrhage on CT (arrows). (c) Asymmetric cerebral watershed injury with atrophy, cystic encephalomalacia, and ulegyria on followup T2 MRI (arrows).

fissures, accessory sutures, intrasutural bones, and lacunar change) or from craniotabes in maternal-fetal vitamin D–deficiency rickets [29,98]. MDCT with 3D surface reconstructions potentially may be needed. MRI is probably necessary when neurologic deficits are present and the CT is negative or nonspecific. In this situation, MRI may reveal lesions such as brainstem infarction, traumatic axonal (shear) injury, cortical contusion, or hypoxic-ischemic injury, as well as sequelae such as gliosis, microcystic encephalomalacia, and hemosiderin deposition (Figure 18.27). MRI is often more specific than CT for hemorrhage beyond the hyperacute/acute stage (Table 18.3). Color Doppler US, contrast-enhanced CT, or MRI may distinguish external hydrocephalus (dilated subarachnoid spaces) from chronic subdural hematomas (e.g., child abuse and its mimics) when nonenhanced CT demonstrates nonspecific extracerebral collections [29]. Furthermore, hemosiderin as demonstrated by MRI is confirmation of a previous hemorrhage. In children with atypical intracranial hemorrhage on CT (e.g., hemorrhage out of proportion to the history of trauma or hemorrhage of varying ages), MRI may show an existing vascular malformation, a hemorrhagic neoplasm, or other findings indicating the need for distinguishing child abuse from its mimics [29].

Initial evaluation of spine trauma (e.g., fracture/dislocation) may include plain films or US, but MDCT (including 2D reformatting and 3D surface reconstructions) is preferred. Abnormality on preliminary imaging, changing clinical signs, or unexplained brain injury may provide the indication for spinal MRI [2,4,29], including a STIR sequence. An existing spinal anomaly or mass should be ruled out. MRI is the procedure of choice to fully evaluate acute spinal injury (e.g., intraspinal hemorrhage, cord contusion, cord edema, transection, brachial plexus injury, and ligamentous injury) and the sequelae of spinal injury (e.g., hydrosyringomyelia, cystic myelopathy, and myelomalacia).

Infections and Inflammatory Processes

US or CT is often used initially to delineate CNS infection or inflammation (e.g., fetal inflammatory response syndrome [FIRS]) and its sequelae or complications. However, MRI is clearly superior for early detection, including the use of diffusion imaging, and for demonstrating the precise nature and extent of involvement using T2, FLAIR, GRE, and gadolinium-enhanced sequences (e.g., CMV) [1–12,101–103]. This includes meningoencephalitis due to TORCH infections (i.e., toxoplasmosis, other [e.g., syphilis], rubella, cytomegalovirus [CMV], herpes simplex virus [HSV2], and human immunodeficiency virus [HIV]), and neonatal meningitis (e.g., group B *Streptococcus, Listeria*, and gram-negative bacteria) (Figures 18.28–18.33). Less common but increasingly prevalent causes of subacute and chronic CNS inflammation are granulomatous meningoencephalitic infections (e.g., tuberculosis, spirochete, fungal, and parasitic), particularly in immunocompromised hosts. The imaging pattern is often asymmetric and progressive. Such findings may include subarachnoid exudate, ventriculitis, edema, cerebritis, infarction, hydrocephalus, effusion, empyema, abscess, and in the chronic phase cystic encephalomalacia, atrophy, gliosis, and calcification.

Recurrent infectious or noninfectious CNS infection (e.g., meningitis) may require investigation for a *parameningeal focus* (e.g., sinus or mastoid infection,

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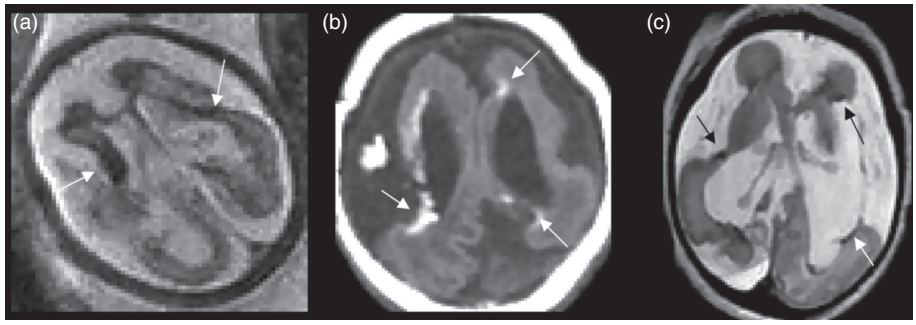


Figure 18.28 Congential CMV on (a) fetal T2 and (b) neonatal T1 plus (c) GRE MRI including dysplastic (microcephaly, undergyration) and encephaloclastic (cavitations) components plus T1 hyperintense/T2 hypointense mineralization (arrows).

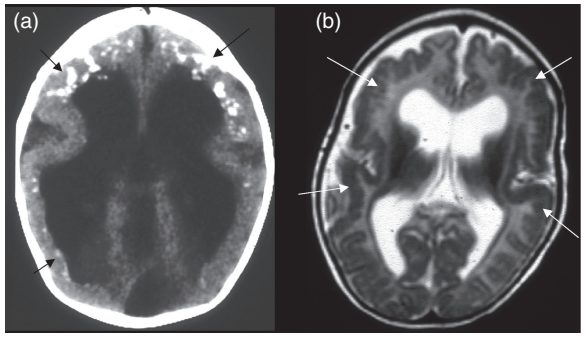


Figure 18.29 Congenital CMV: (a) calcification (arrows) on CT; (b) diffuse polymicrogyria (arrows) on axial T2 MRI.

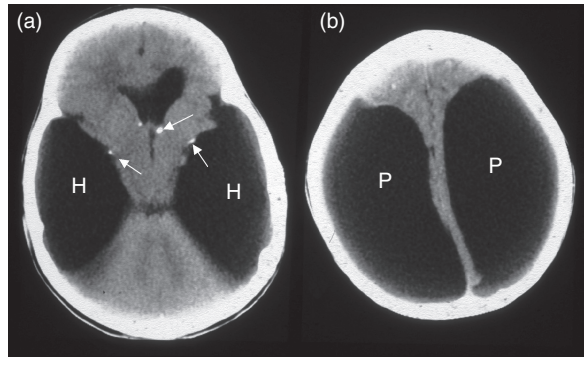


Figure 18.30 Congenital toxoplasmosis: (a,b) CT with hydrocephalus (H), porencephaly (P), and calcifications (arrows).

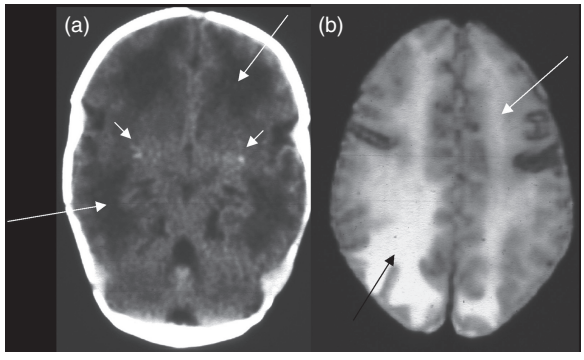


Figure 18.31 Congenital rubella on (a) CT and (b) T2 MRI, including calcifications (short arrows) and leukoencephalitis (long arrows) with white matter low densities and T2 high intensities.

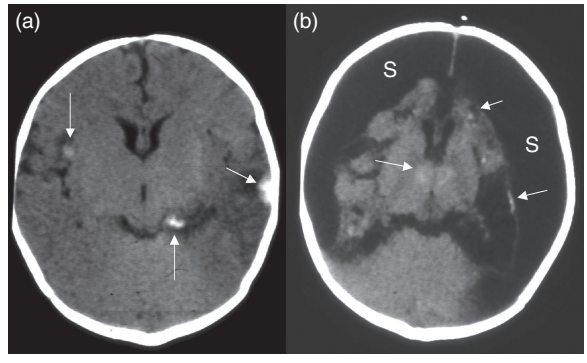


Figure 18.32 HSV2 encephalitis on CT: (a) subacute phase, including hemorrhages (arrows); (b) chronic phase, with encephalomalacia, subdural collections (s), and calcifications (arrows).

dermal sinus, primitive neurenteric connection, CSF leak after trauma, dermoid-epidermoid) [1–12]. Brain abscess or empyema may be associated with gram-negative meningitis (e.g., *Citrobacter*) in neonates. Suppurative collections related to sinus infection, trauma, surgery, sepsis, the immunocompromised state, or uncorrected cyanotic congenital heart disease occur primarily in older children. MRI is the imaging modality of choice for definitive evaluation and follow-up. Multiplanar T2, FLAIR, GRE, and DWI sequences are often necessary, along with gadolinium-enhanced T1 images, in order to delineate collections requiring

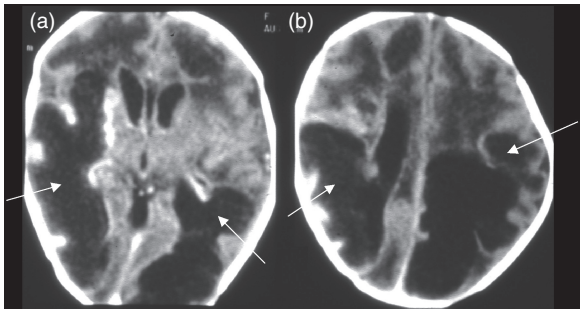


Figure 18.33 *Citrobacter* meningitis: (a,b) CT with contrast-enhancing abscesses (arrows), ventriculitis, and hydrocephalus.

drainage. Contrast-enhanced stereotactic MRI or CT and intraoperative US may provide additional guidance for surgery.

Plain films and SPECT have been used in the past for screening of suspected spinal column infection (e.g., discitis and osteomyelitis) [2,5]. MRI, however, is now preferred for definitive diagnosis, treatment planning, and follow-up. CT may further assist in the delineation of bony involvement. MRI is also the procedure of choice for evaluating spinal neuraxis infection. STIR sequences and fat-suppressed gadolinium-enhanced techniques are particularly important for demonstrating suppurative collections (e.g., epidural abscess).

Metabolic, Toxic, and Neurodegenerative Disorders

In the evaluation of neonatal encephalopathy and developmental delay (e.g., static encephalopathy versus progressive encephalopathy), MRI is the only modality that can provide an accurate assessment of brain maturation based on myelination and cortical development [2–5,7,8,12,30,38,39,104–107] (Figures 18.1–18.4). The clinical hallmark of a metabolic, toxic, or neurodegenerative disorder is *progressive* neurologic impairment in the absence of another readily identifiable process. These are to be distinguished from the *nonprogressive* encephalopathies, for example, due to maldevelopment, hypoxia-ischemia, or infection. These disorders may be exogenous and internal (e.g., hypoglycemia and hyperbilirubinemia) or external (e.g., fetal alcohol syndrome). The endogenous disorders (e.g., inborn errors of metabolism) are not as rare as previously considered, and some are specifically treatable. Many are genetic and heredofamilial disorders such that genetic counseling and prenatal screening are important. Metabolic disorders may be classified in a number of ways, including anatomic predilection (e.g., gray matter, white matter, or both) and metabolic defect. Diagnosis is primarily a clinical one and may involve metabolic testing, genetic evaluation, or biopsy of CNS or extra-CNS tissues. MRI is superior to US and CT in evaluating disease extent and anatomic distribution. Occasionally, MRI may demonstrate characteristic imaging findings (e.g., kernicterus, Zellweger disease). MRS contributes to the specific metabolic characterization of these disorders [39]. Stereotactic CT or MRI may serve as a guide for biopsy.

The classification of metabolic diseases may be biochemical, molecular, genetic, pathologic, or clinical [2–5,7,8,12,30,38,39,104–113] (Table 18.5). These disorders are often categorized according to the metabolic defect. Such a classification includes the lysosomal disorders (e.g., Krabbe), peroxisomal defects (e.g., Zellweger), mitochondrial disorders (e.g., Leigh, Menkes), organic and aminoacidopathies (e.g., nonketotic hyperglycinemia), disorders of carbohydrate metabolism (e.g., glycogen storage disease), liver metabolic disorders, and miscellaneous. Certain clinical features that assist in directing the initial evaluation of these patients may also provide a basis for classification (e.g., macrocephaly in maple syrup urine disease). The ideal radiologic classification would categorize the diseases by the anatomic distribution of the pathologic process using CT and MRI. Unfortunately, most of these conditions affect multiple sites, and considerable overlap in appearance is found. However, a practical imaging classification may be based on the predominant areas of involvement, including the white matter (subcortical, periventricular), gray matter (cortical, deep), basal ganglia, brainstem, cerebellum, spinal cord, and peripheral nervous system [2,5,7,8,12,39,104–107].

Disorders Primarily Affecting Cortical Gray Matter

Endogenous metabolic disorders that primarily or predominantly affect the cortical gray matter include the storage diseases that result from lysosomal enzyme defects [2,5,39,107]. However, these findings are often nonspecific, and the differential diagnosis may include diffuse cortical atrophy due to any number of causes. Other considerations include the end stage of a static encephalopathy (e.g., post-HIE or

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Table 18.5 Metabolic, Toxic, and Neurodegenerative Disorders

Lysosomal disorders	Amino acid disorders	Inflammatory, toxic, and anoxic conditions
Lipidoses	Phenylketonuria	Radiation therapy
Fabry, Gaucher, and Niemann-Pick disease	Homocystinuria	Renal tubular acidosis and osteoporosis
GM_1 gangliosidosis	Nonketotic hyperglycinemia	Huntington's disease
GM_2 gangliosidosis (Tay-Sachs and Sandhoff diseases)	Maple syrup urine disease	Fahr disease
	Glutaric aciduria, type I	PKAN
Neuronal ceroid lipofuscinosis	Glutaric aciduria, type II	Cockayne
Mucopolysaccharidoses (MPS)	Methylmalonic and propionic acidurias	Wilson
Hurler, Scheie, Hurler-Scheie	Urea cycle defects (e.g., OTC deficiency)	Toxic encephalopathies
Hunter	Oculocerebrorenal syndrome	Exogenous internal toxicities
Sanfilippo A–D	Pyridoxine dependency	Hyperbilirubinemia
Morquio A and B	Carbohydrate and other storage disorders	Hepatocerebral syndromes
Matoreaux-Lamy	Galactosemia	Hypoglycemia
Sly	Glycogen storage diseases (i.e. Pompe)	Hypothermia and hyperthermia
Mucolipidoses	Carbohydrate-deficient glycoprotein syndrome	Paraneoplastic toxins
Mannosidosis, fucosidosis, sialidosis		Hemolytic uremic syndrome
Lysosomal leukodystrophies	Niemann-Pick	Uremia
Metachromatic leukodystrophy	Gaucher	Ion imbalance disorders
Globoid cell leukodystrophy (Krabbe)	Farber	Endocrinopathies
Peroxisomal disorders	Infantile sialidosis	Porphyria
Adrenoleukodystrophy complex	Liver metabolic disorders	Exogenous external toxicities
Neonatal leukodystrophy	Wilson disease (hepatolenticular degeneration)	*Vitamin deficiencies/depletions*
Zellweger syndrome	PKAN	Vitamin B_1
Infantile Refsum syndrome	Hyperbilirubinemia (see toxic encephalopathies)	Folate
Rhizomelic chondrodysplasia punctata	Hepatocerebral syndromes (see toxic encephalopathies)	Vitamin B_{12}
Hyperpipecolic acidemia	Biotin	
Cerebrotendinous xanthomatosis	Diseases of the cerebellum, brainstem, and spinal cord	Vitamin K
Other leukodystrophies	Friedreich ataxia	Vitamin C
Pelizaeus-Merzbacher disease	Olivopontocerebellar atrophies	Vitamin D
Canavan disease	Ataxia-telangiectasia	*Toxins*

Table 18.5 (cont.)

Lysosomal disorders	Amino acid disorders	Inflammatory, toxic, and anoxic conditions
Alexander disease	Carbohydrate-deficient glycoprotein syndrome	Mercury poisoning
Cockayne syndrome	Infantile neuraxonal dystrophy	Methanol
Leukodystrophy with calcifications	Other metabolic and neurodegenerative diseases	Toluene
Mitochondrial (respiratory oxidative) disorders	Juvenile multiple sclerosis	Carbon monoxide
Leigh disease	Molybdenum cofactor deficiency	Cyanides and sulfides
Kearns-Sayre syndrome	3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency	Lead
MELAS syndrome	Idiopathic leukoencephalopathy	Alcohol
MERRF syndrome	Diseases of the basal ganglia	Cocaine and heroin
Alper syndrome (poliodystrophy)	Sulfite oxidase deficiency	*Anticonvulsants*
Menkes disease (trichopoliodystrophy)	Parathyroid disease	*Drug-induced*
Marinesco-Sjögren syndrome	Tuberous sclerosis	Methotrexate
Infantile bilateral striatal necrosis	Down syndrome	Cyclosporine
Lebers hereditary optic atrophy	Progressive encephalopathy with basal ganglia calcifications and CSF lymphocytosis	Tacrolimus
L-Carnitine deficiency		Carmustine, cytosine arabiniside

See references [2,4,5,106,107].

postinfection) or "atrophy" related to chronic systemic disease, malnutrition, or certain types of therapy (e.g., steroids).

Disorders Primarily Affecting Deep Gray Matter

Metabolic disorders may primarily involve the deep gray matter (including mineralization) [2,5,39,107,110–113]. Disorders primarily involving the corpus striatum (i.e., caudate and putamen) include the mitochondrial disorders, organic and aminoacidopathies, juvenile Huntington disease, Wilson disease, and Cockayne syndrome. Disorders primarily involving the globus pallidus include the aminoacidopathies, hyperbilirubinemia, pentothenate kinase–associated neurodegeneration (PKAN, formerly Hallervorden-Spatz disease), and toxic exposure (e.g., carbon dioxide) (Figures 18.34 and 18.35). It is unusual to see isolated involvement of the thalami in any of the metabolic disorders. However, thalamic involvement may be an early or dominant feature of Krabbe disease or GM2 gangliosidosis. It may also be seen in the infantile form of Leigh disease along with extensive brainstem, basal ganglia, and cerebral white matter involvement. In

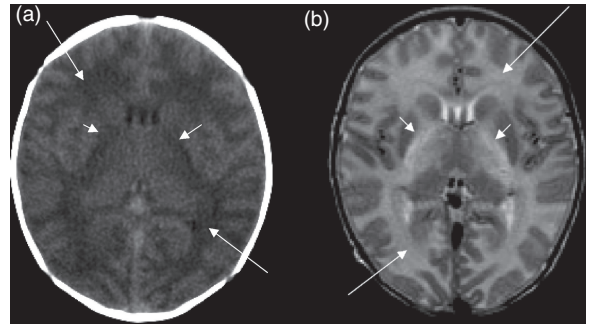


Figure 18.34 Maple syrup urine disease in a neonate with globus pallidus (short arrows) and white matter (long arrows) edema on (a) axial CT and (b) axial T2 MRI.

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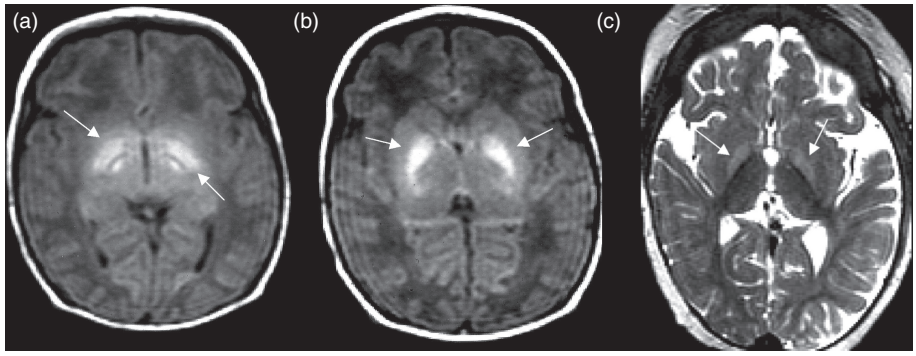


Figure 18.35 Bilirubin encephalopathy and kernicterus on MRI with (a,b) globus pallidus and subthalamic T1 hyperintensity (arrows) in subacute phase and (c) T2 hyperintensity (arrows) plus atrophy in chronic phase.

general, the differential diagnosis, depending on the clinical picture and timing of the imaging, may also include profound HIE, hypoglycemia, toxic exposure (e.g., methane, cyanide), osmolar myelinolysis, striatal necrosis, and meningoencephalitis.

Disorders Primarily Affecting White Matter

Disorders that primarily or predominantly affect the white matter are known as the *leukoencephalopathies* [2,5,39,107–109]. Traditionally, leukoencephalopathies have been divided into dysmyelinating and myelinoclastic disorders. In dysmyelinating disorders, an intrinsic (inherited) enzyme deficiency results in the disturbed formation, destruction, or turnover of the essential components of myelin. They are also referred to as the *leukodystrophies*. The pattern of damage is symmetric in both hemispheres, has diffuse margins, often spares the arcuate fibers, and consistently involves the cerebellar white matter. The leukodystrophies are primarily associated with the lysosomal and peroxisomal disorders (e.g., metachromatic leukodystrophy, Krabbe leukodystrophy, and the adrenoleukodystrophy complex [ALD]) and with diseases of white matter (e.g., Pelizaeus-Merzbacher, Canavan, Alexander, and Cockayne). Included in the differential diagnosis is infantile-onset leukoencephalopathy with swelling (macrocephaly) and mild clinical course. Early central white matter involvement may suggest Krabbe (also abnormal thalami), ALD, phenylketonuria, maple syrup urine disease (MSUD: Figure 18.34), or Lowe syndrome. The lack of myelination (hypomyelination) may suggest Pelizaeus-Merzbacher disease or Menkes disease. In myelinoclastic disorders, the myelin sheath is intrinsically normal until it yields to exogenous or endogenous myelinotoxic factors. The pattern of damage is asymmetric, is sharply demarcated, irregularly involves the subcortical arcuate fibers, and may spare the cerebellum. Examples are the infectious and postinfectious demyelinating diseases (e.g., TORCH, HIV, SSPE, and ADEM) and the vasculitides (e.g., lupus). Nonspecific white matter abnormalities may be seen with a variety of metabolic, neurodegenerative, infectious, postinfectious, toxic, and vascular processes. In this situation, the clinical findings must be relied on. An important example is posterior reversible leukoencephalopathy (e.g., hypertension, transplant, cyclosporine, renal disease). Also, it is important to remember that the most common causes of cerebral white matter abnormalities (particularly periventricular) and prominent Virchow-Robin spaces in children with developmental delay are the static leukoencephalopathies (e.g., maldevelopmental, undermyelination, postinflammatory, postischemic, and idiopathic).

Disorders Affecting Both White Matter and Cortical Gray Matter

A number of metabolic disorders involve both gray and white matter [2,5,39,107–109]. Disorders associated with cortical atrophy along with white matter involvement include lysosomal disorders such as the lipidoses and mucopolysaccharidoses (also associated skeletal dysplasia) and mitochondrial disorders such as Alper disease and Menkes disease. If there is a diffuse cortical dysgenesis (e.g., lissencephaly, polymicrogyria) associated with white matter abnormalities, then peroxisomal disorders such as Zellweger syndrome should be considered along with congenital infections (e.g., cytomegaloviral) and the congenital muscular dystrophies (e.g., Fukuyama, Walker-Warburg, Santavuori) (Figure 18.36).

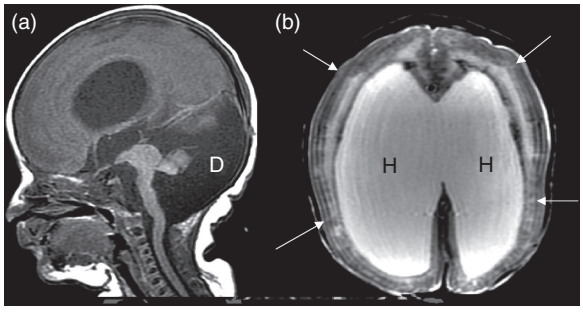


Figure 18.36 Walker-Warburg with Dandy-Walker malformation (D) on (a) sagittal T1 plus (b) cobblestone lissencephaly (arrows) with extensive white matter dysplasia and hydrocephalus (H) on axial T2 MRI.

matter and especially the primary visual cortex (Figure 18.37). This pattern is to be distinguished from a predominant posterior border zone HIE and from dural venous sinus thrombosis primarily in the distribution of the straight sinus, posterosuperior sagittal sinus and/or the inferior sagittal sinus.

Disorders Affecting both White Matter and Deep Gray Matter

Disorders associated with deep gray matter involvement, in addition to white matter abnormalities,

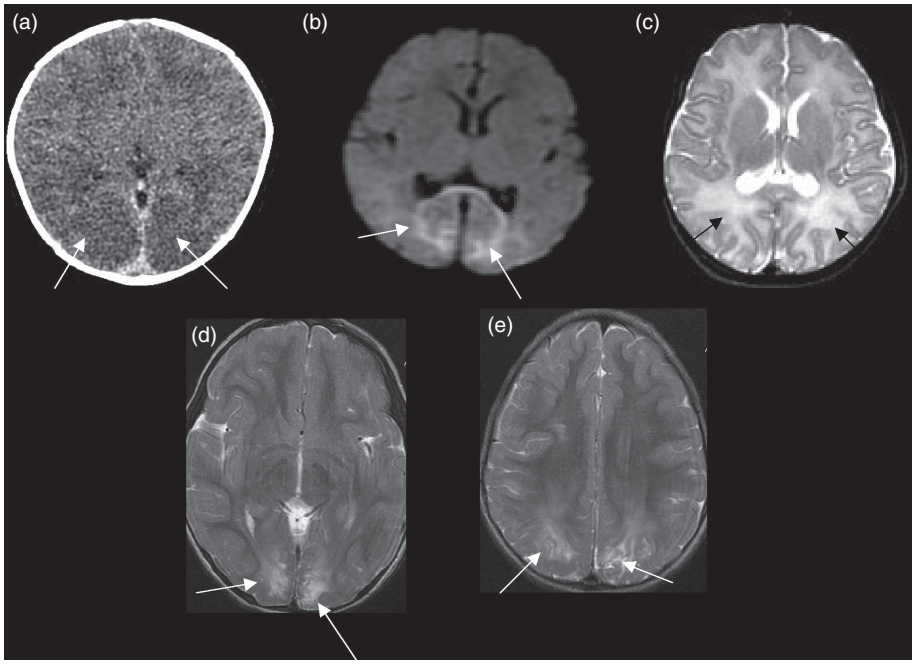


Figure 18.37 Hypoglycemia with parieto-occipital involvement (arrows) in the subacute phase with edema as (a) low density on CT and as high intensity on (b) DWI and (c) T2 MRI; also (d,e) the chronic phase with atrophy and gliosis on T2 MRI.

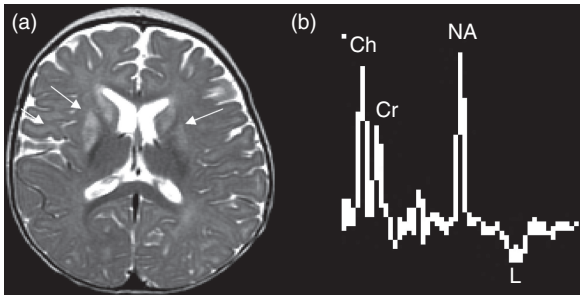


Figure 18.38 Leigh syndrome with basal ganglia lesions (arrows) and white matter involvement: (a) axial T2 MRI; (b) lactate doublet (L) on MRS.

In hypoglycemia, there is predominant involvement of the parieto-occipital gray and white

include those with primarily corpus striatum involvement (Leigh: Figure 18.38, MELAS, Wilson, Cockayne), those with predominant thalamic abnormalities (Krabbe, GM2 gangliosidoses), and those with primarily globus pallidus involvement (Canavan, MSUD, methylmalonic/propionic acidopathy, Kearns-Sayre) [2,5,39,107–113]. Sulfite oxidase deficiency also involves the basal ganglia and white matter and can mimic HIE [114] (Figure 18.39). Included in the differential diagnosis, depending on the clinical context, are profound HIE, osmolar myelinolysis, bilirubin encephalopathy (kernicterus), toxic exposure, and infectious or postinfectious processes (e.g., TORCH, HIV, and ADEM).

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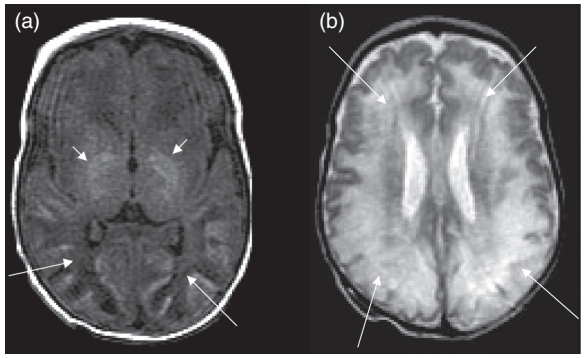


Figure 18.39 Sulfite oxidase deficiency with thalamic (short arrows) and diffuse white matter involvement (long arrows) on (a) axial T1 and (b) T2 MRI.

MR Spectroscopy (MRS) in Metabolic Disorders

Proton (^{1}H) MRS using both short and long TE acquisitions (e.g., TEs 35, 144) is being used increasingly clinically to evaluate brain development and maturation, as well as patients with metabolic and other disorders [12,38,39]. The normal MR brain spectra show an evolution from the immature infantile pattern (e.g., decreased *N*-acetyl-aspartate [NAA] relative to choline [Ch]) to the mature, adult pattern (e.g., increased NAA to Ch) (Figure 18.3). Although many of the metabolic and neurodegenerative disorders have specific biochemical markers, most of the disorders have no differentiating features. Nonspecific MRS abnormalities are those that reflect brain destruction and reactive changes, including delayed maturation, neuronal loss, axonal degeneration, demyelination, and gliosis. Alterations in metabolites are often displayed as a ratio relative to the reference metabolite creatine (Cr), an energy marker. In disorders in which there is predominant neuronal degeneration (i.e., loss of cell bodies, axons) and atrophy or oligodendroglial loss, the major MRS finding is a decrease in NAA, a neuronal (neurons including axons) and immature oligodendroglial marker. In disorders in which there is predominant loss of myelin sheaths with secondary axonal degeneration and gliosis (e.g., demyelination), the characteristic spectral abnormalities are characterized by elevated lipids, a marker for myelin destruction; elevated choline (Ch), a marker of membrane turnover (e.g., myelin, glial); variable increases in lactate (L), a marker of anaerobic glycolysis; elevated glutamate/glutamine (Glx), neuroexcitatory amino acid markers; and elevated myoinositols (mI), also an osmolyte and glial marker. Associated neuronal (e.g., axonal) or oligodendroglial damage is indicated by a decrease in NAA.

More specific MRS abnormalities may be seen in a number of disorders [39]. Abnormal MRS spectra have been reported with some of the lysosomal defects such as Niemann-Pick disease (abnormal lipid peak at 1.2 ppm), the mucopolysaccharidoses (decreased NAA late), and metachromatic leukodystrophy (decreased NAA, Ch, and Cr; increased mI and L). MRS abnormalities have been observed with a number of the peroxisomal disorders, including adrenoleukodystrophy (decreased NAA with increased Ch, Glx, mI, lipids, and L) and Zellweger syndrome (decreased NAA with increased lipids and Glx). Other leukodystrophies associated with observed MRS findings are Canavan disease (increased NAA with decreased Ch and Cr plus increased mI and L), Alexander disease (decreased NAA with increased L), and Pelizaeus-Merzbacher disease (normal early; decreased NAA and increased Ch late). Primary and secondary disorders of energy metabolism have been associated with MRS findings of decreased NAA and increased L, including mitochondrial disorders such as Leigh disease and MELAS (Figure 18.38). Similar findings, however, are present with acute/subacute hypoxia-ischemia (plus elevated Glx, decreased Cr, and increased lipids) (Figure 18.18). Aminoacidopathies with reportedly abnormal spectra include phenylketonuria (increased phenylalanine peak at 7.37 ppm), maple syrup urine disease (abnormal peak at 0.9 ppm), and nonketotic hyperglycinemia (elevated glycine peak at 3.55 ppm). Other metabolic disorders associated with abnormal MRS findings include the creatine deficiencies (decreased, absent Cr), hepatic encephalopathy (increased Glx with decreased inositols and Ch), and hyperosmolar states (increased inositols, Cr, and Ch). Neoplastic processes characteristically show elevated Ch/Cr, decreased NAA/Cr, and decreased NAA/Cr ratios. Inflammatory processes may be differentiated from neoplastic and other processes by the suppressed mI peak [12].

Summary

US and CT may provide important screening information, particularly with regard to hemorrhage, trauma, hydrocephalus, infection, and gross macrostructural anomalies. However, current and advanced MRI techniques provide more definitive macrostructural, microstructural, and functional imaging information in both the early and late assessment of fetal and neonatal CNS injuries.

References

1. Barnes P. Pediatric brain imaging. In Blickman J, Parker B, Barnes P, eds., *Pediatric Radiology: The Requisites*, 3rd edn. Philadelphia: Elsevier, 2009: 205–70.
2. Barnes P. Neuroimaging in the evaluation of pattern and timing of fetal and neonatal brain abnormalities. In Stevenson D, Benitz W, Sunshine P, eds., *Fetal and Neonatal Brain Injury*, 4th edn. New York: Cambridge University Press, 2009: 209–31.
3. Izbudak I1, Grant PE. MR imaging of the term and preterm neonate with diffuse brain injury. *Magn Reson Imaging Clin North Am* 2011; **19**(4): 709–31.
4. Barkovich AJ, Raybaud C:*Pediatric Neuroimaging*, 5th edn. Philadelphia: Lippincott Williams & Wilkins, Wolters Kluwer, 2011.
5. Volpe JJ. *Neurology of the Newborn*, 5th edn. Philadelphia: Saunders Elsevier, 2008.
6. Ment L, Bada H, Barnes P, et al. Practice parameter: neuroimaging of the neonate. *Neurology* 2002; **58**: 1726–38.
7. D'Alton ME, Hankins GDV, et al. *Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology*, 1st edn. (Washington, DC: American College of Obstetricians and Gynecologists, 2003), table 5-2, 570; *Neonatal Encephalopathy and Neurologic Outcome*, 2nd edn. (2014), 149–72).
8. Barkovich A. MR imaging of the neonatal brain. *Neuroimag Clin North Am* 2006; **16**: 117–36.
9. Rutherford M, Srinivasan L, Dyet L, et al. MRI in perinatal brain injury. *Pediatr Radiol* 2006; **36**: 582–92.
10. Zimmerman R, Bilaniuk L. Neuroimaging evaluation of cerebral palsy. *Clin Perinatol* 2006; **33**: 517–44.
11. Triulzi F, Parazzini C, Righini A. Patterns of damage in the mature neonatal brain. *Pediatr Radiol* 2006; **36**: 608–20.
12. Panigrahy A, Blumel S. Advances in MR neuroimaging techniques in the evaluation of neonatal encephalopathy. *Top Magn Reson Imaging* 2007; **18**: 3–30.
13. Barnes PD, Taylor GA. Imaging of the neonatal central nervous system. *Neurosurg Clin North Am* 1998; **1**: 17–48.
14. Allison JW, Seibert JJ. Transcranial Doppler in the newborn with asphyxia. *Neuroimag Clin North Am* 1999; **9**: 11–16.
15. Epelman M1, Daneman A, Chauvin N, Hirsch W. Head Ultrasound and MR imaging in the evaluation of neonatal encephalopathy: competitive or complementary imaging studies? *Magn Reson Imaging Clin North Am*. 2012; **20**(1): 93–115.
16. Debillon T, N'Guyen S, Muet A, et al. Limitations of ultrasonography for diagnosing white matter damage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**: F275–9.
17. Laptook A, O'Shea M, Shankaran S, et al. Adverse neurodevelopmental outcomes among extremely low birth weight infants with normal head ultrasound. *Pediatrics* 2005; **115**: 673–80.
18. Pinto-Martin JA, Riolo S, Cnaan A, et al. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birthweight population. *Pediatrics* 1995; **95**: 249–54.
19. Maalouf EF, Duggan PJ, Counsell SJ, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm neonates. *Pediatrics* 2001; **107**: 719–27.
20. Sie LT, van der Knapp MD, van Wezel-Meijler G, et al. Early MR features of hypoxic-ischemic brain injury in neonates with periventricular densities on sonograms. *AJNR Am J Neuroradiol* 2000; **21**: 852–61.
21. Childs AM, Cornette L, Romenghi LA, et al. Magnetic resonance and cranial ultrasound characteristics of periventricular white matter abnormalities in newborn infants. *Clin Radiol* 2001; **56**: 647–55.
22. Roelants-van Rijn AM, Groenendaal F, Beek FJ, et al. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. *Neuropediatrics* 2001; **32**: 80–9.
23. Inder TE, Anderson NJ, Spencer C, et al. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. *AJNR Am J Neuroradiol* 2003; **24**: 805–9.
24. Miller SP, Cozzio C, Goldstein RB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. *AJNR Am J Neuroradiol* 2003; **24**: 1661–9.
25. Hintz SR, Barnes PD, Bulas D, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics*. 2015; **135**(1): e32–42.
26. Mirmiran M, Barnes P, Keller K, et al. Neonatal brain MRI before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. *Pediatrics* 2004; **114**: 992–8.
27. Sanchez R, Khong PL, Ringertz H. Radiologic protection in pediatric radiology: ICRP recommendations. *Pediatr Radiol.* 2013; **43**(8): 920–1.
28. Vertinzksy A, Barnes P. Macrocephaly, increased intracranial pressure, and hydrocephalus in the infant and young child. *Top Magn Reson Imaging* 2007; **18**: 31–52.

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.019

29. Barnes P. Imaging of NAI and the mimics: issues and controversies in the era of evidence-based medicine. *Radiol Clin North Am* 2011; **49**: 205–29.
30. Mukherjee P. Advanced pediatric imaging. *Neuroimag Clin North Am* 2006; **16**: 1–210.
31. Levine D, Barnes PD, Robertson RR, et al. Fast MR imaging of fetal central nervous system abnormalities. *Radiology* 2003; **229**: 51–61.
32. Garel C, Delezide A, Elmaleh-Berges M, et al. Contribution of fetal MRI in the evaluation of cerebral ischemic lesions. *AJNR Am J Neuroradiol* 2004; **25**: 1563–8.
33. Levine D, Barnes P. MR imaging of fetal CNS abnormalities. In Levine D, ed., *Atlas of Fetal MRI*. Boca Raton, FL: Taylor & Francis, 2005: 25–72.
34. Griffiths P, Widjaja E, Paley M, et al. Imaging of the fetal spine in utero: diagnostic accuracy and impact on management. *Pediatr Radiol* 2006; **36**: 927–33.
35. Garel C. New advances in fetal MR neuroimaging. *Pediatr Radiol* 2006; **36**: 621–5.
36. Glenn O, Barkovich J. Magnetic resonance imaging of the fetal brain and spine, part 1. *AJNR Am J Neuroradiol* 2006; **27**: 1604–11; Part 2. *AJNR Am J Neuroradiol* 2006; 27: 1807–14.
37. Barkovich AJ, Baranski K, Vigneron D, et al. Proton MR spectroscopy in the evaluation of asphyxiated term neonates. *AJNR Am J Neuroradiol* 1999; **20**: 1399–405.
38. Vigneron DB. Magnetic resonance spectroscopic imaging of human brain development. *Neuroimag Clin North Am* 2006; **16**; 75–86.
39. Cecil K. MR spectroscopy of metabolic disorders. *Neuroimag Clin North Am* 2006; **16**: 87–116.
40. Barkovich A, Miller S, Bartha A. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *AJNR Am J Neuroradiol* 2006; **27**: 533–47.
41. Wang J, Licht D. Pediatric perfusion MRI using arterial spin labeling. *Neuroimag Clin North Am* 2006; **16**: 149–68.
42. Huppi PS, Maier SE, Peled S, et al. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res* 1998; **44**: 584–90.
43. Neil JJ, Shiran SI, McKinstry RC. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. *Radiology* 1998; **209**: 57–66.
44. Johnson AJ, Lee BCP, Lin W. Echoplanar diffusion-weighted imaging in neonates and infants with suspected hypoxic–ischemic injury. *AJNR Am J Neuroradiol* 1999; **172**: 219–26.
45. Robertson RL, Ben-Sira L, Barnes PD, et al. MR line scan diffusion imaging of term neonates with perinatal brain ischemia. *AJNR Am J Neuroradiol* 1999; **20**: 1658–70.
46. Phillips MD, Zimmerman RA. Diffusion imaging in pediatric hypoxic-ischemic injury. *Neuroimag Clin North Am* 1999; **9**: 41–52.
47. Inder T, Huppi PS, Zientara GP, et al. Early detection of periventricular leukomalacia by diffusion-weighted magnetic resonance imaging techniques. *J Pediatr* 1999; **134**: 631–4.
48. Inder TE, Huppi PS, Warfield S, et al. Periventricular white matter injury in the premature infant followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol* 1999; **46**: 755–60.
49. Huppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor MR imaging. *Pediatrics* 2001; **107**: 455–60.
50. Arzoumanian Y, Mirmiran M, Barnes P, et al. Diffusion tensor brain imaging findings at term-equivalent age may predict neurologic abnormalities in low birth weight preterm infants. *AJNR Am J Neuroradiol* 2003; **24**: 1646–53.
51. Counsell S, Allsop J, Harrison M, et al. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics* 2003; **112**: 1–7.
52. Sagar P, Grant PE. Diffusion-weighted imaging: pediatric clinical applications. *Neuroimag Clin North Am* 2006; **16**: 45–74.
53. Mukherjee P, McKinstry R. Diffusion tensor imaging and tractography of human brain development. *Neuroimag Clin North Am* 2006; **16**: 19–44.
54. van der Knaap M, Valk J. Classification of congenital abnormalities of the CNS. *AJNR Am J Neuroradiol* 1988; **9**: 315–26.
55. Barkovich AJ, Truwit CL. Brain damage from perinatal asphyxia:correlation of MR findings with gestational age. *AJNR Am J Neuroradiol* 1990; **11**: 1087–96.
56. Aida N, Nishimura G, Hachiya Y, et al. MR imaging of perinatal brain damage: comparison of clinical outcome with initial follow-up MR findings. *AJNR Am J Neuroradiol* 1992; **19**: 1909–22.
57. Barkovich A, Hallam D. Neuroimaging in perinatal hypoxic–ischemic injury. *Ment Retard Dev Disabil Res Rev* 1997; **3**: 28–41.
58. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.

.019

59. Miller S, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005; **146**: 453–60.

60. Lupton BA, Hill A, Roland EH, et al. Brain swelling in the asphyxiated term newborn:pathogenesis and outcome. *Pediatrics* 1988; **82**: 139–46.

61. Vannucci RC, Christensen MA, Jager JY. Nature, time-course, and extent of cerebral edema in perinatal hypoxic–ischemic brain damage. *Pediatr Neurol* 1993; **9**: 29–34.

62. Pinto-Martin JA, Riolo S, Cnaan A, et al. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birthweight population. *Pediatrics* 1995; **95**: 249–54.

63. Goetz MC, Gretebeck RJ, Oh KS, et al. Incidence, timing and follow-up of periventricular leukomalacia. *Am J Perinatol* 1995; **12**: 325–7.

64. Valkama AM, Pääkkö ELE, Vainionpää LK, et al. Magnetic resonance imaging at term and neuromotor outcome in preterm infants. *Acta Paediatr* 2000; **89**: 348–55.

65. Perlman JM, Rollins N. Surveillance protocol for the detection of intracranial abnormalities in premature neonates. *Arch Pediatr Adolesc Med* 2000; **154**: 822–6.

66. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 2001; **50**: 553–62.

67. Panigrahy A, Barnes PD, Robertson RL, et al. Volumetric brain differences in children with periventricular T2-signal hyperintensities:a grouping by gestational age at birth. *AJR Am J Roentgenol* 2001; **177**: 695–702.

68. Miller SP, Hoque NN, Piecuch RE, et al. The spectrum of cerebellar hemorrhage in premature newborns. *Pediatr Res* 2003; **53**: 537A (abstract #3040).

69. Austin NC, Woodward L, Spencer C, et al. Neurodevelopmental outcome at one year in a regional cohort of very low birth weight infants:correlation with MRI at term. *Pediatr Res* 2003; **53**: 398A (abstract #2253).

70. Jenster M, Bonifacio S, Ruel T, et al. Maternal or neonatal infection:association with neonatal encephalopathy outcomes. *Pediatric Res* 2014; **76**: 93–9.

71. Inder TE, Wells SJ, Mogridge NB, et al. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003; **143**: 171–9.

72. Panigrahy A, Barnes PD, Robertson RL, et al. Quantitative analysis of the corpus callosum in children with cerebral palsy and developmental delay: correlation with cerebral white matter volume. *Pediatr Radiol* 2005; **35**: 1199–207.

73. Bodensteiner J, Johnsen S. MRI findings in children surviving extremely premature delivery and extremely low birthweight with cerebral palsy. *J Child Neurol* 2006; **21**: 743–7.

74. Dyet L, Kennea N, Counsell S, et al. Natural history of brain lesions in extremely preterm infants studied with serial MRI from birth and neurodevelopmental assessment *Pediatrics* 2006; **118**: 536–48.

75. Khwaja O, Volpe J. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F153–61.

76. Barkovich AJ. MR and CT evaluation of profound neonatal and infantile asphyxia. *AJNR Am J Neuroradiol* 1992; **13**: 959–72.

77. Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. *AJNR Am J Neuroradiol* 1995; **16**: 1837–46.

78. Barkovich AJ, Westmark K, Partridge C, et al. Perinatal asphyxia: MR findings in the first 10 days. *AJNR Am J Neuroradiol* 1995; **16**: 427–39.

79. Roland EH, Poskitt K, et al. Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. *Ann Neurol* 1998; **44**: 161–6.

80. Sargent M, Poskitt K, Roland E, et al. Cerebellar vermian atrophy after neonatal hypoxic–ischemic encephalopathy. *AJNR Am J Neuroradiol* 2004; **25**: 1008–15.

81. Boichot C, Walker P, Durand C, et al. Term neonate prognosis after perinatal asphyxia: contributions of MR imaging, MR spectroscopy, relaxation times, and ADCs. *Radiology* 2006; **239**: 839–48.

82. Shankaran S, Barnes P, Hintz S, et al. Brain injury following trial of hypothermia for neonatal hypoxic-ischemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**(6): F398–404.

83. Bulas D, Glass P. Neonatal ECMO: neuroimaging and neurodevelopmental outcome. *Semin Perinatol* 2005; **29**: 58–65.

84. Zuerrer M, Martin E, Boltshauser E. MRI of intracranial hemorrhage in neonates and infants at 2.35 tesla. *Neuroradiology* 1991; **33**: 223–9.

85. DeVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001; **345**: 417–23.

86. Carvalho K, Bodensteiner J, Connolly P, et al. Cerebral venous thrombosis in children. *J Child Neurol* 2001; **16**: 574–85.

87. Lynch J, Hirtz D, deVeber G, et al. Report of the National Institute of Neurologic Disorders and Stroke Workshop on Perinatal and Childhood Stroke. *Pediatrics* 2002; **109**: 116–23.

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88. DeVeber G. Arterial ischemic strokes in infants and children: an overview of current approaches. *Semin Thrombos Hemost* 2003; **29**: 567–73.
89. Sebire G, Tabarki B, Saunders DE, et al. Cerebral venous thrombosis in children: risk factors, presentation, diagnosis, and outcome. *Brain* 2005; **128**: 477–89.
90. Kirton A, deVeber G. Cerebral palsy secondary to perinatal ischemic stroke. *Clin Perinatol* 2006; **33**: 367–86.
91. Fitzgerald K, Williams LS, Garg BP, et al. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol* 2006; **63**: 405–9.
92. Barnes C, deVeber G. Prothrombotic abnormalities in childhood ischaemic stroke. *Thromb Res* 2006; **118**: 67–74.
93. Ehtisham A, Stern B. Cerebral venous thrombosis: a review. *Neurologist* 2006; **12**: 32–8.
94. Huang A, Robertson R. Spontaneous superficial parenchymal and leptomeningeal hemorrhage in term neonates. *AJNR Am J Neuroradiol* 2004; **25**: 469–75.
95. Govaert P, Vanhaesebrouck P, de Praeter C. Traumatic neonatal intracranial bleeding and stroke. *Arch Dis Child* 1992; **67**: 840–5.
96. Castillo M, Fordham LA. MR of neurologically symptomatic newborns after vacuum extraction delivery. *AJNR Am J Neuroradiol* 1995; **16**: 816–18.
97. Heuser C, Knight S, Esplin S, et al. Tachysystole in term labor:incidence, risk factors, outcomes, and effect on fetal heart tracings. *Am J Obstet Gynecol* 2013; **209**: 32e1–6.
98. Keller K, Barnes P. Rickets vs. abuse: a national and internationsl epidemic. *Pediatr Radiol* 2008; **38**: 1210–16.
99. Alexander J, Leveno K, Hauth J, et al. Fetal injury associated with cesarean delivery. *Obstet Gynecol* 2006; **108**: 885–90.
100. Doumouchtsis S, Arulkumaran S. Head trauma after instrumental births. *Clin Perinatol* 2008; **35**: 69–83.
101. Schneider JF1, Hanquinet S, Severino M, Rossi A. MR imaging of neonatal brain infections. *Magn Reson Imaging Clin North Am*. 2011; **19**(4): 761–75.
102. Jenster M, Bonifacio S, Ruel T, et al. Maternal or neonatal infection: association with neonatal encephalopathy outcomes. *Pediatr Res* 2014; **76**: 93–9.
103. DeVries L, Verboon-Maciolek M, Cowan F, et al. The role of cranial US and MRI in the diagnosis of infections of the central nervous system. *Early Hum Dev* 2006; **82**: 819–25.
104. Hoon AH. Neuroimaging in cerebral palsy:patterns of brain dysgenesis and injury. *J Child Neurol* 2005; **12**: 936–9.
105. Rodriguez D, Young Poussaint T. Neuroimaging of the child with developmental delay. *Top Magn Reson Imaging* 2007; **18**: 75–92.
106. Valk J, van der Knapp MS. Toxic encephalopathy. *AJNR Am J Neuroradiol* 1992; **13**: 747–60.
107. van der Knaap MS, Valk J. *Magnetic Resonance of Myelination and Myelin Disorders*, 3rd edn. New York: Springer, 2005.
108. Patay Z. MR imaging workup of inborn errors of metabolism of early postnatal onset. *Magn Reson Imaging Clin North Am*. 2011; **19**(4): 733–59;
109. Vanderver A. Tools for diagnosis of leukodystrophies and other disorders presenting with white matter disease. *Curr Neurol Neurosci Rep* 2005; **5**: 110–18.
110. Murakami Y, Yamashita Y, Matsuishi T, et al. Cranial MRI of neurologically impaired children suffering from neonatal hypoglycemia. *Pediatr Radiol* 1999; **29**: 23–7.
111. Alkalay A, Flores-Sarnat L, Sarnat H, et al. Brain imaging findings in neonatal hypoglycemia. *Clin Pediatr* 2005; **44**: 783–90.
112. Barkovich A, Ali F, Rowley H, et al. Imaging patterns of neonatal hypoglycemia. *AJNR Am J Neuroradiol* 1998; **19**: 523–8.
113. Govaert P, Lequin M, Swarte R, et al. Changes in globus pallidus with (pre) term kernicterus. *Pediatrics* 2003; **112**: 1256–63.
114. Dublin A, Hald J, Wootton-Gorges S. Isolated sulfite oxidase deficiency: MR imaging features. *AJNR Am J Neuroradiol* 2002; **23**: 484–5.

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Chapter 19

Light-Based Assessment of the Brain

Valerie Y. Chock

Introduction

Light-based assessment of the brain has a long history of development for use in the medical field. While light in the visible part of the spectrum was used initially; more successful interrogation of the brain was accomplished using a narrower band of wavelengths in the near-infrared spectrum. Near-infrared spectroscopy (NIRS) monitoring of the brain has the advantage of being noninvasive, easily accomplished at the patient bedside, and able to provide continuous measurements, similar to a pulse oximeter, for ongoing patient care. Some neonatal intensive care units (NICUs) have explicitly focused on neurologic intensive care for infants at highest risk for neurologic injury. State-of-the-art neuromonitoring technology including NIRS has been an important part of this neurologic focus in the NICU. Given the rapidly growing use of NIRS in the neonatal community, it is critically important for clinicians to be familiar with NIRS brain monitoring, including its benefits and limitations, for vulnerable infants.

Jobsis in 1977 first demonstrated that tissue absorption of near-infrared light in the 700- to 1,000-nm wavelength range allowed for spectral measurements across the head of an animal with a diameter of 5 to 6 cm [1]. From these early studies, refinement of NIRS as a brain monitoring tool and commercial development of various NIRS devices ensued. NIRS has slowly emerged from being a research tool alone to a bedside technology capable of being integrated into daily clinical care for critically ill patients. NIRS monitoring was once limited to adult medicine, but as NIRS sensors have progressively decreased in size without loss of spatial resolution, monitoring has progressed to encompass the pediatric population, with frequent NIRS employment in the field of pediatric cardiac anesthesia and cardiovascular critical care [2,3]. Only recently has NIRS monitoring increasingly been used in the NICU. Commercially available NIRS devices have been approved by the Food and Drug Administration (FDA) for use in infants, even in those weighing less than 2.5 kg. Detection of neonatal brain injury and potentially avoiding the progression of such injury provide a valuable rationale for its use. However, it is imperative to implement an evidence-based approach to NIRS use in the NICU so that its growing use takes into account both the strengths and the limitations of the technology.

Theory

The basic principle behind NIRS monitoring involves the differential absorption of near-infrared light by chromophores in underlying tissue. Light of a known intensity is emitted from a sensor on the skin. It penetrates through the underlying tissue at a depth depending on the distance between the emitter and detector used by the particular device, but typically this depth ranges between 2.5 and 3 cm. The NIR light is then differentially absorbed by deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2) in the tissues and reflected back to a detector on the same sensor (Figure 19.1). Relative absorbances of HbO_2 and Hb are unique at each wavelength. Modifications of the Beer-Lambert law thus allow for determination of the concentrations of HbO_2 and Hb by the following equation:

$$A = -\log(I/I_0) = \varepsilon_\lambda LC$$

where A is absorbance, I_0 is the intensity of light before passing through the tissue, and I is the intensity of light after passing through the tissue. This absorbance is also a function of the molar absorptivity of the chromophore at the specific wavelength used ε_λ, distance traveled by the light through the tissue (path length) L, and concentration C of the chromophore. Through the use of multiple wavelengths of light, the

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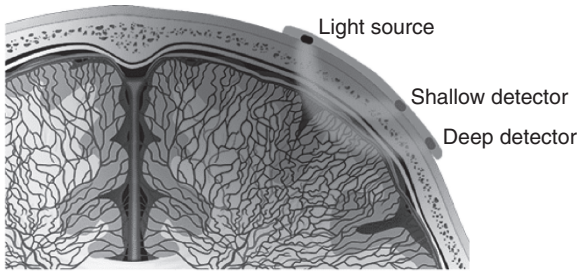


Figure 19.1 Sensor affixed to the skin emits near-infrared light, which penetrates through the skull and is differentially absorbed by oxygenated and deoxygenated hemoglobin in the underlying brain. The near-infrared light is then reflected back to detectors on the same sensor, and a regional tissue oxygenation value is calculated. (© 2016, Medtronic. All rights reserved. Used with the permission of Medtronic.)

percentage of oxygenated hemoglobin in the underlying tissue can be determined and reported as a regional oxygen saturation level (rSO_2) or a tissue oxygenation index (TOI). This is estimated to include 70% venous, 25% arterial, and 5% capillary blood. Thus regional oximetry using NIRS more closely correlates with a mixed venous saturation value compared with a systemic arterial oxygen saturation level from pulse oximetry, which relies on the pulsatile blood flow of arterial blood.

Adjustments must be made for both scattering of light and variable underlying tissue composition causing nonhemoglobin absorbance of light. Each type of NIRS device uses a slightly different algorithm in its calculation of an absolute value for tissue saturation. Improved spatial resolution has also been achieved through the use of additional detection points on the same sensor as well as an additional number of light wavelengths emitted. However, until recently, NIRS devices have long been criticized for the difficulty in achieving consistent absolute measures between patients and have primarily been valued for trend monitoring for an individual subject.

Other Available NIRS Measurements

NIRS can measure a hemoglobin difference signal (HbD) and in some commercial devices can be used for calculation of cerebral blood volume and cerebral blood flow [4]. While hemoglobin is the most widely used chromophore in NIRS devices, cytochrome aa_3, the terminal enzyme in the mitochondrial electron transport chain, can also be measured in some NIRS devices. Measurement of cytochrome aa_3 may allow for assessment of oxygenation at the cellular level and changes in molecular oxygen availability. Lastly, fractional tissue oxygen extraction (FTOE) can be easily calculated with NIRS monitoring through the following relationship:

$$FTOE = (SaO_2 - rSO_2)/SaO_2$$

where SaO_2 is overall systemic oxygenation, and rSO_2 is the regional tissue oxygenation of the brain. Increased FTOE reflects higher oxygen consumption by tissues in relation to oxygen delivery to the brain. Similarly, decreased FTOE suggests decreased use of oxygen by brain tissue [5]. While this chapter focuses on NIRS monitoring of the brain, similar principles apply to the monitoring of other tissue regions, including kidney, mesentery, and muscle. Investigations into the utility of NIRS monitoring of these tissue beds are ongoing. Two-site monitoring with simultaneous cerebral and somatic measures has been advocated during clinical application because hemodynamic compromise results first in a reduction of somatic tissue saturation levels due to the relative preservation of cerebral autoregulation. The concept of autoregulation and its measurement using NIRS will be discussed further in a later section of this chapter.

Validation

Validation studies are available for each of the different commercially available NIRS devices. Good correlation of rSO_2 levels with jugular venous bulb saturation measurements have been made ($r^2 = .9$) [6]. Validation of NIRS values with cerebral T2 MRI imaging of oxygen saturation ($r^2 = .7$) has also been reported [7]. NIRS measurements of rSO_2 provide a good estimate of end-organ perfusion, as established by Doppler flow studies [8]. In addition, NIRS measures are reproducible in neonates [9], making application by various bedside caregivers in the NICU a reasonable process.

Limitations

While NIRS monitoring of cerebral oxygenation obviously has significant clinical potential, limitations of this technology must be considered. Excessive light or poor sensor adhesion may interfere with signal detection. The depth of signal penetration also limits measurement of regional oxygenation to the cerebral cortex rather than deeper structures in the brain. Interpretation of NIRS measures must be made in

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the context of other factors that influence oxygen extraction and delivery, including anemia, hypotension, hypocarbia, and metabolic rate. Of most concern, however, is the potential for significant variability in NIRS measures between patients.

Differences between commercially available NIRS devices contributes to measurable variability in absolute cerebral oxygenation values and lends credence to the argument that NIRS is only suitable for monitoring cerebral oxygenation trends [10]. For example, one manufacturer uses a laser-based light source with generation of four narrow wavelengths, whereas another manufacturer uses a single LED-based emitter with two wider wavelengths, and a third device uses a dual LED emitter with four wavelengths. Differences also exist in the frequency of measurements per minute, spatial resolution technique, and algorithm to calculate regional saturation values based on weighting of oxygenated to deoxygenated hemoglobin. Although well correlated, depending on type of NIRS monitor and sensor size, differences in absolute cerebral rSO_2 values of up to 10–15% were noted by Bland-Altman analysis [11]. Further development of this technology will better standardize the optimal type of commercially available NIRS device in the future. Many clinical centers have also chosen to focus on one particular type of NIRS device and have learned to use that one device well. Arguably, current device differences should not prevent NIRS monitoring from becoming a useful adjunct to improve care for infants at high risk for impaired brain oxygenation.

Normal and Abnormal NIRS Measures

NIRS has historically been touted as a device best suited for trend monitoring of values due to the wide range of what can be considered "normal" absolute values for cerebral oxygenation. This wide range is related to several factors, including changes with postnatal age [12], increased cerebral rSO_2 levels with increasing gestational age [13], sex differences with small-for-gestational-age males having higher values than females [13,14], and regional left and right hemisphere differences up to 10% during unstable arterial saturations [15]. Several large studies have been conducted in both term and preterm infants to establish normative ranges [12,13,16,17]. The largest study from Alderliesten et al. monitored 999 preterm infants at fewer than 32 weeks' gestational age with NIRS in the first 72 hours of life and found a cerebral rSO_2 range between 55% and 85% to be within 2 standard deviations of a median value of 71% [13]. This range of normal values was the basis for the European SAFEBOOS II study, a large randomized, controlled trial investigating clinical interventions based on cerebral NIRS measures [18]. Thus validation of this normal range will occur once long-term outcomes from this study are available.

Despite the wide range of normal NIRS values between neonates, threshold values for abnormal NIRS measures have been better established through pathology and biochemical, functional, and imaging studies in both animal models and neonatal human subjects. In a piglet model of anoxic brain injury, animals with rSO_2 values greater than 60% for 30 minutes had normal histologic brain tissue structure compared with animals with rSO_2 values less than 40% who demonstrated mitochondrial injury and absent or fragmented cellular structure by hippocampal histology [19]. In a different hypoxic piglet model, NIRS cerebral saturation values below 40–50% were correlated with significant decreases in electroencephalographic (EEG) activity of the brain and increases in brain lactate levels, indicating that this is the threshold for serious tissue damage [20]. A study of 22 neonates with hypoplastic left heart syndrome undergoing a Norwood surgical procedure found an association between new or worsened ischemic brain MRI changes if the subject had rSO_2 values of less than 45% for more than 180 cumulative minutes in the postoperative period [21]. This body of evidence suggests cerebral rSO_2 measures of less than 40–45% as a lower threshold for ongoing ischemic brain injury.

Response to Abnormal Cerebral Oximetry

A clinician's response to abnormally low cerebral rSO_2 values should focus on determinants of cerebral blood flow and cerebral oxygenation. Table 19.1 delineates factors that contribute to cerebral oxygenation and potential interventions to consider.

NIRS Monitoring and Long-Term Neurodevelopmental Outcomes

NIRS monitoring cannot be widely accepted as standard of care for neuromonitoring in the NICU until the association between NIRS monitoring and long-term outcomes has been established. Currently, there

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Table 19.1 Troubleshooting Low Cerebral Oxygenation Measures

Factor	Potential intervention
Hypotension	Initiate or increase pressors or consider fluid resuscitation Consider evaluation for significant patent ductus arteriosus
Hypocarbia	Check blood gases and adjust ventilator settings if hypocarbic
Anemia	Check hemoglobin/ hematocrit and consider red blood cell transfusion
Hypoxia	If systemic hypoxia, increase ventilator support or fraction of inspired oxygen
High metabolic rate	Control hyperthermia and consider reducing cerebral metabolic rate with appropriate sedation
Decreased systemic perfusion in infant with congenital heart disease (imbalance of pulmonary to systemic blood flow or Qp:Qs)	In addition to the preceding measures, consider increasing positive end-expiratory pressure, use of subatmospheric oxygen, reducing prostaglandin dose, or need for earlier surgical intervention

are limited studies with this focus in addition to ongoing research with this goal. Verhagen et al. monitored cerebral rSO_2 in 83 preterm infants at fewer than 32 weeks' gestational age over the first 5 days of life and followed these infants with neurodevelopmental testing at 2 to 3 years of age [22]. The authors found that a lower area under the curve of cerebral rSO_2 (lower rSO_2 over longer periods of time) was associated with poorer cognitive outcome ($p = 0.01$). The amount of time with rSO_2 less than 50% on the first day of life was also associated with worse gross motor outcome ($p = 0.002$), whereas the best cognitive outcomes were associated with rSO_2 values between 79% and 83%.

The Effect of Blood Transfusion Practices on Cerebral and Somatic Oximetry is an ongoing multicenter ancillary study conducted through the Eunice Kennedy Shriver NICHD Neonatal Research Network. This study is enrolling more than 350 extremely low-birth-weight preterm infants and performing NIRS monitoring in the first week of life and around the time of red blood cell transfusions to determine the association between NIRS measures and 18- to 22-month neurodevelopmental outcomes.

The only randomized neonatal study investigating cerebral oximetry for clinical decision making in a NIRS-monitored versus a nonmonitored group was the SAFEBOOS II trial conducted in eight different European centers [18]. This study enrolled 166 preterm infants at fewer than 28 weeks' gestation and randomized infants to cerebral NIRS monitoring or blinded monitoring (control group) for the first 72 hours of life. Treatment guidelines in the monitored group were then followed to maintain cerebral rSO_2 at between 55% and 85% by performing interventions such as increasing FiO_2, correcting hypocarbia, or evaluating for a patent ductus arteriosus. Infants in the NIRS-monitored group had a lower burden of cerebral hypoxia or hyperoxia compared with the control group with a trend toward lower mortality and decreased severe intraventricular hemorrhage (IVH) rates. Neurodevelopmental outcomes at 2–3 years of age are currently being acquired.

Clinical Applications of NIRS for Neonates

Specific clinical applications for NIRS monitoring in neonates have been described in the literature and remain under investigation. For the purposes of consistency, cerebral oxygen saturation or cerebral rSO_2 will hereafter be referred to as Csat.

Preterm Infants

Delivery Room Management

Neuromonitoring in the delivery room with NIRS may help to guide resuscitation and can feasibly be applied to infants in the first few minutes of life [23]. Preterm infants requiring respiratory support in the delivery room had lower Csat levels than those requiring no intervention [24]. In addition, effective ventilatory resuscitation after birth resulted first in increased Csat levels, followed by a subsequent

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increase in systemic oxygen saturation (SpO_2) levels [25]. Cerebral NIRS measures thus may be a better reflection than SpO_2 alone of adequate cerebral oxygen delivery and response to resuscitation in the delivery room. Further research is necessary to establish the utility of NIRS monitoring in this transitional setting.

Detection of Impaired Cerebral Autoregulation

The cerebral autoregulatory process maintains a constant cerebral blood flow despite changing cerebral perfusion pressure and protects the brain during periods of fluctuating arterial blood flow. Impaired cerebral autoregulation leads to a state of cerebral pressure passivity and increased risks for hemorrhage and ischemia. The degree of correlation between Csat and mean arterial blood pressure (MAP) has been determined with various techniques to assess cerebral autoregulation, with Csat serving as a surrogate for cerebral blood flow [26–28]. Concordant changes between MAP and cerebral oxygenation were significantly associated with increased severe IVH and periventricular leukomalacia (PVL) in preterm infants [29,30]. Pressure passivity was also associated with lower gestational age and birth weight, systemic hypotension, and maternal hemodynamic factors [31]. NIRS monitoring may be of benefit in detecting vulnerable periods with impaired autoregulation for the neonate such as postoperatively [32]. During these vulnerable periods, strategies to maintain stable cerebral blood flow such as optimization of systemic blood pressure and carbon dioxide tension could be implemented. Conversely, verifying intact cerebral autoregulation may limit the amount of intervention required. Hypotensive preterm infants may still have appropriate cerebral oxygenation [33], whereas those treated with dopamine or volume expansion may have increased systemic blood pressure but no change in cerebral oxygenation if autoregulatory capacity remains intact [34].

Intraventricular Hemorrhage (IVH)

In preterm infants with germinal matrix–intraventricular hemorrhages, lower Csat, and higher cerebral FTOE were found compared with matched controls in the first 2 weeks of life [35]. NIRS measures were not associated with the grade of hemorrhage in this investigation, although a smaller study found significantly lower Csat values in infants with more severe IVH [36]. It remains unclear whether low cerebral blood flow puts preterm infants at risk of IVH or whether hemorrhage itself results in a lower cerebral blood flow state. The presence of excess venous blood in an area of hemorrhage could also contribute to lower Csat values. Also, higher FTOE could be a result of increased oxygen consumption in infants with IVH. A contrasting study found higher Csat and lower FTOE in the first 72 hours of life in infants just prior to the development of severe IVH compared with matched controls [37]. These findings may also implicate periods of cerebral hyperperfusion and impaired autoregulation in the development of IVH. Further research into the temporal changes associated with Csat and FTOE in relation to the exact occurrence of hemorrhage is needed.



Figure 19.2 A 24-week preterm infant with known bilateral grade 4 IVH and ventriculomegaly demonstrated cerebral oxygenation levels ranging from 15–50%. Even a blood transfusion (indicated by the arrow) only minimally increased cerebral oxygenation levels into the detectable range, and there were prolonged periods with levels less than 40%. These abnormally low values assisted with end-of-life discussions with the family.

Figure 19.2 demonstrates a preterm 24-week-gestation infant with bilateral grade 4 IVH with ventriculomegaly. Csat values ranged from 15–50% but displayed prolonged periods with abnormally low values of less than 40% despite normal systemic oxygenation. Corresponding amplitude-integrated EEG (aEEG) demonstrated a discontinuous low-voltage tracing. In this situation, NIRS evidence assisted with end-of-life discussions with the family and the eventual decision to withdraw intensive care support.

Patent Ductus Arteriosus

Diagnosis of a hemodynamically significant patent ductus arteriosus (PDA) may be verified with NIRS monitoring. Due to ductal steal and possible

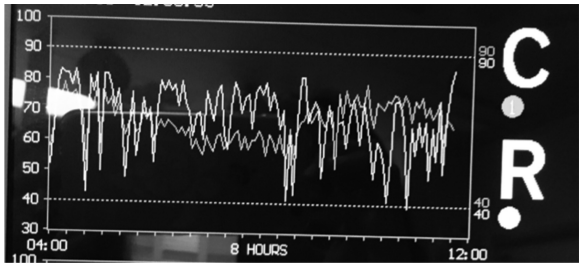


Figure 19.3 Preterm infant with a hemodynamically significant patent ductus arteriosus demonstrates lower cerebral oxygenation levels (blue tracing) ranging between 50% and 75% with considerable variability and renal oxygenation levels (white tracing) also with notable variability.

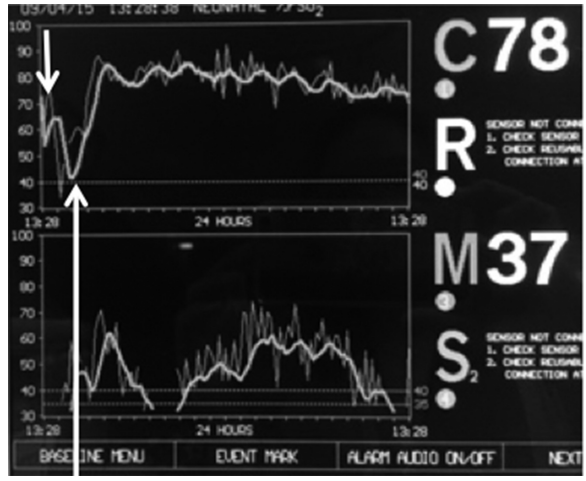


Figure 19.4 A 25-week preterm infant demonstrated a sudden decrease in cerebral oxygenation after a position change while on the ventilator (short arrow). Ventilator settings were optimized, but a further decrease in cerebral oxygenation occurred (long arrow). Blood pressure and systemic oxygenation were stable, but hematocrit was found to be acutely low at 24%, revealing significant anemia. Subsequent red blood cell transfusion improved cerebral oxygenation measures.

impairment of cerebral autoregulation in the preterm infant, cerebral oxygenation may be compromised. Lemmers et al. demonstrated decreased Csat (62% ± 9%) in 20 infants with a significant PDA by echocardiogram compared with matched controls without a PDA (72% ± 10%) ($p < 0.05$) in the first 3 days of life [38]. These differences resolved after treatment with indomethacin. We also measured NIRS differences after 1–2 weeks of life in the era of conservative ductal management (unpublished data), with lower cerebral and renal saturation levels in infants with a significant PDA (Figure 19.3). In combination with clinical signs such as poor urine output, metabolic acidosis, rising creatinine, difficulty weaning the ventilator, and widened pulse pressure, abnormal NIRS measures may indicate the presence of a hemodynamically significant PDA. NIRS monitoring may assist in determining when to order an echocardiogram and further establish the significance of a PDA to guide treatment decisions.

Furthermore, treatment of a PDA by either indomethacin or surgical ligation leads to changes in cerebral oxygenation. Given its vasoconstrictive effects, it is not surprising that transient decreases in Csat after indomethacin administration have been documented [39,40]. Changes in Csat after surgical ligation have been variable. Several investigators have described a sudden and persistent elevation in Csat after placement of the PDA clip, which is also associated with an increase in diastolic and mean blood pressures [39,41,42]. In contrast, others have described a decrease in Csat immediately after ligation, which may reflect increased oxygen consumption [43] or hemodynamic instability postligation, but with a subsequent increase in Csat after 24 hours [44]. The postoperative ligation period may lend itself to continued NIRS monitoring because it is a vulnerable interval for the preterm infant, with increased risk for impaired cerebral autoregulation [32].

Anemia and Red Blood Cell Transfusions

When troubleshooting a low cerebral oxygenation value, anemia must be considered as a possible etiology. Figure 19.4 demonstrates the utility of NIRS monitoring in the detection of hemorrhage with acute anemia. In this case, a preterm 25-week-gestation infant developed increased oxygen requirements and hypercarbia after a position change while on the ventilator. Csat levels also declined. Ventilator settings were increased, but further drop in Csat to approximately 40% was noted. The infant had an adequate blood pressure and was already on maximal 100% oxygen support with stable systemic oxygenation (SpO_2) in the mid-80% range. Due to the persistently low Csat levels, the medical team immediately checked a hematocrit level and simultaneously ordered packed red blood cells in anticipation of transfusion. As the transfusion was initiated, the hematocrit value returned at 24%. The infant subsequently was noted to have fresh blood suctioned from the endotracheal tube and complete opacity of the

right lung by chest radiograph, all findings consistent with an acute pulmonary hemorrhage. The low cerebral saturation levels from NIRS monitoring allowed the team to diagnose the sudden anemia and initiate transfusion in an expedient manner, which may have prevented additional adverse consequences for this infant.

The utility of NIRS monitoring in the setting of anemia is an active area of research. Multiple studies have delineated an increase in both cerebral and somatic oxygenation levels after initiation of transfusion, whereas FTOE of these tissues decreases [45–48]. These values are typically sustained for at least 24 hours after the transfusion. van Hoften et al. found that infants with hemoglobin levels of less than 9.7 g/dL had the lowest Csat levels and were at greatest risk for impairment of cerebral oxygen delivery [48]. However, hematocrit levels do not necessarily correlate with Csat levels. Therefore, a hematocrit level may not accurately reflect end-organ oxygenation of the brain after a transfusion. Csat may be a better measure of the brain's need for a transfusion and response to transfusion. An ongoing randomized multicenter study through the NICHD Neonatal Research Network is investigating the change in Csat levels over the course of a transfusion depending on the infant's initial degree of anemia. This trial will also provide vital neurodevelopmental outcome data to correlate with physiologic differences in Csat that may be discovered between infants randomized to either low or high hemoglobin transfusion thresholds. A goal of NIRS research for the field of anemia of prematurity would be to optimize transfusion guidelines for this vulnerable population.

Term Infants

Hypoxic-Ischemic Encephalopathy

NIRS monitoring of infants with HIE around the time of therapeutic hypothermia has been instituted at several centers. Small studies suggest that infants with adverse 1- to 2-year-old neurodevelopmental outcomes after cooling for HIE had abnormally high Csat values in the first 24–36 hours of life (>80% or 90%) [49–51]. These findings are thought to be related to a lower fractional tissue oxygen extraction by cerebral tissue due to secondary energy failure and have been correlated with ischemic changes on MRI [52–54]. Other investigators have found impaired cerebral autoregulation in infants with adverse outcomes and

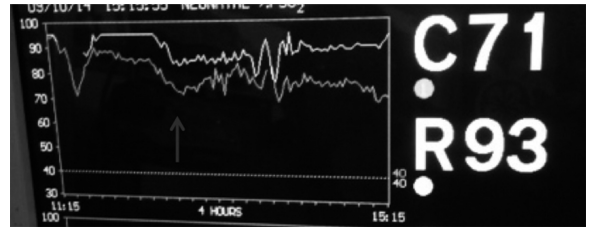


Figure 19.5 A term infant who completed 72 hours of therapeutic hypothermia after suspected hypoxic ischemic encephalopathy had notably elevated cerebral (blue tracing) and renal (white tracing) oxygenation levels. After rewarming was completed (red arrow), the cerebral oxygenation levels decreased to a more normal range.

MRI changes after HIE and therapeutic hypothermia [55]. Typically, the clinician will see a slight increase in Csat levels after initiation of therapeutic hypothermia [54], followed by a subsequent decrease in Csat after the rewarming period due to increased oxygen use by the brain (Figure 19.5). However, it appears that early abnormally elevated Csat levels are more predictive of long-term outcomes. The adjunctive value of cerebral oxygenation in predicting outcomes, potentially in combination with aEEG, has yet to be fully established [51,56].

Congenital Heart Disease

For infants with congenital heart disease, NIRS monitoring has a long history of use during the intraoperative period to guide anesthesiologists in managing the ventilator, adjusting pressor use, and assessing the need for blood transfusions for infants on cardiopulmonary bypass [2,3]. Untreated low Csat values intraoperatively have been associated with a higher incidence of postoperative neurologic sequelae [57]. NIRS monitoring research has also been conducted in the perioperative period by investigators who found an association between low Csat values and new or worsened ischemic brain lesions on MRI [21], lower receptive language scores and cognitive outcomes at 24 months of age [58], and abnormal visual-motor and neurodevelopmental index scores at age 4–5 years [59].

Less NIRS research has been done exclusively in the preoperative period for infants with congenital heart disease, although this population also is at high risk for brain injury. Infants with congenital heart disease may have altered cerebral blood flow due to ductal-dependent lesions, unbalanced pulmonary to systemic blood flow, ongoing systemic inflammation, altered cerebral autoregulation, or preexisting brain

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abnormalities. Others may undergo catheterization procedures leading to fluctuations in cerebral oxygenation. Infants with transposition of the great vessels have an increased risk of emboli after balloon atrial septostomy [60], and in this population, those with a low preoperative Csat of less than 35% had lower developmental quotient scores at 30–36 months of age [61]. Poor end-organ oxygenation may require further interventions to increase systemic blood flow, such as adjusting prostaglandin dose, manipulating the ventilator, using subatmospheric oxygen, or advocating for earlier surgical intervention. The added benefit of NIRS monitoring in the preoperative period was investigated in a population of infants with hypoplastic left heart syndrome [62]. A historical cohort of these patients without NIRS monitoring was compared with a cohort that received routine preoperative NIRS monitoring of cerebral and somatic tissue saturation levels. The cohort with routine NIRS monitoring was found to have a reduced use of mechanical ventilation, reduced use of inspired nitrogen, and no difference in mortality or length of hospital stay. The study demonstrates the feasibility and potential benefit of routine NIRS monitoring in the preoperative period for specific infants with congenital heart disease.

Infants on Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO) represents another clinical situation in which NIRS monitoring may be of benefit. Prior to ECMO cannulation, infants may have respiratory failure and/or pulmonary hypertension with profound impairment of oxygenation. Interventions to improve systemic oxygenation may have implications for cerebral oxygenation as well. Increased ventilatory support may lead to significant hypocarbia and associated cerebral vasoconstriction with low Csat levels. NIRS monitoring may therefore assist with maximizing both cerebral and systemic oxygenation levels.

During and after the ECMO cannulation process, the infant may be at continued risk for hemodynamic disturbances affecting cerebral oxygenation levels. One study demonstrated loss of cerebral autoregulation at lower venoarterial flow levels [63]. These differences were more pronounced on the side of cannulation, potentially indicating that these infants were more susceptible to differential cerebral ischemia or hemorrhage.

Future Directions

Other areas of interest with NIRS monitoring include cerebral oxygenation changes during surgical procedures, the effect of various types of anesthetics on brain oxygenation, and use of NIRS during the prenatal period to investigate fetal or placental well-being [64–66]. Clinical situations with risks for evolving neonatal brain injury including metabolic disorders and severe hyperbilirubinemia are further areas where the potential benefit of cerebral NIRS monitoring may be investigated, whereas somatic oximetry in the neonate continues to be a robust area of ongoing investigation.

Functional NIRS (fNIRS) has been an area of extensive research in the adult and older pediatric population but with limited investigation in the neonate. The premise of fNIRS is that increased neuronal activity in response to a cognitive task or a visual, auditory, or other stimulus can result in changes in cerebral cortical blood flow and corresponding changes in Csat levels. This neurovascular coupling allows for a noninvasive assessment of functional brain activity in the neonate. For example, full-term infants had increased cerebral oxygenated hemoglobin levels in response to speech stimuli, with laterality differences based on speech features [67], and increased Csat has been described in preterm neonates after both tactile and painful (venipuncture) stimuli [68].

While this chapter has focused on NIRS, light-based interrogation of tissues has also extended into the visible-light spectrum. Visible-light spectroscopy (VLS) noninvasively measures hemoglobin oxygen saturation of tissues using visible light in the wavelengths of 475–600 nm [69]. Compared with NIRS, visible light does not penetrate as deeply into tissues. Therefore, VLS works best with thin, capillary-rich tissues, typically at mucosal surfaces such as the esophageal, rectal, or buccal mucosa, and penetrating to a superficial depth of about 0.25 mm. VLS also is more heavily weighted for capillary blood compared with NIRS. Esophageal tissue saturation has been measured with VLS in neonates undergoing cardiac surgery with antegrade cerebral perfusion [70]. Early detection of tissue ischemia using VLS remains under clinical investigation, but VLS could be a complementary monitoring technique to NIRS in the evaluation of neonatal ischemic injury.

Conclusion

Noninvasive assessment of brain oxygenation with NIRS monitoring is an expanding modality in the neonatal population. NIRS has transitioned from a research tool only to one that has rapidly been introduced into clinical practice. The wide adoption of this technique, however, must be tempered with critical evaluation of its utility in specific patient care settings, particularly given the limitations and added costs associated with this technology. Monitoring of infants with congenital heart disease, prematurity, and hypoxic-ischemic encephalopathy represent only a few of the potential intensive care applications for NIRS. Ongoing responsible investigation into this area of neonatal brain monitoring with a focus on patient outcomes is essential.

References

1. Jöbsis FF. Non-invasive, infra-red monitoring of cerebral O_2 sufficiency, blood volume, HbO_2-Hb shifts and bloodflow. *Acta Neurol Scand Suppl* 1977; **64**: 452–3.
2. Andropoulos DB, Stayer SA, Diaz LK, Ramamoorthy C. Neurological monitoring for congenital heart surgery. *Anesth Analg* 2004; **99**(5): 1365–75.
3. Hoffman GM. Neurologic monitoring on cardiopulmonary bypass: what are we obligated to do? *Ann Thorac Surg* 2006; **81**(6): S2373–80.
4. Meek JH, Elwell CE, McCormick DC, et al. Abnormal cerebral haemodynamics in perinatally asphyxiated neonates related to outcome. *Arch Child Fetal Neonatal Ed* 1999; **81**(2): F110–5.
5. Lemmers PMA, Toet M, van Schelven LJ, van Bel F. Cerebral oxygenation and cerebral oxygen extraction in the preterm infant: the impact of respiratory distress syndrome. *Exp Brain Res Exp* 2006; **173**(3): 458–67.
6. Benni PB, Chen B, Dykes FD, et al. Validation of the CAS neonatal NIRS system by monitoring vv-ECMO patients: preliminary results. *Adv Exp Med Biol* 2005; **566**: 195–201.
7. Jain V, Buckley EM, Licht DJ, et al. Cerebral oxygen metabolism in neonates with congenital heart disease quantified by MRI and optics. *J Cereb Blood Flow Metab* 2014; **34**(3): 380–8.
8. Bassan H, Gauvreau K, Newburger JW, et al. Identification of pressure passive cerebral perfusion and its mediators after infant cardiac surgery. *Pediatr Res* 2005; **57**(1):35–41.
9. Menke J, Voss U, Möller G, Jorch G. Reproducibility of cerebral near infrared spectroscopy in neonates. *Biol Neonate* 2003; **83**(1): 6–11.
10. Schneider A, Minnich B, Hofstätter E, et al. Comparison of four near-infrared spectroscopy devices shows that they are only suitable for monitoring cerebral oxygenation trends in preterm infants. *Acta Paediatr Oslo Nor* 2014; **103**(9): 934–8.
11. Dix LML, van Bel F, Baerts W, Lemmers PMA. Comparing near-infrared spectroscopy devices and their sensors for monitoring regional cerebral oxygen saturation in the neonate. *Pediatr Res* 2013; **74**(5): 557–63.
12. McNeill S, Gatenby JC, McElroy S, Engelhardt B. Normal cerebral, renal and abdominal regional oxygen saturations using near-infrared spectroscopy in preterm infants. *J Perinatol* 2011; **31**(1): 51–7.
13. Alderliesten T, Dix L, Baerts W, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. Pediatr Res 2016; **79**: 55–64.
14. Cohen E, Baerts W, Alderliesten T, et al. Growth restriction and gender influence cerebral oxygenation in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2016; **101**(2): F156–61.
15. Lemmers PM, van Bel F. Left-to-right differences of regional cerebral oxygen saturation and oxygen extraction in preterm infants during the first days of life. *Pediatr Res* 2009; **65**(2): 226–30.
16. Grossauer K, Pichler G, Schmölzer G, et al. Comparison of peripheral and cerebral tissue oxygenation index in neonates. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**(2): F156.
17. Bernal NP, Hoffman GM, Ghanayem NS, Arca MJ. Cerebral and somatic near-infrared spectroscopy in normal newborns. *J Pediatr Surg* 2010; **45**(6): 1306–10.
18. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ* 2015; **350**: g7635.
19. Hou X, Ding H, Teng Y, et al. Research on the relationship between brain anoxia at different regional oxygen saturations and brain damage using near-infrared spectroscopy. *Physiol Meas* 2007; **28**(10): 1251–65.
20. Kurth CD, Levy WJ, McCann J. Near-infrared spectroscopy cerebral oxygen saturation thresholds for hypoxia-ischemia in piglets. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 2002; **22**(3): 335–41.
21. Dent CL, Spaeth JP, Jones BV, et al. Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. *J Thorac Cardiovasc Surg* 2005; **130**(6): 1523–30.
22. Verhagen EA, Van Braeckel KNJA, van der Veere CN, et al. Cerebral oxygenation is associated with

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neurodevelopmental outcome of preterm children at age 2 to 3 years. *Dev Med Child Neurol* 2015; **57**(5): 449–55.

23. Fuchs H, Lindner W, Buschko A, et al. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. *J Perinatol Off J Calif Perinat Assoc* 2012; **32**(5): 356–62.
24. Binder C, Urlesberger B, Avian A, et al. Cerebral and peripheral regional oxygen saturation during postnatal transition in preterm neonates. *J Pediatr* 2013; **163**(2): 394–9.
25. Fuchs H, Lindner W, Buschko A, et al. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. *Pediatr Res* 2011; **70**(2): 176–80.
26. Brady KM, Mytar JO, Lee JK, et al. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke J Cereb Circ* 2010; **41**(9): 1957–62.
27. Wong FY, Leung TS, Austin T, et al. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. *Pediatrics* 2008; **121** (3): e604–11.
28. Eriksen VR, Hahn GH, Greisen G. Cerebral autoregulation in the preterm newborn using near-infrared spectroscopy: a comparison of time-domain and frequency-domain analyses. *J Biomed Opt* 2015; **20** (3): 37009.
29. Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000; **106**(4): 625–32.
30. O'Leary H, Gregas MC, Limperopoulos C, et al. Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage. *Pediatrics* 2009; **124**(1): 302–9.
31. Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007; **61**(4): 467–73.
32. Chock VY, Ramamoorthy C, Van Meurs KP. Cerebral autoregulation in neonates with a hemodynamically significant patent ductus arteriosus. *J Pediatr* 2012; **160**: 936–42.
33. Binder-Heschl C, Urlesberger B, Schwaberger B, et al. Borderline hypotension: how does it influence cerebral regional tissue oxygenation in preterm infants? *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2016; **29**(14): 2341–6.
34. Garner RS, Burchfield DJ. Treatment of presumed hypotension in very low birthweight neonates: effects on regional cerebral oxygenation. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**(2): F117–21.
35. Verhagen EA, Ter Horst HJ, Keating P, et al. Cerebral oxygenation in preterm infants with germinal matrix-intraventricular hemorrhages. *Stroke* 2010; **41**(12): 2901–7.
36. Sorensen LC, Maroun LL, Borch K, et al. Neonatal cerebral oxygenation is not linked to foetal vasculitis and predicts intraventricular haemorrhage in preterm infants. *Acta Paediatr* 2008; **97**(11): 1539–34.
37. Alderliesten T, Lemmers PMA, Smarius JJM, et al. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr* 2013; **162** (4):698–704.e2.
38. Lemmers PM, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. *Pediatrics* 2008; **121**(1): 142–7.
39. Chock VY, Ramamoorthy C, Van Meurs KP. Cerebral oxygenation during different treatment strategies for a patent ductus arteriosus. *Neonatology* 2011; **100**: 233–40.
40. Underwood MA, Milstein JM, Sherman MP. Near-infrared spectroscopy as a screening tool for patent ductus arteriosus in extremely low birth weight infants. *Neonatology* 2007; **91**(2): 134–9.
41. Vanderhaegen J, De Smet D, Meyns B, et al. Surgical closure of the patent ductus arteriosus and its effect on the cerebral tissue oxygenation. *Acta Paediatr* 2008; **97** (12): 1640–4.
42. Meier SD, Eble BK, Stapleton GE, et al. Mesenteric oxyhemoglobin desaturation improves with patent ductus arteriosus ligation. *J Perinatol* 2006; **26**(9): 562–4.
43. Zaramella P, Freato F, Quaresima V, et al. Surgical closure of patent ductus arteriosus reduces the cerebral tissue oxygenation index in preterm infants: a near-infrared spectroscopy and Doppler study. *Pediatr Int* 2006; **48**(3): 305–12.
44. Lemmers PM, Molenschot MC, Evens J, et al. Is cerebral oxygen supply compromised in preterm infants undergoing surgical closure for patent ductus arteriosus? *Arch Child Fetal Neonatal Ed* 2010; **95**(6): F429–34.
45. Bailey SM, Hendricks-Muñoz KD, Wells JT, Mally P. Packed red blood cell transfusion increases regional cerebral and splanchnic tissue oxygen saturation in anemic symptomatic preterm infants. *Am J Perinatol* 2010; **27**(6): 445–53.
46. Dani C, Pratesi S, Fontanelli G, et al. Blood transfusions increase cerebral, splanchnic, and renal oxygenation in anemic preterm infants. *Transfusion (Paris)* 2010; **50**(6): 1220–6.

47. Wardle SP, Weindling AM. Peripheral fractional oxygen extraction and other measures of tissue oxygenation to guide blood transfusions in preterm infants. *Semin Perinatol* 2001; **25**(2): 60–4.
48. van Hoften JC, Verhagen EA, Keating P, et al. Cerebral tissue oxygen saturation and extraction in preterm infants before and after blood transfusion. *Arch Child Fetal Neonatal Ed* 2011; **95**(5): F352–8.
49. Toet MC, Lemmers PM, van Schelven LJ, van Bel F. Cerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. *Pediatrics* 2006; **117**(2): 333–9.
50. Ancora G, Maranella E, Grandi S, et al. Early predictors of short term neurodevelopmental outcome in asphyxiated cooled infants: a combined brain amplitude integrated electroencephalography and near infrared spectroscopy study. *Brain Dev* 2013; **35**(1): 26–31.
51. Lemmers PM, Zwanenburg RJ, Benders MJ, et al. Cerebral oxygenation and brain activity after perinatal asphyxia: does hypothermia change their prognostic value? *Pediatr Res* 2013; **74**(2): 180–5.
52. Massaro AN, Bouyssi-Kobar M, Chang T, et al. Brain perfusion in encephalopathic newborns after therapeutic hypothermia. *AJNR Am J Neuroradiol* 2013; **34**(8): 1649–55.
53. Wintermark P, Hansen A, Warfield SK, et al. Near-infrared spectroscopy versus magnetic resonance imaging to study brain perfusion in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *NeuroImage* 2014; **85**(1): 287–93.
54. Peng S, Boudes E, Tan X, et al. Does near-infrared spectroscopy identify asphyxiated newborns at risk of developing brain injury during hypothermia treatment? *Am J Perinatol* 2015; **32**(6): 555–64.
55. Massaro AN, Govindan RB, Vezina G, et al. Impaired cerebral autoregulation and brain injury in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *J Neurophysiol* 2015; **114**(2): 818–24.
56. Shellhaas RA, Thelen BJ, Bapuraj JR, et al. Limited short-term prognostic utility of cerebral NIRS during neonatal therapeutic hypothermia. *Neurology* 2013; **81**(3): 249–55.
57. Austin EH 3rd, Edmonds HLJ, Auden SM, et al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 1997; **114**(5): 707–15, 717; discussion 715–6.
58. Sood ED, Benzaquen JS, Davies RR, et al. Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy. *J Thorac Cardiovasc Surg* 2013; **145**(2): 438–45.e1; discussion 444–5.
59. Hoffman GM, Brosig CL, Mussatto KA, et al. Perioperative cerebral oxygen saturation in neonates with hypoplastic left heart syndrome and childhood neurodevelopmental outcome. *J Thorac Cardiovasc Surg* 2013; **146**(5): 1153–64.
60. McQuillen PS, Hamrick SEG, Perez MJ, et al. Balloon atrial septostomy is associated with preoperative stroke in neonates with transposition of the great arteries. *Circulation* 2006; **113**(2): 280–5.
61. Toet MC, Flinterman A, Laar I, et al. Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome. *Exp Brain Res* 2005; **165**(3): 343–50.
62. Johnson BA, Hoffman GM, Tweddell JS, et al. Near-infrared spectroscopy in neonates before palliation of hypoplastic left heart syndrome. *Ann Thorac Surg* 2009; **87**(2): 571–7.
63. Papademetriou MD, Tachtsidis I, Elliot MJ, et al. Multichannel near infrared spectroscopy indicates regional variations in cerebral autoregulation in infants supported on extracorporeal membrane oxygenation. *J Biomed Opt* 2012; **17**(6): 067008.
64. Rhondali O, Juhel S, Mathews S, et al. Impact of sevoflurane anesthesia on brain oxygenation in children younger than 2 years. *Paediatr Anaesth* 2014; **24**(7): 734–40.
65. Conforti A, Giliberti P, Mondi V, et al. Near infrared spectroscopy: experience on esophageal atresia infants. *J Pediatr Surg* 2014; **49**(7): 1064–8.
66. Kawamura T, Kakogawa J, Takeuchi Y, et al. Measurement of placental oxygenation by transabdominal near-infrared spectroscopy. *Am J Perinatol* 2007; **24**(3): 161–6.
67. Arimitsu T, Uchida-Ota M, Yagihashi T, et al. Functional hemispheric specialization in processing phonemic and prosodic auditory changes in neonates. *Front Psychol* 2011; **2**: 202.
68. Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJS. Pain activates cortical areas in the preterm newborn brain. *Pain* 2006; **122**(1–2): 109–17.
69. Benaron DA, Parachikov IH, Friedland S, et al. Continuous, noninvasive, and localized microvascular tissue oximetry using visible light spectroscopy. *Anesthesiology* 2004; **100**(6): 1469–75.
70. Heninger C, Ramamoorthy C, Amir G, et al. Esophageal saturation during antegrade cerebral perfusion: a preliminary report using visible light spectroscopy. *Paediatr Anaesth* 2006; **16**(11): 1133–7.

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Chapter 20

Placental Pathology and the Etiology of Fetal and Neonatal Brain Injury

Theonia K. Boyd and Rebecca N. Baergen

Introduction

In the context of untoward fetal and/or neonatal outcome, the purpose of performing placental pathology determination is to identify responsible mechanism(s) and their timing with respect to stillbirth or delivery. Placental pathologic correlates of intrauterine stressors resulting in fetal and neonatal brain injury are fairly well defined. The dilemma arises not in identifying placental abnormalities but in their interpretation in the clinical context. This is due primarily to a paucity of prospective studies directly linking specific clinical abnormalities with placental pathology, which are rarely done in humans because they present practical and ethical problems. In addition, there are relatively few animal models of induced pregnancy disorders that have analyzed placental correlates. Instead, associations have largely arisen from clinically or pathologically driven retrospective studies. As a result, in an individual case there is room for interpretation with respect to the likelihood of abnormal placental findings in contributing to or causing untoward neurologic outcome. The benefit of gaining a body of experience in examining placentas and recognizing patterns of association narrows an individual pathologist's interpretive variability. Still there remains scant bedrock of experimental data on which to build clinicopathologic interpretation. Consensus provides a surrogate mode of demonstrating confidence in placental interpretation, and to this end, two coauthors have collaborated in constructing this chapter. The information and opinions expressed herein reflect our collective experience and understanding of the relationship between placental pathology and intrauterine stressors leading to clinically determined fetal and neonatal brain injury. In some instances, our opinions diverge; those passages reflect variance in pathologic interpretation.

Timing Intrauterine Stress

Meconium

Meconium visually detectable in amniotic fluid is usually (though perhaps at term not always) released in response to fetal stress. It has been stated, but not proven, that meconium is released in small amounts in the last weeks of normal intrauterine life. If this is true, then there is no convincing correlate in placentas delivered without a history of meconium detected during the intrapartum period. Meconium release is uncommon prior to the third trimester, even in severely stressed fetuses; thus, in second-trimester premature infants the absence of meconium does not necessarily equate to the absence of intrauterine stress. Animal models have shown that hypoxia is a potent stimulator of meconium passage in utero at term [1].

There is a time lag between the onset of intrauterine stress and meconium release, as evidenced by hyperacute mechanisms of demise (e.g., acute cord prolapse or ruptured vasa previa), when the fetus dies within 15 or 30 minutes of the event onset. In such cases, meconium will not be released prior to demise despite the fact that the stressor is severe enough to be rapidly fatal. At the other end of the time spectrum, if a fetus is chronically stressed in utero, that is, for week(s), the fetal body may adapt to the stressor so as not to elicit meconium despite a stressor's obvious deleterious effect. The window of intrauterine stress in which meconium is most likely to be seen is within the acute and subacute phases, namely, from intrauterine stressors of a duration between hours and days if demise does not intervene.

Once meconium is released into the amniotic fluid and comes into contact with amnion epithelium, it can

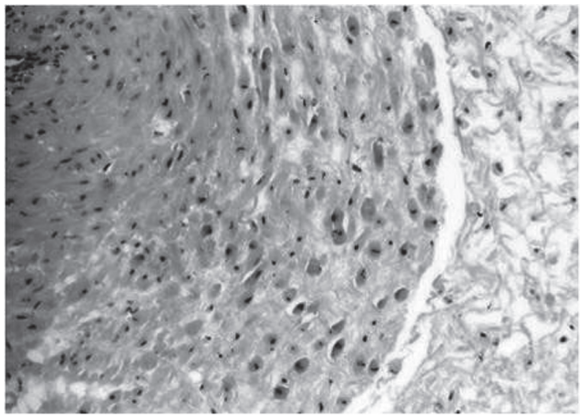


Figure 20.1 Meconium-induced umbilical vascular necrosis. Outer wall myocytes exhibit pyknosis in the presence of meconium macrophages. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

be taken up by macrophages into the extraplacental membranes and chorionic plate. In general, the longer the elapsed time between the onset of meconium release and placental delivery, the deeper the meconium pigment penetrates into the affected tissue layers. An older but oft-quoted ex vivo study was performed to plot the time between application of meconium to delivered placentas and the appearance of meconium macrophages in the component layers of the extraplacental membranes [2]. More recently, another study used the timing of clinical meconium detection prior to delivery in comparison with the extent of meconium uptake in placental macrophages [3].

Meconium-induced vascular necrosis (Figure 20.1) is a very important lesion to recognize within the umbilical cord because it not only indicates prolonged meconium release due to prolonged intrauterine stress but also carries an independent risk of untoward neonatal outcome due to meconium chemical-induced alteration of vascular tone [4–8]. Ex vivo studies have assessed the interval between meconium application to the umbilical cord surface and the histologic appearance of vascular necrosis [9,10]. Although the authors did not address this particular point, it is implicit in these cases not only that meconium release starts many hours prior to delivery but also that there is continued release, or at least that the stressor eliciting its release persists until the time of delivery. In our experience, this is borne out by clinical and pathologic correlation. Clinically, there is invariably description of abundant meconium, either thick in quality and/or noted to be of prolonged duration, prior to delivery. Grossly, the placenta is deeply green or green-brown discolored; umbilical cord discoloration is also present.

On gross placental examination, meconium released shortly prior to delivery will discolor the amniotic membranes and chorionic plate green, perhaps with a patchy distribution, and the discoloration can be wiped from the amnion surface. Often, recently released meconium is described clinically as "particulate"; this can also be seen microscopically as entrapped amorphous orange-brown pigment apposed to the amniotic surface. Meconium taken into the tissue, however, remains green even with handling (Figure 20.2a). Meconium of long-standing duration appears green-brown to brown grossly. This green-brown or brown discoloration may also occur with blood breakdown pigment (biliverdin, hemosiderin), and green discoloration can also be seen sometimes in chorioamnionitis (neutrophil myeloperoxidase): thus green and brown gross discolorations are not restricted to meconium alone.

Microscopically, meconium uptake is seen as an orange-brown, nonrefractile, opaque macrophage cytoplasmic pigment (Figure 20.2b). Particulate surface meconium, not yet taken up into tissue macrophages, has the same hue but appears amorphous and globular. Meconium that has been partially digested by lysozymes – implying some passage of time between uptake and tissue sampling – however, imparts a more lightly hued vacuolated or "bubbly" appearance to the cytoplasm. The density of meconium macrophages reflects meconium thickness, while, as stated earlier, the depth to which meconium macrophages penetrate reflects the interval between meconium discharge and delivery.

There is a general correlation between the thickness of clinically identified meconium and the combination of chronicity and severity of the stressor that elicited its release. Moderate to thick meconium occurs in conditions of overt and/or prolonged intrauterine stress and according to the clinical literature is associated with an increased risk of adverse outcome [11,12]. Amniotic fluid volume may be one factor that mitigates meconium density; regardless, thick meconium is a marker of nonacute fetal stress.

As a corollary, evidence exists to support the contention that meconium can induce neutrophil chemotaxis via noninfectious but toxic chemical components of bile acids [13–15]. Histologically, this may mimic "chorioamnionitis" considered to be of infectious origin. However, in the setting of meconium chemotaxis, the fetal inflammatory response is commonly more advanced than the maternal inflammatory response.

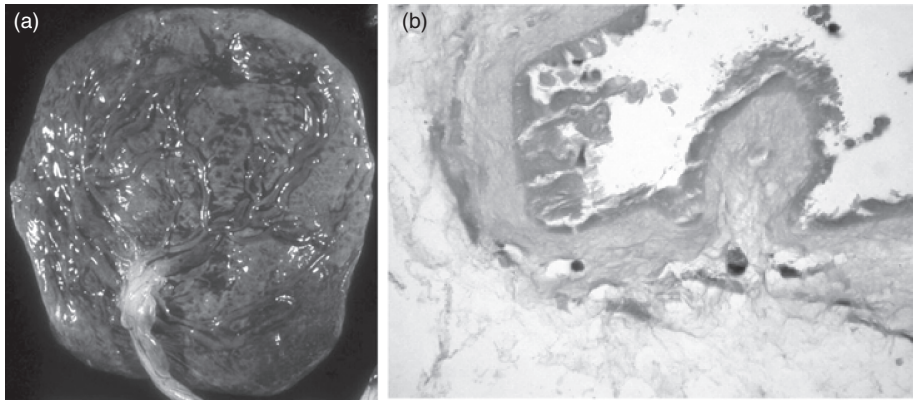


Figure 20.2 (a) Gross meconium staining: the fetal surface is discolored green to green-brown; the surface typically feels diffluent ("slimy") on palpation. (b) Microscopic meconium uptake into membrane macrophages: through the microscope, meconium appears as a globular or amorphous orange-brown pigment. Note the reactive amnion and amnion necrosis due to meconium. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

This view is not universally shared among pathologists with placental expertise, however.

It is important to point out that not all extraplacental membrane, chorionic, or umbilical macrophages exhibiting yellow-orange-brown spectrum pigmentation are meconium macrophages. Sometimes the pigment represents blood breakdown products such as hemosiderin (refractile, brown) or bilirubin (refractile, golden); sometimes the pigment is meconium; but not rarely, there can be pigmented macrophages of uncertain origin. Some authors have suggested that lipofuscin, a nonpathologic pigment resulting from the cytoplasmic accumulation of metabolic by-products, may be one alternative explanation. In these circumstances, there is no clinical or grossly visible correlate of meconium, and none of the ancillary membrane features that may be associated with meconium discharge (reactive amnion "atypia," amnion necrosis, amnion edema, and chorion epithelial necrosis). Using a constellation of clinical, gross, and microscopic findings strengthens the ability to discriminate clinically insignificant macrophage pigment from potentially pathologic meconium.

Nucleated Red Blood Cells

In principle, nucleated red blood cells (NRBCs) are not found under normal conditions within the fetal circulation, including that of the placental-fetal vascular tree, after the first trimester. In practice, rare NRBCs, either by visual or automated count, may be seen in uncomplicated deliveries. NRBCs represent the immature erythrocyte series (normoblasts) still containing their nuclei. They are normally seen in sites of erythropoiesis, such as the fetal liver and bone marrow, prior to enu-

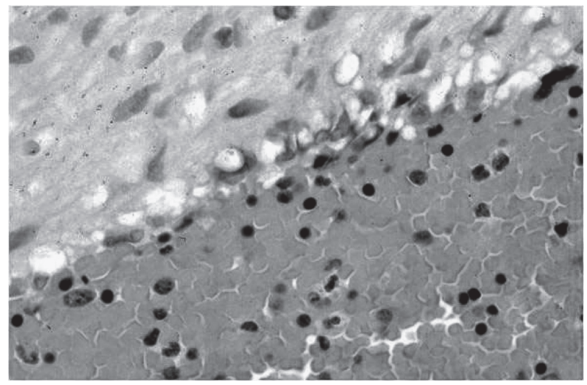


Figure 20.3 Nucleated red blood cells (NRBCs) are identified by their round hyperchromatic nuclei and pink-red cytoplasm. NRBCs of this proportion indicate nonacute hypoxic stress, in this case from a stillbirth due to umbilical cord hypercoiling. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

mature erythrocytes comprised entirely of oxygen-carrying cytoplasm. However, when stimulated, preformed NRBCs are released into the peripheral circulation. These cells have round, dense, hyperchromatic nuclei and the tinctorial cytoplasmic qualities of their enucleate counterparts (Figure 20.3). Conditions that stimulate intrauterine release of NRBCs include acute and chronic hypoxic stress, anemia, infection, and maternal diabetes. Initially, preformed normoblasts circulate (normoblastemia), but with prolonged stimulation, ever more primitive NRBCs are seen in addition to elevated normoblasts, a likely combination of release and enhanced erythropoiesis. In conditions of prolonged persistent hypoxic stress that permit intrauterine survival, such as alloimmune hemolytic anemia or

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nucleated erythrocytes – erythroblasts – are released into the fetal circulation (erythroblastosis). In these circumstances, erythropoiesis is markedly accelerated, often in atypical visceral sites (e.g., kidney, pancreas).

Pure hypoxic stimulation is mediated by the release of erythropoietin. The factors(s) that mediate NRBC release in infection are not well understood. One possible mechanism may be nonspecific release of hematopoietic elements in response to cytokine stimulation, perhaps due to immaturity of the fetal immune system and its signals [16–18]. A second potential mechanism may include a component of hypoxic stimulation in the setting of infection, perhaps mediated by erythropoietin [19,20].

The timing of NRBC release in response to stimulation has undergone a conceptual shift. Older literature stated that erythropoiesis occurred prior to the appearance of peripherally circulating erythrocytes, meaning that the interval between stimulus and release was on the order of days or more. More recent literature indicates that stimulation leads to release of preformed NRBCs, truncating the time interval between stimulus and response. In this latter model, stimulus-driven erythropoiesis occurs only when the stimulus is prolonged. Thus both acute and chronic modes of hypoxic stress can induce normoblastemia [21,22].

How long after a hypoxic stimulus does it take to detect circulating NRBCs? In our experience, and supported by some literature, NRBCs can begin to be seen within about an hour to a few hours following the onset of hypoxia. With continued intrauterine hypoxic stress, the number of NRBCs will continue to rise such that at any given time point NRBC values will reflect both the chronicity and severity of the stimulus eliciting their production and/or release. Erythroblastosis, however, occurs only in conditions of chronic persistent hypoxia lasting weeks rather than hours or days.

How long after the cessation of a hypoxic stimulus, for example, interruption by parturition, does it take for circulating NRBCs to disappear? As a general principle (in one author's experience), the rate of fall approximately mirrors the rate of rise. Thus a hypoxic stressor of some hours' onset prior to delivery will elicit NRBC release that concomitantly falls also within hours, perhaps up to a day (as opposed to days or weeks) following delivery. In contradistinction, chronic hypoxic stress results in postnatal NRBCs that fall over days to a week or more [23–26]. Persistent elevation of NRBC counts for several days following delivery should also suggest other causes, such as congenital infection or maternal diabetes.

NRBCs are counted in peripheral blood in reference to the normally nucleated peripheral blood cells, the leukocytes (white blood cells [WBCs]). This can be done microscopically because NRBCs are discriminated based on their nuclear and cytoplasmic morphology from myeloid and lymphoid leukocytes. In the laboratory, NRBCs can also be discriminated from leukocytes by automated separation. In histologic evaluation, and in most laboratory reports, the NRBC count is expressed as a number per 100 WBCs. Some laboratories instead, or also, report an absolute NRBC count, expressed as the number of NRBCs per cubic millimeter. In our experience, semiquantitative counts or estimates of NRBCs per 100 WBCs correlate well with automated counts in initial neonatal laboratory values, if drawn within a short time after delivery. In uncomplicated deliveries, there is excellent correlation between automated absolute NRBC counts and automated counts expressed per 100 WBCs [27]. Absolute counts are preferred if the leukocyte count is abnormally high or low or rapidly changing. Early neonatal counts greater than 2,500/mm^3 in the face of subacute to chronic placental lesions have been associated with an increased risk of cerebral palsy (CP) in term infants [28].

While the majority of the clinical literature supports reliability in using NRBC counts and/or clearance times to assess the timing and severity of stress in utero [29–34], conflicting results have been reported [35]. The latter may reflect multiple factors. There may be limitations in the use of dichotomous relative NRBC counts (less than or greater than 10 NRBCs/100 WBCs) rather than continuous absolute NRBC counts (NRBCs/mm^3). In addition, there exists literature ambiguity regarding NRBC values and their utility in timing stress versus injury. In asphyxiated neonates, for example, there is evidence that elevated NRBCs are associated with an increased risk of neurologic injury [36–38]. However, these studies compare neonatal presentation, NRBCs, and outcome. Placental pathology was not used in assessing mechanism(s) of intrauterine stress and their timing prior to delivery.

Acute Blood Flow Disruption, Fetal Hemorrhage, and Anemia

Acute interruption of maternal or fetal blood flow can occur from obstruction or disruption of blood vessels. Acute interruption of maternal blood flow to the

placenta is generally caused by uterine rupture, placental abruption, or maternal circulatory collapse, whereas interruption of fetal blood flow is usually caused by disruption of large fetal vessels in the placenta or acute cord obstruction.

Traumatic uterine rupture may occur as a result of a motor vehicle accident, abdominal trauma, or dehiscence of a previous cesarean section scar. Uterine rupture is often associated with life-threatening maternal hemorrhage necessitating hysterectomy, and it may lead to sudden, severe fetal hypoxia sufficient to cause severe neurologic injury or death [39]. Pathologic examination of the uterus can identify the site of the uterine rupture and the associated dissection of blood through the uterine wall. In acute abruption, the placenta separates from the uterus prior to delivery of the infant with loss of blood flow to the placental tissue underlying the abruption. It is estimated that an acute abruption of 50% will lead to fetal demise [40]. Lesser degrees of separation and more chronic abruptions can lead to sublethal injury [28,41,42]. If cesarean section is performed, direct visualization of placental detachment is possible, and bleeding from the torn decidual vessels will result in a retroplacental hematoma. Gross examination of the delivered placenta will often show compression of the villous tissue underlying the hematoma. Within a few hours, villous stromal hemorrhage will also develop, and over the next few days progressive indications of ischemic change in the underlying chorionic villi and eventual infarction occur [43]. In the following days to weeks, the clot organizes, and the villous infarction becomes a firm tan-white scar. However, many acute abruptions extend over time, and thus the pathologic changes may be of different ages.

Interruption of fetal blood flow most often is caused by trauma. It may occur through any fetal vessel, from the umbilical vessels and their tributaries coursing over the chorionic plate down to the villous capillaries [44,45]. Interruption of fetal blood flow is usually associated with acute fetal blood loss and anemia, which, in turn, may lead to hypotension and significant neurologic injury or death. Disruption of larger vessels will result in a large fetal hemorrhage relatively quickly, potentially leading to severe hypovolemia and circulatory collapse, while hemorrhage from small vessels tends to be more chronic but may still be quite significant. The most common etiology of large-vessel hemorrhage is disruption of velamentous or membranous vessels. Because these vessels travel in the membranes without the protection of Wharton's jelly, they are quite susceptible to damage. The umbilical cord itself can rupture, but this, fortunately, is a rare event. Most cord ruptures are partial but still lead to severe fetal hemorrhage and anemia, with a significant risk of neurologic injury in the infants who survive. The etiologies of cord rupture are very rare but include excessive traction on the cord during delivery from either a short cord [44], abnormal placental adherence in placenta accreta [42], or friability of the cord due to aneurysms of the umbilical vessels [45], hemangiomas [45], necrotizing funisitis [46], or meconium-induced myonecrosis [47]. Cord rupture most often occurs at the site of its placental attachment [48]. When fetal vessels or the umbilical cord is disrupted, careful, directed pathologic examination is necessary to document the specific underlying lesion as well as to confirm that the rupture is not a postdelivery event. In some cases, subtlety of findings or lack of clinical correlative information may make diagnosis problematic. However, placental findings indicative of severe fetal anemia are quite straightforward. Because the blood content, and therefore the color, of the villous tissue is generally reflective of the fetal hematocrit, in a significant fetal anemia the placental parenchyma is usually strikingly pale (Figure 20.4) [49]. On microscopic examination, one finds a marked increase in fetal NRBCs and villous edema. The fetal blood vessels may also appear relatively "empty" of blood [42,43].

Fetal hemorrhage from the villous capillaries will cause fetal blood to escape into the intervillous space, resulting in a fetomaternal hemorrhage. This is thought to develop from damage to the trophoblastic cover of



Figure 20.4 Cut section of a formalin-fixed placenta from a severe fetomaternal hemorrhage. Note the markedly pale parenchymal tissue. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

the chorionic villi [43], but in most cases there is no history of trauma, and the exact cause is obscure. Fetomaternal hemorrhage is seen with increased frequency in the presence of placental choriocarcinomas and large placental chorangiomas [48]. In many cases, there are multiple episodes of bleeding leading to chronic blood loss. Placental findings include evidence of fetal anemia as described earlier and, in some cases, multiple or large intervillous thrombi. Definitive diagnosis rests on identification of fetal blood in the maternal circulation, most commonly determined by the Kleihauer-Betke test. However, other tests, such as the Apt test or flow cytometry, are also used. The Kleihauer-Betke test is reported as a percentage of fetal red blood cells in the maternal circulation. Confounding factors in interpretation include a falsely low result when the mother and infant have ABO-incompatible blood types, which causes the fetal blood cells to be quickly cleared from the maternal circulation, or a falsely high result when there is maternal persistence of fetal hemoglobin. Because fetal cells persist in the maternal circulation for up to a month or more, performing the test is useful even if it is not done immediately after delivery. It is strongly recommended that it be performed in any case in which neonatal anemia is diagnosed or there is an unexplained stillbirth.

A specific type of acute exsanguination takes place in monozygotic twins with monochorionic placentas. In these placentas, vascular anastomoses between the two placentas are always present to some degree. In a minority of cases, there is a dominant artery-to-vein anastomosis causing a chronic shunt of blood from one twin, the donor, to the other twin, the recipient. This is the basis for the twin-to-twin transfusion syndrome, also called *chronic twin-to-twin transfusion*. The donor twin suffers from lack of growth, anemia, and hypovolemia, while the recipient twin suffers from edema, congestion, and hypervolemia. Both are at risk for heart failure, death, and neurologic injury [42,43,49]. However, even when this condition is not present, there is always the potential for acute transfusion of blood from one twin to the other in monochorionic placentas [42]. If one twin dies in utero, the dead twin becomes a "sink" into which the surviving twin bleeds. The surviving twin will be severely anemic, and the corresponding placenta will be markedly pale. Depending on the size of the anastomoses, hemorrhage can lead to a variety of outcomes from minimal blood loss to profound neurologic injury or death, all of which will occur within a matter of minutes of death of the cotwin [49]. This type of "acute" transfusion of blood accounts for a significant portion of the increased morbidity and mortality seen in monochorionic twins [43]. The previous theory that embolization of thrombotic material from the dead twin causes damage to the surviving twin makes little sense and has been shown to be untenable [43].

Trauma is an important cause of fetal hemorrhage and may result from fetal blood sampling, cordocentesis, amniocentesis, fetal transfusion, or direct needle puncture of the fetus during various procedures [42,43]. Blood will often be present in the amniotic fluid, causing a "port wine" discoloration of the fluid. Trauma to the umbilical cord can cause formation of a hematoma, which can be identified as an elongated, fusiform swelling of the cord with a dark red discoloration and dissection of blood through Wharton's jelly. In very acute injury to fetal vessels, extravasated fresh blood may be visible in the site of the trauma. In subacute injury, there may be hemolysis of the extravasated blood leading to a reddish discoloration of the umbilical cord or fetal surface of the placenta, most prominent in the area of trauma. With remote injury, an organizing blood clot can be visible with hemosiderin deposition that will stain the surface yellow to brown. On microscopic examination, hemosiderin-laden macrophages will be visible, and the presence of an organizing hematoma can provide an estimate of the timing of the traumatic event.

Severe fetal anemia may also occur without trauma or disruption, but it still has the same potential for neurologic injury and death. Other causes include infections, such as parvovirus, which have a predilection for red blood cells; Rh incompatibility (erythroblastosis fetalis); genetic disorders associated with red blood cell destruction, such as hemolytic anemia; and disorders associated with poor production, such as thalassemia. Clinical suspicion and specific diagnostic tests are needed to confirm these conditions in most cases.

Mechanisms of Umbilical Cord Blood Flow Compromise

Umbilical Cord Compression and Obstruction

Most types of cord obstruction are associated with compression of the umbilical cord through some type of mechanical force. Compression may be from the

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fetus itself, as with cord entanglements, membranous vessels, prolapsed, and oligohydramnios, or may be from an abnormal configuration of the cord such as a true knot, abnormal coiling, abnormal length, or a constriction. All have been associated with adverse outcome, including fetal demise, neurologic injury, and abnormal developmental outcome [41,43,44,50–52]. Often structural abnormalities occur together; for example, entanglements and knots are frequently associated with long cords, and excessive coiling is often seen with constrictions. If obstruction is sudden and complete, fetal death will usually result, and in those that do survive, significant neurologic damage is likely [41,43,50,53–56]. The same is true for prolonged partial obstruction. Thus long-standing conditions such as long cords, hypercoiling, constrictions, and velamentous insertions are significantly more common in infants with CP [28,50,55,56]. Experimental studies in lambs have shown that intermittent partial cord occlusion leads to the development of cerebral necrosis and serious neurologic damage [57]. Furthermore, in these conditions, there is often an acute exacerbation of obstruction during delivery; for example, a cord entanglement or knot may tighten during fetal descent in labor, or membranous vessels may become compressed after membrane rupture with loss of the cushioning effect of the amniotic fluid. In cord compression, the umbilical vein, being more distensible than the arteries, will be compressed more easily, and Doppler studies have confirmed that cord obstruction and compression lead to impeded venous return from the placenta [53]. Placental venous and capillary congestion will result, and the fetus may develop some degree of hypovolemia and anemia. In acute compression, placental examination will show marked distension of the umbilical vessels, particularly the vein, tributaries of the umbilical vein in the chorionic plate, and villous capillaries. Direct compression of a portion of the cord by fetal parts or the cervix may also cause some localized degenerative change in Wharton's jelly, ischemic necrosis of umbilical vessel walls, and sometimes fetal vasculitis in response to cellular damage.

Chronic cord compression develops from the same types of mechanical forces that lead to acute compression. Except for cord entanglement and prolapse, the cord abnormalities are easily diagnosed by gross examination of the placenta. Chronic obstruction of blood flow through the venous circulation leads to venous stasis in the short term and vascular thrombosis in the long term, which can further embarrass the fetal blood supply. The resulting thrombotic lesions are called *fetal thrombotic vasculopathy* (see below). Not only have the underlying causes of cord compression been associated with adverse outcome, the resulting thrombotic lesions in the placenta have also been associated with poor outcome including stroke [41,51,58,59].

Umbilical Cord Coiling and Constriction

The umbilical cord is usually twisted to the left, or counterclockwise, in a ratio of about 7:1 [43]. The direction of coiling is not associated with handedness, but right twisting has been associated with placenta previa and perinatal hemorrhage [60]. The direction and amount of coiling are established early in gestation and can be seen by sonography as early as the ninth week. Normally, the number of coils in the cord is about 0.2 coils/cm of cord, which is referred to as the *coiling index* [53]. The origin of umbilical cord coiling has long been debated, but studies suggest that it is due, at least in part, to fetal activity in utero. Thus, hypocoiling reflects fetal inactivity, while hypercoiling reflects increased fetal activity, at least to some degree [43]. Absent or minimal coiling is rare but, when present, has an ominous prognosis because it is associated with fetal distress, increased perinatal mortality, fetal demise, fetal anomalies, and chromosomal errors [53,61–63]. Hypercoiling, however, has been associated with preterm labor, fetal demise, fetal asphyxia, and chronic fetal hypoxia [53,61–63]. It is also seen more frequently in cords with constrictions and those of excessive length, both of which are also associated with adverse outcome [51,53].

A significant reduction in the diameter of the umbilical cord is referred to as *constriction, stricture, torsion*, or *coarctation* (Figure 20.5). Constrictions are found most commonly near or at the insertion into the fetal abdomen, and they are seen with increased frequency in long or hypercoiled cords [62]. Obstruction of blood flow occurs by the same mechanism as with excessive coiling, namely, compression of umbilical vessels by the cord itself. Some authors have been skeptical about this lesion, suggesting that it is merely secondary to fetal demise, gradually diminishing Wharton's jelly at the fetal end of the cord [64], or a primary deficiency of Wharton's jelly [65]. However, there is often congestion on one side of the constriction and thrombosis of fetal vessels, which is proof that it is not an artifact at least in those cases. Furthermore, if these were artifacts, they would be seen in the majority of fetal demises, if

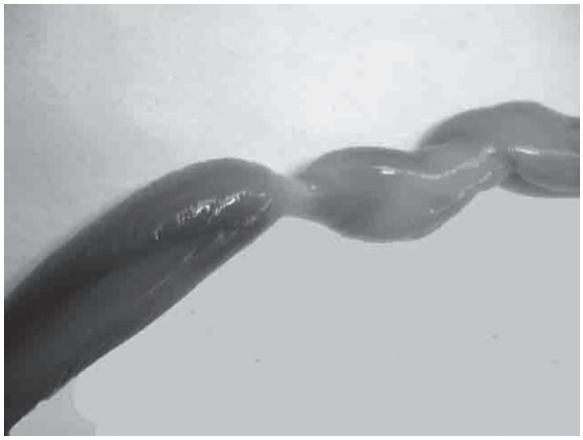


Figure 20.5 Portion of umbilical cord with constriction in the center of the figure. The cord is discolored green due to long-standing meconium staining.

not all – and this is not the case. Hypercoiling and constriction, like other types of mechanical obstruction, can lead to fetal thrombotic vasculopathy. There have been many publications demonstrating the poor outcome of umbilical cord stricture, including fetal demise, fetal growth restriction, and fetal intolerance to labor [43,53–55].

The Excessively Long or Short Cord

The umbilical cord is, on average, 55–61 cm in length at term [66]. The cord lengthens throughout gestation, although growth slows after 28 weeks. At 6 weeks postconception, the cord has an average length of 0.5 cm; by the fourth month, it is between 16 and 18 cm; and by the sixth month, it is 33–35 cm [43]. It is interesting to note that measurements of cord length can shrink up to 7 cm in the first few hours following delivery. For this reason, and because portions of the cord may be used for laboratory tests or discarded in the delivery room, accurate measurement of the entire length of the cord at the time of birth is optimal. However, attempts to convince delivering physicians of the importance of such measurements have generally failed. For this reason, the diagnosis of a short cord is generally not possible in the pathology laboratory.

As with umbilical cord coiling, cord length has been correlated with fetal activity in utero [43]. This is supported by the fact that short cords are present in conditions where there is intrauterine constraint due to uterine anomalies, amnionic adhesions, or ectopic pregnancies [44] or where there is decreased fetal movement due to neurologic conditions, skeletal dysplasias, or other anomalies [67]. The relationship between long cords and excessive fetal movements is more difficult to assess because of the lack of data on prenatal movements and follow-up on the potential "hyperactivity" in infants with long cords [68,69]. There does appear to be a genetic component as well because mothers with a history of a long cord are at increased risk of a long cord in subsequent pregnancies [51].

There is no consensus on the minimum length for a diagnosis of an excessively long cord, with definitions ranging from 70 to 90 cm. This inconsistency is due in part to the lack of accurate measurement of cord length at the time of delivery such that pathologists are left with a cord length of "at least" a certain measurement rather than the true measurement. A retrospective study of over 38,000 placentas found that excessively long cords occurred in 3.95% of placentas and that right coiling, cord entanglement, hypercoiling, and true knots were more common in long cords [51]. In addition, long cords are associated with histologic findings of villous capillary congestion and fetal thrombotic vasculopathy [51,70], as well as evidence of intrauterine hypoxia such as chorangiosis and increased NRBCs [51]. It appears that such long or hypercoiled cords have increased resistance to flow, which may lead to greater pressures in the fetal circulation [51,71], and this is supported by the presence of cardiac enlargement and hypertrophy in fetuses with long cords [71]. Fetal growth restriction, intrauterine demise, and neonatal coagulation disorders are all seen with increased frequency in long cords. Furthermore, excessive cord length has been associated with increased morbidity, including cerebral degenerative changes [70], brain imaging abnormalities, neurologic injury, and poor long-term neurologic status [51].

As with long cords, the cutoff for short cords is also not well defined, and figures are reported to be from 32 to 40 cm at term. Short cords correlate well with depressed IQ and a variety of fetal and neonatal problems [72]. The essential question is whether the short cord is due to prenatal problems that caused diminished activity or the problems resulted from perinatal complications from delivery of an infant with a short cord. Extremely short cords (<15 cm) are commonly seen in infants with fetal anomalies, particularly abdominal wall defects and spinal and limb deformities. Short cords can cause problems at delivery because they may prevent descent of the

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infant and thus lead to abruption, uterine inversion, and even cord rupture. If this occurs, serious neurologic sequelae or death may result [43]. These complications may also be seen even when there is a "relatively" short cord created by cord entanglement.

Cord Entanglement, True Knots, and Cord Prolapse

The umbilical cord may become entangled around any fetal part, but the most common is a nuchal cord, in which the cord is looped around the fetal neck. Entanglements have been found as early as 10 weeks' gestation, and nuchal cords in particular are commonly diagnosed by sonography, but some of these appear to resolve by delivery [46]. Even so, at term, the incidence of nuchal cords is 15–20%. Infrequently, multiple loops of cord may become wrapped around the neck, and up to eight loops have been reported [43]. Cords may encircle the neck in an unlocked or locked pattern, the latter having more severe consequences for fetal outcome [73].

The association of nuchal cords with fetal growth restriction implies that entanglements and their associated cord compression are long-standing prenatal events [62,74]. Since most cord entanglements are relatively loose, they do not lead to adverse outcome, but they may tighten after membrane rupture when the infant descends down the birth canal. If one looks only at tight entanglements, there is an increase in perinatal complications, low Apgar scores, and fetal demise [50]. Neonates with nuchal cords are also significantly more anemic than controls, presumably because of decreased venous return from compression of the umbilical vein [75]. Rarely, they can be so tight as to lead to hypovolemic shock in the neonate [75]. A correlation between tight nuchal cords and CP has also been shown [76].

True knots, like cord entanglements, may be tight or loose. Venous distension distal to the knot and vascular congestion in the placenta are characteristic findings in tight knots of clinical significance (Figure 20.6). These are often associated with thrombosis of placental surface veins. The incidence of true knots is reported to be from 0.4% to 1.2% [43], but they are more common with long or hypercoiled cords [42,43,51]. Complex knots and cord entanglements are especially frequent in monoamnionic-monochorionic twins and cause significant morbidity and mortality [43]. True knots have also been associated with variable decelerations on fetal heart tracings, fetal distress, fetal hypoxia, long-term neurologic damage, and perinatal morbidity [43].

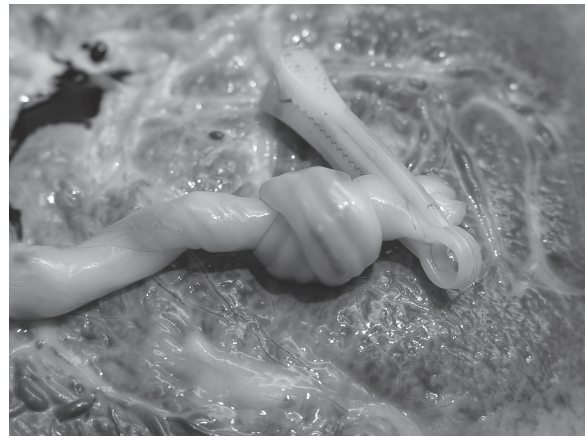


Figure 20.6 Tight true knot of the umbilical cord. Although congestion was not present on the placental side of the knot grossly, on histologic section the umbilical vein was dilated and early thrombosis was identified.

Cord prolapse occurs when the umbilical cord precedes the presenting fetal part during labor and delivery, whereby the cord becomes acutely compressed as the fetus descends into the vaginal canal. Prolapse is uncommon, occurring in less than 1% of deliveries, but has significant perinatal mortality, from 10% to 13% [43]. It can also lead to serious neurologic consequences for the fetus [43] Risk factors include abnormal fetal presentation, preterm labor, multiparity, multiple gestation, low birth weight, obstetric manipulation, polyhydramnios, abruption, placenta previa, and a long cord [77]. Pathologic examination will reveal acute congestion and, rarely, localized damage to the umbilical cord at the site of compression.

Velamentous Vessels

The umbilical cord normally inserts on the placenta near or at the center. In about 7% of term placentas the cord inserts at the margin, and in about 1% it inserts into the membranes – a velamentous insertion [42,43]. Velamentous vessels are present in velamentous and furcate insertions of the umbilical cord, between accessory lobes, and occasionally in marginal cord insertions. These vessels run within the membranes without the protection of Wharton's jelly and thus are susceptible to thrombosis, compression, disruption, or other trauma. This is particularly true in velamentous insertions when the cord inserts far from the placental margin and the vessels have a long



Figure 20.7 Placenta with a velamentous insertion. Note that the umbilical cord inserts far from the placental margin and numerous membranous vessels are present. In this case there is no disruption of vessels or hemorrhage in the surrounding membranes. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

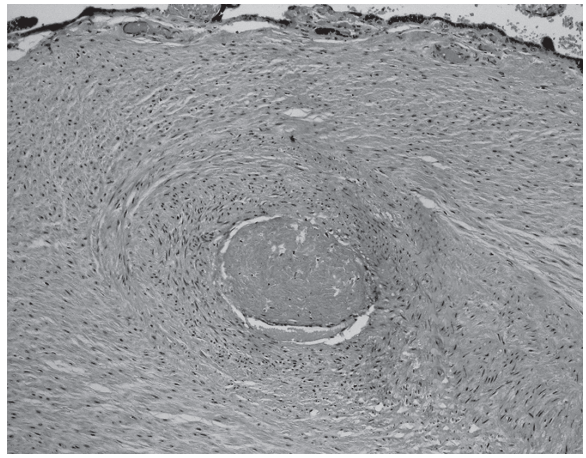


Figure 20.8 Fetal vessel in a stem villus with a recent, nearly occlusive thrombus. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

membranous course (Figure 20.7). Velamentous vessels are most vulnerable after membrane rupture, when the protection of the amniotic fluid is lost. Although hemorrhage from ruptured velamentous vessels occurs only in about 1 in 50 velamentous cord insertions, mortality from the subsequent fetal hemorrhage is 58–73% [78]. Velamentous cord insertions are also associated with abnormal fetal heart rate tracings, fetal growth restriction, low birth weight, and low Apgar scores [43,79]. Velamentous vessels may also be associated with vasa previa, where the membranous vessels cross the cervical os, preceding the presenting fetal part. These vessels may be compressed during labor and cause fetal distress and hypoxia [80]. If a vaginal delivery is attempted, the membranous vessels will be disrupted, and fetal hemorrhage will result. Depending on the extent of the hemorrhage, exsanguination and fetal death may result, or there may be serious neurologic injury in the infants who survive. Examination of the placenta is essential to document the presence of disrupted velamentous vessels and hemorrhage into the surrounding membranes. It is crucial that the suspicion of ruptured velamentous vessels be communicated to the pathologist prior to examination so that extra care can be taken to preserve these findings.

Fetal Vascular Thrombosis

Obstruction of blood flow through the cord leads to decreased venous return from the placenta, venous stasis, and subsequent thrombosis in the fetal circulation, which can further embarrass blood supply to the fetus. Thrombosis may occur not only from cord compression or obstruction but also due to a hypercoagulable state, maternal diabetes, infection, and other miscellaneous conditions [81]. There are a number of thrombotic lesions comprising this group, including occlusive and nonocclusive thrombi, mural thrombi, intimal fibrin cushions, avascular villi, and villous stromal karyorrhexis [82]. On microscopic examination, recent thrombi contain fibrin, clot, and extracellular material, which most often does not completely occlude the vascular lumen (Figure 20.8). Older thrombi are recognizable by the presence of calcification within the vessel wall, indicating a duration of many weeks (Figure 20.9). In mural thrombi or intimal fibrin cushions, fibrin is attached to the endothelium or incorporated into a neointima (Figure 20.10). This is sometimes associated with an increase in ground substance, forming the appearance of a vascular cushion. Lack of blood flow in the fetal circulation will eventually lead to involution of the "downstream" villi, resulting in the formation of avascular villi, a process also occurring over a period of weeks. Avascular villi contain hyalinized stroma and no fetal vessels but have a normal-appearing trophoblastic cover (Figure 20.11). Villous stromal karyorrhexis is most commonly, but not exclusively, found in the smaller villous capillaries but also appears in affected stem villi [83]. Obstruction of blood flow leads to damage of the vascular wall, endothelial necrosis, perivascular extravasation of blood, and the accumulation of stromal nuclear debris (karyorrhexis). Villous stromal karyorrhexis represents

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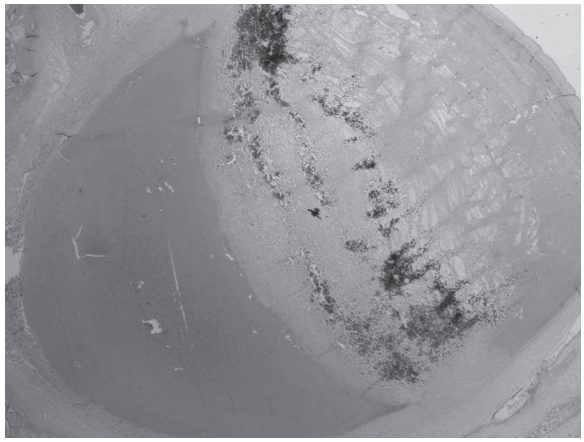


Figure 20.9 Large fetal chorionic plate vessel with distension and partially occlusive thrombus. Calcification in the thrombus is indicative of chronicity. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

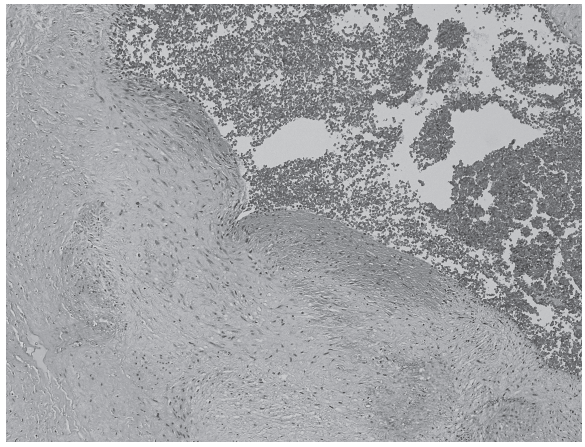


Figure 20.10 Large fetal chorionic plate vessel with intimal fibrin cushion. Note fibrin deposition in the wall of the vessel in the lower left of the figure and deposition of pale-blue ground substance forming a "cushion." (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

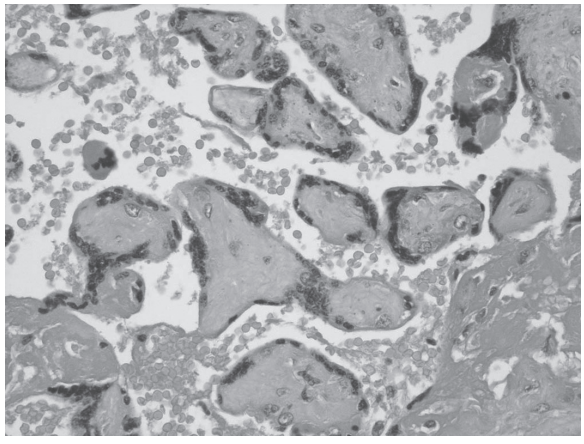


Figure 20.11 Avascular villi. Focus of villi lacking any villous capillaries and with marked hyalinization of the stroma indicative of upstream fetal vascular thrombosis. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

the intermediate phase in the evolution of avascular villi [82]. Fetal thrombotic vasculopathy, the term applied to regional villous stromal karyorrhexis and/or avascular villi, and fetal vascular thrombosis in muscularized upstream vessels have been linked to adverse neurologic outcome [83,84].

Amniotic Fluid Infection

Amniotic fluid infection can elicit both maternal and fetal inflammatory responses. Acute chorioamnionitis, a maternal inflammatory response, is defined histologically as acute inflammatory cells within the fetal membranes – specifically, the amnion and the chorion. Contrary to what is often suggested, the presence of acute inflammatory cells in the membranes is not a normal response to labor or other influences. It is usually, and some believe always, indicative of an ascending bacterial infection, an intrauterine infection. Bacteria ascend from the vagina through the cervix and into the uterine cavity. Whether they gain access to the uterine cavity appears to be due to various host factors in the presence of an intact mucus plug and the cervix and not due to the presence of ruptured membranes. Indeed, most infections arise in the face of intact membranes, and bacteria have been shown to invade through these layers to infect the amniotic fluid without membrane rupture [47]. Initially, when the bacteria first enter the uterine cavity, the inflammatory response is maternal in origin and is localized to the membranes in the area of the cervical os. If the infection goes unchecked, bacteria will gain access to the amniotic cavity, and the fetus will be exposed to bacterial antigens and other products. Once this happens, a fetal inflammatory response will ensue. The difference between maternal and fetal response can be seen quite readily through the microscope when one observes from which vessels the inflammatory cells are migrating. Maternal cells migrating from the decidua will be present in the extraplacental membranes and decidua basalis (Figure 20.12). Maternal cells also migrate from the blood in the intervillous space and can be found under and within

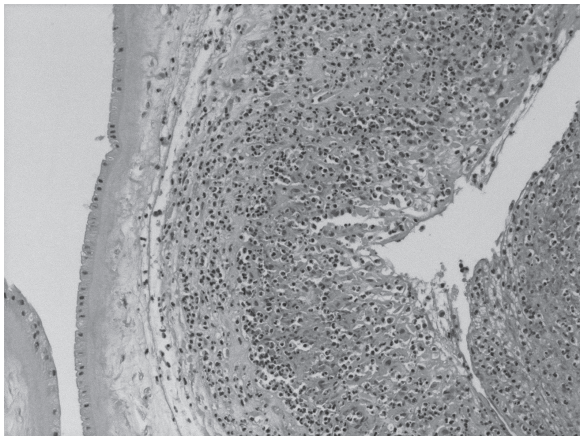


Figure 20.12 Section of extraplacental membranes with acute chorioamnionitis. Notice infiltration of numerous neutrophils within all layers of the membranes: these are derived from the decidua and thus the maternal circulation. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

the chorionic plate. Fetal inflammatory cells will be seen migrating out of fetal vessels in the umbilical cord (acute funisitis) and chorionic plate (chorionic plate vasculitis). Inflammation of chorionic vessels can result in endothelial damage and even fetal vascular thrombosis. These events generally occur over a period of days. An alternative perspective suggests that noxious but noninfectious substances such as meconium may elicit a neutrophilic placental inflammatory response (see section on meconium above).

Ascending infection is a major cause of preterm delivery as well as neonatal morbidity and mortality, and this is mostly due to the elaboration of inflammatory mediators or cytokines by the fetus [47]. The fetal inflammatory response occurs initially, at least, without infection of the fetus. The fetus is exposed to bacterial products and elicits an inflammatory response. This, in turn, causes the production of numerous cytokines and inflammatory mediators. In preterm infants, cytokines interfere with maturation of oligodendrocytes. In both term and preterm infants, many systemic and CNS effects are caused by cytokines. In particular, the permeability of the blood-brain barrier may be altered, vasoactive effects may lead to hypoperfusion of the brain, and there can be direct toxic effects on brain cells by inflammatory mediators [28,74,75]. Furthermore, if the fetus becomes infected, usually the lungs are initially involved, and acute bronchopneumonia develops. This leads to decreased pulmonary function and oxygenation. If the fetus becomes septic, hypotension and decreased vascular perfusion will also occur. Therefore, it is not surprising that the presence of a severe fetal inflammatory response has been linked to adverse neurologic outcome, periventricular leukomalacia, and CP [28,83–85].

Mechanisms of Chronic Diminished Placental Reserves

Maternal Vascular Malperfusion

Conditions in this category are secondary to suboptimal uteroplacental perfusion. Those that are chronic, which are the majority, are at risk for recurrence in future pregnancies unless the underlying disorder is modified or modifiable. The common pathophysiologic pathway is one of maternal vascular disease that alters spiral arteriolar perfusion leading to diminished placental and fetal growth associated with a panoply of placental ischemic changes. Diseased arterioles are prone to thrombosis, leading to placental infarction, and to disruption of the arteriolar-intervillous interface, leading to abruption (Figure 20.13).

Maternal diseases that fall into this category include chronic hypertension, chronic insulin-dependent diabetes mellitus, preeclampsia, certain forms of autoimmunity such the lupus-anticoagulant family of autoantibody disorders including but not limited to systemic lupus erythematosus, connective tissue diseases such as scleroderma, and, rarely, abnormal uterine anatomy with intrinsically deficient vasculature such as uterine septum and bicornuate uterus. Some authors believe that maternal thrombophilias can also lead to malperfusion, although this view is not widely supported in the literature.

In severely affected pregnancies, the placenta is invariably growth restricted and exhibits microscopic features of villous ischemia [86]: distal villous hypoplasia, aggregated terminal villi (Figure 20.14), so-called villous hypermaturation, increased syncytial knots, intervillous cytotrophoblast/fibrinoid islands, and decidual arteriopathy. Additional features, as noted earlier, include placental infarction and abruption, which in this may be multifocal and temporally heterogeneous, reflecting the multifocal and progressive nature of maternal vascular abnormalities. The sine qua non of vascular disease is the microscopic phenotype of decidual arteriopathy. In its milder form there is persistence and hypertrophy of decidual arteriolar smooth muscle, so-called nontransformation of spiral arterioles. The more severe form manifests so-called fibrinoid necrosis,

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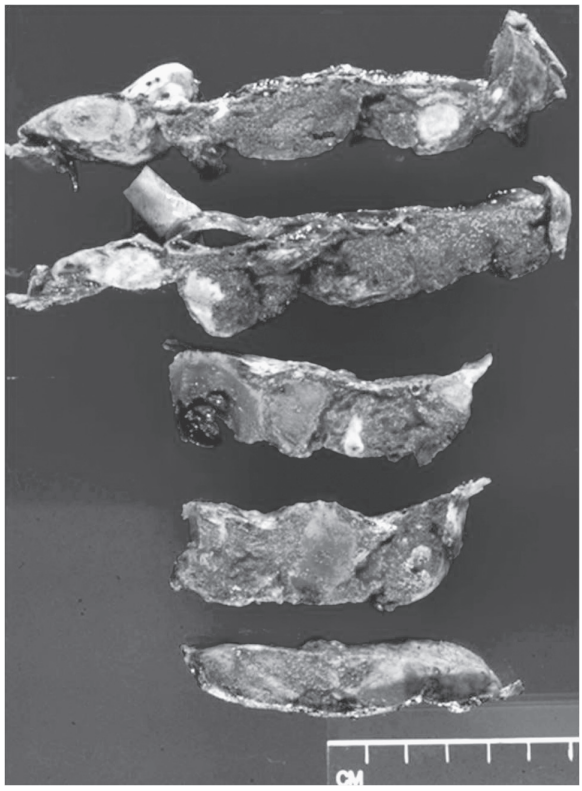


Figure 20.13 Gross pathology of intrinsic maternal vascular disease leading to chronic maternal vascular malperfusion. Multiple temporally heterogeneous infarcts with or without placental abruption (present in this case, middle section on left). (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

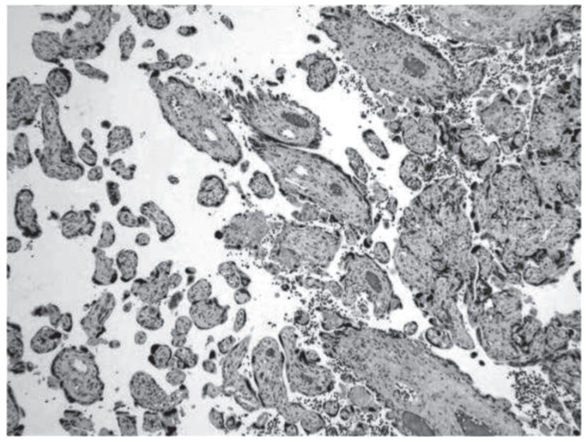


Figure 20.14 Some of the microscopic features of chronic maternal malperfusion: villous ischemic changes, manifested as distal villous hypoplasia (on left) and villous agglutination (on right). (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

histologically represented by hyalinized eosinophilic arterial walls; if lipid-laden macrophages are also present, then the term *with acute atherosis* is applied (Figure 20.15). These pathologic vessels are thrombogenic, leading to placental infarction, and they are prone to loss of vascular integrity, resulting in acute abruption.

In more severely affected patients, fetuses are commonly growth restricted. This is due to chronically compromised oxygen and nutrient delivery, a consequence of suboptimal maternal intervillous blood flow. Placental growth restriction, also caused by reduced maternal blood flow, may compound fetal growth restriction via impaired placental-to-fetal blood flow, manifested by abnormal Doppler umbilical arterial studies. Chronically reduced maternal-to-placental blood flow renders the placental-fetal vascular tree underdeveloped, with narrow villous caliber and diminished generational branching (distal villous hypoplasia).

The resulting reduction in distal villous fetal vascular caliber and global volume leads to increased placental vascular resistance by Doppler imaging and, if severe, to reversed diastolic umbilical arterial Doppler flow. While many, perhaps most, live-born fetuses with placental features of malperfusion demonstrate no clinical evidence of neurologic impairment, possibly due to adaptive cerebroprotective mechanisms of persistent hypoxic stress, there are exceptions in infants classified as small for gestational age (SGA), fetal growth restriction/intrauterine growth restriction (FGR/IUGR), and very low birth weight (VLBW) [87–89]. The risk of abnormal perinatal and neonatal outcomes, including neurodisability, trends in proportion to the severity/extent of placental lesions but in inverse proportion to birth weight [90].

Other conditions associated with diminished placental reserves, due presumably to maternal immune-mediated mechanisms, including autoantibody and other immune dysregulation, include villitis of unknown etiology (VUE or nonspecific chronic villitis) [91], maternal floor infarction (MFI) [92], and a disorder likely related to MFI, massive perivillous fibrin deposition (MPFD) [93]. Indirect evidence for maternal-based pathophysiology in these conditions comes from (1) high recurrence rates in subsequent pregnancies [94] and (2) case reports of recurrent pregnancy loss rescue by immunomodulatory therapy during gestation [95–97].

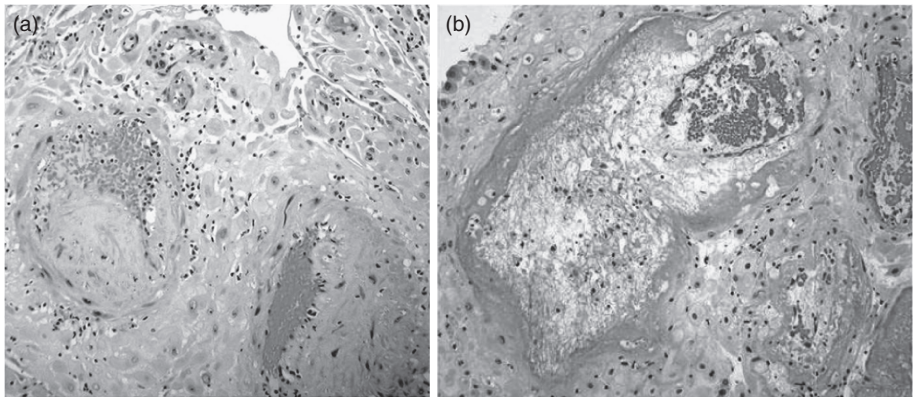


Figure 20.15 Decidual arteriopathy. (a) Milder phenotype: nontransformation of spiral arterioles. (b) More severe phenotype: fibrinoid necrosis with acute atherosis. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

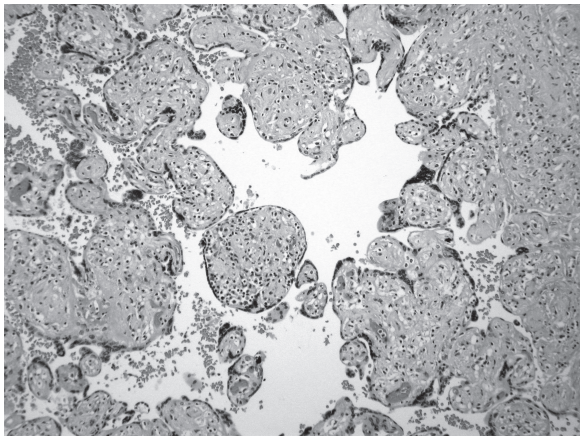


Figure 20.16 Severe chronic villitis. Widespread obliteration of terminal villous capillaries and distal stem villous vessels (so-called obliterative vasculopathy). (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

Villitis of Unknown Etiology, Nonspecific Chronic Villitis

Villitis of unknown etiology (VUE) is represented microscopically by maternal T-lymphocyte and histiocyte infiltration into villous stroma; increasing evidence indicates that the pathophysiology represents a host-versus-graft (aka maternal-versus-fetal, antifetal rejection) phenomenon [98,99]. Affected villi exhibit inflammation-induced vascular obliteration; when extensive, the term *obliterative fetal vasculopathy* is used. Extensive villous involvement by VUE with obliterative fetal vasculopathy is associated with growth restriction, stillbirth, and neurologic impairment [100–102] (Figure 20.16). More recently, a systemic fetal inflammatory response has been described, involving fetal plasma CXCL10 in addition to other proteins, that differs from the pattern associated with ascending infection [103]. As mentioned previously, with severe VUE there is an increased risk of pathologically recurrent placental VUE and untoward pregnancy outcome in future pregnancies. There are no relevant animal models to date.

Maternal Floor Infarction and Massive Perivillous Fibrin Deposition

Maternal floor infarction (MFI) and massive perivillous fibrin deposition (MPFD) are likely variant expressions of pathologically related, if not identical, phenomena. MFI is characterized by a thick fibrin(oid) rind that coats the basal placenta. Although commonly referred to as *fibrin*, the component products include not only maternal blood-derived fibrin but also protein-rich extracellular substrate of extravillous trophoblast (X-cell) derivation, presumably the result of altered metabolism by cytotrophoblast hypoxia. Grossly, regions of firm off-white deposits replace the normally spongy red placental parenchyma. Microscopically, the maternal intervillous space is packed with eosinophilic proteinaceous material that prohibits blood flow to entrapped villi, leading to ischemic villous damage of affected villi and reduced flow to overlying areas unaffected by the fibrin band. MPFD similarly packs the intervillous space with fibrin (oid), but the distribution is different. There is a regional serpentine involvement that may extend the full thickness of the placental disk (Figure 20.17). Fetal associations with both MFI and MPFD include recurrent pregnancy loss, prematurity, growth restriction, adverse

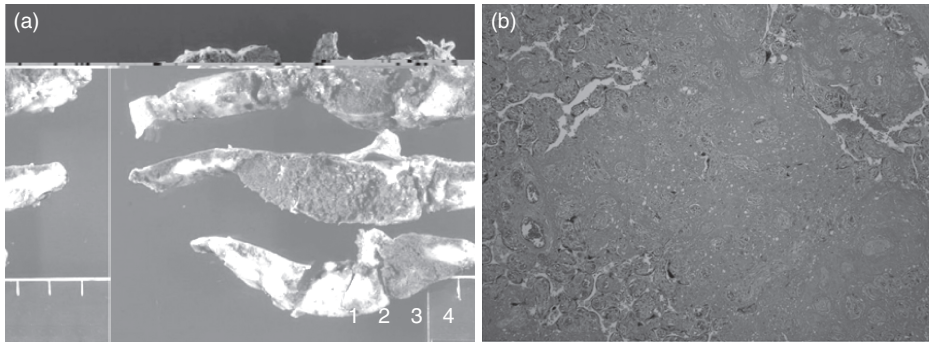


Figure 20.17 Massive perivillous fibrin deposition (MPFD). (a) Grossly, affected regions appear dense and off-white. (b) Microscopically, affected regions demonstrate intervillous deposition of pink (eosinophilic) material, so-called fibrin(oid). (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

neurodevelopmental outcome, and stillbirth [104,105]. Attributed etiologies revolve around aberrant maternal immune-mediated responses to various infectious and noninfectious maternal and fetal conditions, including heritable disorders [106–110]. As with nonspecific chronic villitis, animal models have not been identified or constructed for experimental evaluation.

Summary

1. Numerous mechanisms of intrauterine stress exist capable of leading to fetal morbidity – including neurodisability – and to fetal and neonatal mortality.
2. Many, but not all, mechanisms of intrauterine stress operative in the last half of gestation are hypoxic and/or infectious in mode.
3. Most, but not all, mechanisms of intrauterine stress have specific placental correlates – "footprints" of their presence during gestation. The presence and extent of placental pathology depend in part on timing because events occurring shortly prior to delivery may not have time to manifest pathologic abnormalities.
4. Sometimes the absence of placental footprints in the setting of untoward neonatal outcome is attributable to a mechanism (e.g., head trauma due to external mechanical forces) that has no placental correlates.
5. The placenta therefore is a critical adjunct in assessing mechanisms and timing of intrauterine stressors. Furthermore, both the presence and absence of findings are relevant to clinicopathologic interpretation.
6. Pathologic interpretation in a given case is in part evidence based but in part must rely on pathology expertise borne of individual experience and interobserver consensus.
7. Placental pathology determinants of intrauterine stress, both mechanisms and their timing, are not synonymous with determinants of injury. Except in certain specific circumstances, assessing the extent and timing of injury requires clinical acumen beyond the purview of pathologic evidence and interpretation alone.

References

1. Lakshmanan J, Ross MG. Mechanism(s) of in utero meconium passage. *J Perinatol* 2008; **28**(Suppl 3): S8–13.
2. Miller PW, Coen RW, Benirschke K. Dating the time interval from meconium passage to birth. *Obstet Gynecol* 1985; **66**: 459–62.
3. Incerti M, Locatelli A, Consonni S, et al. Can placental histology establish the timing of meconium passage during labor? *Acta Obstet Gynecol Scand* 2011; **90**: 863–8.
4. Sepulveda WH, Gonzalez C, Cruz MA, et al. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. *Eur J Obstet Gynecol* 1995; **173**: 1075–8.
5. Holcberg G, Huleihel M, Katz M, et al. Vasoconstrictive activity of meconium stained amniotic fluid in the human placental vasculature. *Eur J Obstet Gynecol Reprod Biol* 1999; **87**: 147–50.
6. King EL, Redline RW, Smith SD, et al. Myocytes of chorionic vessels from placentas with meconium-associated vascular necrosis exhibit apoptotic markers. *Hum Pathol* 2004; **35**: 412–17.
7. Holcberg G, Sapir O, Huleihel M, et al. Vasoconstrictive activity of oxytocin in meconium impregnated human

placentas. *Eur J Obstet Gynecol Reprod Biol* 2002; **101**: 139–42.

8. Cimic A, Baergen R. Meconium-associated umbilical vascular myonecrosis: correlations with adverse outcome. *Pediatr Dev Pathol* 2016; **19**(4): 315–9.
9. Altshuler G, Hyde S. Meconium-induced vasocontraction: a potential cause of cerebral and other fetal hypoperfusion and of poor pregnancy outcome. *J Child Neurol* 1989; **4**: 137–42.
10. Altshuler G, Arizawa M, Molnar-Nadasy G. Meconium-induced umbilical cord vascular necrosis and ulceration: a potential link between the placenta and poor outcome. *Obstet Gynecol* 1992; **79**: 760–6.
11. Locatelli A, Regalia AL, Patregnani C, et al. Prognostic value of change in amniotic fluid color curing labor. *Fetal Diagn Ther* 2005; **20**: 5–9.
12. Sheiner E, Hadar A, Shoham-Vardi I. The effect of meconium on perinatal outcome: a prospective analysis. *J Matern Fetal Neonat Med* 2002; **11**: 54–9.
13. De Beaufort AJ, Pelikan DMV, Elferink JGR, et al. Effect of interleukin 8 in meconium on in vitro neutrophil chemotaxis. *Lancet* 1998; **352**: 102–5.
14. Burgess AM, Hutchins GM. Inflammation of the lungs, umbilical cord and placenta associated with meconium passage in utero. *Pathol Res Pract* 1996; **192**: 1121–8.
15. Yamada T, Minakami H, Matsubara S, et al. Meconium-stained amniotic fluid exhibits chemotactic activity for polymorphonuclear leukocytes in vitro. *J Reprod Immunol* 2000; **46**: 21–30.
16. Ferber A, Minior VK, Bornstein E, et al. Fetal "nonreassuring status" is associated with elevation of nucleated red blood cell counts and interleukin-6. *Am J Obstet Gynecol* 2005; **192**: 1427–9.
17. Dulay AT, Buhimschi IA, Zhao G, et al. Nucleated red blood cells are a direct response to mediators of inflammation in newborns with early-onset neonatal sepsis. *Am J Obstet Gynecol* 2008; **198**: 426.
18. Ferber A, Minior VK, Bornstein E, et al. Fetal "nonreassuring status" is associated with elevation of nucleated red blood cell counts and interleukin-6. *J Obstet Gynecol* 2005; **192**: 1427–9.
19. Ferber A, Fridel Z, Weissmann-Brenner A, et al. Are elevated nucleated red blood cell counts an indirect reflection of enhanced erythropoietin activity? *Am J Obstet Gynecol* 2004; **190**: 1473–5.
20. Maier RF, Gunther A, Vogel M, et al. Umbilical venous erythropoietin and umbilical arterial pH in relation to morphologic placental abnormalities. *Obstet Gynecol* 1994; **84**: 81–7.
21. Hermansen MC. Nucleated red blood cells in the fetus and newborn. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**: F211–15.
22. Silva AM, Smith RN, Lehmann CU, et al. Neonatal nucleated red blood cells and the prediction of cerebral white matter injury in preterm infants. *Obstet Gynecol* 2006; **107**: 550–6.
23. Phelan JP, Korst LM, Ahn MO, et al. Neonatal nucleated red blood cell and lymphocyte counts in fetal brain injury. *Obstet Gynecol* 1998; **91**: 485–9.
24. Korst LM, Phelan JP, Ahn MO, et al. Nucleated red blood cells: an update in the marker for fetal asphyxia. *Am J Obstet Gynecol* 1996; **175**: 843–6.
25. Phelan JP, Ahn MO, Korst LM, et al. Nucleated red blood cells: a marker for fetal asphyxia? *Am J Obstet Gynecol* 1995; **173**: 1380–4.
26. Axt-Fliedner R, Hendrik HJ, Schmidt W. Nucleated red blood cell counts in growth-restricted neonates with absent or reversed-end-diastolic umbilical artery velocity. *Clin Exp Obstet Gynecol* 2002; **29**: 242–6.
27. McCarthy JM, Capullari T, Thompson Z, et al. Umbilical nucleated red blood cell counts: normal values and the effect of labor. *J Perinatol* 2006; **26**: 89–92.
28. Redline RW, O'Riordan A. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Arch Pathol Lab Med* 2000; **124**: 1785–91.
29. Manegold G, Meyer-Monard S, Tichelli A, et al. Cesarean section due to fetal distress increases the number of stem cells in umbilical cord blood. *Transfusion* 2008; **48**: 871–6.
30. Baschat AA, Gungor S, Kush ML, et al. Nucleated red blood cell counts in the first week of life: a critical appraisal of relationships with perinatal outcome in preterm growth-restricted neonates. *Am J Obstet Gynecol* 2007; **197**(286): e1–8.
31. Buonocore G, Perrone S, Gioia D, et al. Nucleated red blood cell count at birth as an index of perinatal brain damage. *Am J Obstet Gynecol* 1999; **181**: 1500–5.
32. Ghosh B, Mittal S, Kumar S, et al. Prediction of perinatal asphyxia with nucleated red blood cells in cord blood of newborns. *Int J Gynaecol Obstet* 2003; **81**: 267–71.
33. Hanion-Lundberg KM, Kirby RS, Gandhi S, et al. Nucleated red blood cells in cord blood of singleton term neonates. *Am J Obstet Gynecol* 1997; **176**: 1149–54.
34. Hebbar S, Misha M, Rai L. Significance of maternal and cord blood nucleated red blood cell count in pregnancies complicated by preeclampsia. *J Pregnancy* 2014; **496416**.
35. Hamrick SE, Miller SP, Newton NR, et al. Neonatal red blood cell counts: not associated with brain injury or outcome. *Pediatr Neurol* 2003; **29**: 278–83.

36. Li J, Kobata K, Kamei Y, et al. Nucleated red blood cell counts: an early predictor of brain injury and 2-year outcome in neonates with hypoxic-ischemic encephalopathy in the era of cooling-based treatment. *Brain Dev* 2014; **36**: 472–8.
37. Walsh BH, Boylan GB, Murray DM. Nucleated red blood cells and early EEG: predicting Sarnat stage and two year outcome. *Early Hum Dev* 2011; **87**: 335–9.
38. Christensen RD, Henry E, Andres RL, et al. Reference ranges for blood concentrations of nucleated red blood cells in neonates. *Neonatology* 2011; **99**: 289–94.
39. Phelan JP, Ahn MO, Korst L, et al. Intrapartum asphyxial brain injury with absent multiorgan system dysfunction. *J Matern Fetal Med* 1998; **7**: 19–22.
40. Benirschke K. The use of the placenta in the understanding of perinatal injury. In Donn SM, Fisher CW, eds., *Risk Management Techniques in Perinatal and Neonatal Practice.* Armonk, NY: Futura, 1996: 325–45.
41. Grafe MR. The correlation of prenatal brain damage with placental pathology. *J Neuropathol Exp Neurol* 1994; **53**: 407–15.
42. Baergen RN. *Manual of Benirschke and Kaufmann's Pathology of the Human Placenta.* New York: Springer, 2005.
43. Benirschke K, Kaufmann P, Baergen RN. *Pathology of the Human Placenta*, 32nd edn. New York: Springer, 2006.
44. Miller ME, Higginbottom M, Smith DA. Short umbilical cord: its origin and relevance. *Pediatrics* 1981; **67**: 618–21.
45. Kumazaki K, Nakayama M, Sumida Y, et al. Placental features in preterm infants with periventricular leukomalacia. *Pediatrics* 2002; **109**: 650–5.
46. Chasen ST, Baergen RN. Necrotizing funisitis with intrapartum umbilical cord rupture. *J Perinatol* 1999; **19**: 325–6.
47. Altshuler G, Arizawa M, Molnar-Nadasdy G. Meconium induced umbilical cord vascular necrosis and ulceration: a potential link between the placenta and poor pregnancy outcome. *Obstet Gynecol* 1992; **79**: 760–6.
48. Santamaria M, Benirschke K, Carpenter PM, et al. Transplacental hemorrhage associated with placental neoplasms. *Pediatr Pathol* 1987; **7**: 601–15.
49. Karsidag ATK, Kars B, Dansuk R, et al. Brain damage to the survivor within 30 minutes of co-twin demise in monochorionic twins. *Fetal Diagn Ther* 2005; **20**: 91–5.
50. Spellancy WN, Gravem H, Fisch RO. The umbilical cord complications of true knots, nuchal coils and cords around the body: a report from the collaborative study of cerebral palsy. *Am J Obstet Gynecol* 1966; **94**: 1136–42.
51. Baergen RN, Malicki D, Behling C, *et al*. Morbidity, mortality, and placental pathology in excessively long umbilical cords: retrospective study. *Pediatr Dev Pathol* 2001; **4**: 144–53.
52. Spinillo A, Cesari S, Bariselli S, et al. Placental lesions associated with oligohydramnios in fetal growth restricted (FGR) pregnancies. *Placenta* 2015; **36**: 538–44.
53. Machin GA, Ackerman J, Gilbert-Barness E. Abnormal umbilical cord coiling is associated with adverse perinatal outcomes. *Pediatr Dev Pathol* 2000; **3**: 462–71.
54. Redline RW. Clinical and pathological umbilical cord abnormalities in fetal thrombotic vasculopathy. *Hum Pathol* 2004; **35**: 1494–8.
55. Peng HQ, Levitin-Smith M, Rochelson B, et al. Umbilical cord stricture and overcoiling are common causes of fetal demise. *Pediatr Dev Pathol* 2006; **9**: 14–19.
56. Murphy DJ, MacKenzie IZ. The mortality and morbidity associated with umbilical cord prolapse. *Br J Obstet Gynaecol* 1995; **102**: 826–30.
57. Ikeda T, Murata Y, Quilligan EJ, et al. Physiologic and histologic changes in near-term fetal lambs exposed to asphyxia by partial umbilical cord occlusion. *Am J Obstet Gynecol* 1998; **178**: 24–32.
58. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies and cerebral palsy. *Hum Pathol* 1999; **30**: 759–69.
59. Heifetz SA. Thrombosis of the umbilical cord: analysis of 52 cases and literature review. *Pediatr Pathol* 1988; **8**: 37–54.
60. Kalish RB, Hunter T, Sharma G, et al. Clinical significance of the umbilical cord twist. *Am J Obstet Gynecol* 2003; **189**: 736–9.
61. Strong TH, Elliott JP, Radin TR. Non-coiled umbilical blood vessels: a new marker for the fetus at risk. *Obstet Gynecol* 1993; **81**: 409–11.
62. Benirschke K. Obstetrically important lesions of the umbilical cord. *J Reprod Med* 1994; **39**: 62–72.
63. de Laat MWM, van Alderen ED, Franx A, et al. The umbilical coiling index in complicated pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2007; **130**: 66–72.
64. Heifetz SA. The umbilical cord: obstetrically important lesions. *Clin Obstet Gynecol* 1996; **39**: 71–87.
65. Hersh J, Buchino JJ. Umbilical cord torsion/constriction sequence. In Saul RA, ed., *Proceedings of the Greenwood Genetics Conference*, vol. 7. Clinton, SC: Jacobs Press, 1988: 181–2.

66. Gardiner JP. The umbilical cord: normal length; length in cord complications; etiology and frequency of coiling. *Surg Gynecol Obstet* 1922; **34**: 252–6.

67. Snider W. Placental pathology casebook. *J Perinatol* 1997; **17**: 327–9.

68. Naeye RL, Tafari N. Noninfectious disorders of the placenta, fetal membranes and umbilical cord. In Naeye RL, Tafari N, eds., *Risk Factors in Pregnancy and Disease of the Fetus and Newborn*. Baltimore: Williams & Wilkins, 1983: 145–72.

69. Moessinger AC, Blanc WA, Marone PA, et al. Umbilical cord length as an index of fetal activity: experimental study and clinical implications. *Pediatr Res* 1982; **16**: 109–12.

70. Boué DR, Stanley C, Baergen RN. Placental pathology casebook. *J Perinatol* 1995; **15**: 429–31.

71. Faye-Petersen O, Baergen RN. Long umbilical cords and pre-viable fetal death. *Pediatr Dev Pathol* 2001; **4**: 414.

72. Gilbert-Barness E, Drut RM, Drut R, et al. Developmental abnormalities resulting in short umbilical cord. *Birth Defects Original Article Series* 1993; **29**: 113–40.

73. Collins JC. Umbilical cord accidents: human studies. *Semin Perinatol* 2002; **26**: 79–82.

74. Soernes T. Umbilical cord encirclements and fetal growth restriction. *Obstet Gynecol* 1995; **86**: 725–8.

75. Vanhaesebrouck P, Vanneste K, de Praeter C, et al. Tight nuchal cord and neonatal hypovolemic shock. *Arch Dis Child* 1987; **62**: 1276–7.

76. Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. *Am J Obstet Gynecol* 1998; **179**: 507–13.

77. Lin, MG. Umbilical cord prolapse. *Obstet Gynecol Surv* 2006; **61**: 269–77.

78. Torrey WE. Vasa previa. *Am J Obstet Gynecol* 1952; **63**: 146–52.

79. Heinonen S, Ryynänen M, Kirkinen P, et al. Perinatal diagnostic evaluation of velamentous umbilical cord insertion: clinical, Doppler, and ultrasonic findings. *Obstet Gynecol* 1996; **87**: 112–17.

80. Cordero DR, Helfgott AW, Landy HJ, et al. A non-hemorrhagic manifestation of *vasa previa*: a clinicopathologic case report. *Obstet Gynecol* 1993; **82**: 698–700.

81. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004; **7**: 443–52.

82. Sander CM, Gilliland D, Akers C, et al. Livebirths with placental hemorrhagic endovasculitis: interlesional relationships and perinatal outcomes. *Arch Pathol Lab Med* 2002; **126**: 157–64.

83. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. *Am J Obstet Gynecol* 2005; **192**: 452–7.

84. Bejar RF, Wozniak P, Allard M, et al. Antenatal origin of neurologic damage in newborn infants. I. Preterm infants. *Am J Obstet Gynecol* 1988; **159**: 357–63.

85. Redline RW, Wilson-Costello D, Borawski E, et al. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. *Pediatr Res* 2000; **47**: 721–6.

86. Redline RW, Boyd T, Campbell V, et al. Maternal vascular malperfusion: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004; **7**: 237–49.

87. Burke CJ, Tannenberg AE, Payton DJ. Ischaemic cerebral injury, intrauterine growth retardation, and placental infarction. *Dev Med Child Neurol* 1997; **39**: 726–30.

88. Redline RW, Wilson-Costello D, Borawski E, et al. Placental lesions associated with neurologic impairment and cerebral palsy in very low-birth-weight infants. *Arch Pathol Lab Med* 1998; **122**: 1091–8.

89. Parra-Saavedra M, Simeone S, Triunfo S, et al. Correlation between histological signs of placental underperfusion and perinatal morbidity in late-onset small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 2015; **45**: 149–55.

90. Ananth CV, Friedman AM. Ischemic placental disease and risks of perinatal mortality and morbidity and neurodevelopmental outcomes. *Semin Perinatol* 2014; **38**: 151–8.

91. Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. *Hum Pathol* 2007; **38**: 1439–46.

92. Bendon RW, Hommel AB. Maternal floor infarction in autoimmune disease: two cases. *Pediatr Pathol Lab Med* 1996; **16**: 293–7.

93. Sebire NJ, Backos M, Goldin RD, et al. Placental massive perivillous fibrin deposition associated with antiphospholipid syndrome. *BJOG* 2002; **109**: 570–3.

94. Katzman PJ, Genest DR. Maternal floor infarction and massive previllous fibrin deposition: histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. *Pediatr Dev Pathol* 2002; **5**: 159–64.

95. Chang P, Miller D, Tsang P, et al. Intravenous immunoglobulin in antiphospholipid syndrome and maternal floor infarction when standard treatment fails: a case report. *Am J Perinatol* 2006; **23**: 125–9.

96. Makino A, Suzuki Y, Yamamoto T, et al. Use of aspirin and low-molecular-weight heparin to prevent recurrence of maternal floor infarction in women without evidence of antiphospholipid antibody syndrome. *Fetal Diagn Ther* 2004; **19**: 261–5.

97. Chang P, Millar D, Tsang P, et al. Intravenous immunoglobulin in antiphospholipid syndrome and maternal floor infarction when standard treatment fails. *Am J Perinatol* 2006; **23**: 125–9.

98. Kim CJ, Romero R, Chaemsaithong P, et al. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol* 2015; **213**(4 Suppl): S53–69.

99. Rudzinski E, Gilroy M, Newbill C, et al. Positive C4d immunostaining of placental villous syncytiotrophoblasts supports host-versus-graft rejection in villitis of unknown etiology. *Pediatr Dev Pathol* 2013; **16**: 7–13.

100. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Arch Pathol Lab Med* 2000; **124**: 1785–91.

101. Scher MS, Trucco GS, Beggarly ME, et al. Neonates with electrically confirmed seizures and possible placental associations. *Pediatr Neurol* 1998; **19**: 37–41.

102. Mir IN, Johnson-Welch SF, Nelson DB, et al. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. *Am J Obstet Gynecol* 2015; **213**:849.e1–7.

103. Lee J, Romero R, Chaiworapongsa T, et al. Characterization of the fetal blood transcriptome and proteome in maternal anti-fetal rejection: evidence of a distinct and novel type of human fetal systemic inflammatory response. *Am J Reprod Immunol* 2013 Oct; **70**: 265–84.

104. Adams-Chapman I, Vaucher YE, Bejar RF, et al. Maternal floor infarction of the placenta: association with central nervous system injury and adverse neurodevelopmental outcome. *J Perinatol* 2002; **22**: 236–41.

105. Andres RL, Kuyper W, Resnik R, et al. The association of maternal floor infarction of the placenta with adverse perinatal outcome. *Am J Obstet Gynecol* 1990; **163**: 935–8.

106. Heller D, Tellier R, Pabbaraju K, et al. Placental massive perivillous fibrinoid deposition associated with coxsackievirus A16: report of a case and review of the literature. *Pediatr Dev Pathol* 2016; **19**(5): 421–3.

107. Romero R, Whitten A, Korzeniewski SJ, et al. Maternal floor infarction/massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection? *Am J Reprod Immunol* 2013; **70**: 285–98.

108. Linn RL, Kiley J, Minturn L, et al. Recurrent massive perivillous fibrin deposition in the placenta associated with fetal renal tubular dysgenesis: *case report and literature review*. Pediatr Dev Pathol 2013; **16**: 378–86.

109. Al-Adnani M, Kiho L, Scheimberg I, et al. Recurrent placental massive perivillous fibrin deposition associated with polymyositis: a case report and review of the literature. *Pediatr Dev Pathol* 2008; **11**: 226–9.

110. Griffin AC, Strauss AW, Bennett MJ, et al. Mutations in long-chain 3-hydroxyacyl coenzyme a dehydrogenase are associated with placental maternal floor infarction/massive perivillous fibrin deposition. *Pediatr Dev Pathol* 2012; **15**: 368–74.

Chapter 21

Timing Perinatal Hypoxic-Ischemic Brain Injury

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Introduction

Brain injury of perinatal origin now accounts for half of all cases of cerebral palsy (CP) [1]. Overall, approximately 40% is associated with premature birth [2]. In contrast, perinatal events at term are estimated to contribute roughly 12–15% of CP [3,4]. The etiology of the remaining cases is, in part, associated with intrapartum events such as intrauterine growth restriction (IUGR) but in many cases is simply unknown [3]. Although CP related to perinatal events represents a small subset of neural injury, the costs to the families and society are huge. CP has one of the very highest indices of burden of disease from loss of potential productive members of society and direct burdens on the individual, family, and social institutions that last the entire life [5]. The *lifetime direct cost* of CP in the United States was estimated to be US $921,000 in 2003 [5] and more recently to be over 800,000 euros in Denmark [6]. These estimates do not include many indirect and social costs.

It is striking that despite significant improvements in obstetric and neonatal medical care, there has been relatively limited change in the overall rates of CP over time and that what changes there were appear to be mainly related to changes in the care of extremely preterm infants [1]. This highlights the fact that for many infants injury processes may start well before birth. Except at the extremes, we lack robust methods to tell us that an insult has occurred, when it may have happened and what stage of injury the brain is in and thus whether the infant may benefit from current therapies. Even when we do know that an insult has occurred, there is still considerable need to counsel parents on the likely neural outcomes.

A wide variety of neurotherapies have been reported, targeted at many different mechanisms. Such neurotherapies may help to protect against hypoxic-ischemic (HI) injury, alleviate acute injury after an HI insult has occurred, or even restore function by supporting surviving cells and promoting growth of new cells. The conceptual advance that ultimately enabled acute postinsult treatment was the demonstration that although some brain injury occurs during a sufficiently prolonged/severe episode of hypoxia-ischemia, in many cases damage actually continued to evolve for hours after resuscitation [7]. This seminal observation offered the tantalizing prospect that there might be a "window of opportunity" to provide treatment to reduce or prevent injury. Currently, cerebral hypothermia is the only established neuroprotective therapy that has been shown to improve survival without disability in some infants with acute moderate to severe encephalopathy at birth [8]. However, these data also show that protection is only partial, so many infants still die or have disabilities at 18 months of age despite treatment with current protocols. This relates in part to the limited window of opportunity for treatment to be successful such that it is critical to start treatment as early as possible after the end of the insult (as discussed below). Conversely, approximately one-third or more of infants receiving conventional normothermic care in major randomized, controlled trials survived without severe disability [8].

The combination of the limited precision of the presently used measures of outcome after perinatal encephalopathy with the reduced absolute rate of adverse outcome after hypothermic treatment dramatically reduces trial power. Given an estimated risk of death or disability of 45% for infants treated with current hypothermia protocols, then, to have 90% power to detect a further 10% reduction in adverse

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outcome, we would need to randomize more than 1,000 babies [9]. This shows that it is very important to more precisely target infants who are at high risk of developing clinically significant injury.

These considerations show that robust biological markers (*biomarkers*) are highly desirable to rapidly determine whether treatment is needed, to assess what stage of evolving injury has been reached (i.e., is the injury still treatable?), what is the long-term prognosis before the start of treatment (i.e., risk of bad outcome), and to provide early feedback on whether treatment is modifying the course of injury and thus long-term neurodevelopmental outcomes. It is important to recognize that biomarkers for hypoxic-ischemic encephalopathy may serve some but not all of these different functions.

This chapter dissects the evidence for some biomarkers of injury and prognosis that are already in use and the potential of novel biomarkers to contribute to refinement of therapeutic hypothermia and other potential acute therapies for infants after hypoxia-ischemia at birth. We will particularly focus on their potential to answer the central questions: (1) will the insult cause injury/ and (2) are we still in time to treat?

Why Is Timing So Critical?

Experimental and clinical studies have shown that while brain cells may die during a sufficiently profound or prolonged episode of HI with primary cerebral energy failure (the *primary phase* of injury, Figure 41.1), even after surprisingly severe insults [10,11], many cells show initial partial or complete recovery in a *latent phase*. However, this recovery is only transient and may be followed by secondary deterioration, as shown by failure of oxidative metabolism (the *secondary phase* of injury). This failure is associated with cytotoxic edema, seizures, cerebral hyperperfusion, and ultimately, cell death [9]. For single, acute insults, the secondary phase may start as late as 6–8 hours after the end of the insult (e.g., as shown in Figure 41.2) [9]. Consistent with this experimental pattern, clinical neurodevelopmental outcomes at 1 and 4 years of age are closely correlated with the severity of the secondary failure of oxidative metabolism at 15 hours of age [12].

Although we do not know precisely when it is no longer possible to prevent acute neuronal loss after hypoxia-ischemia, the preponderance of experimental evidence to date suggests that once the secondary deterioration has started, for practical purposes, cells are becoming irreversibly injured [7]. Preclinical studies of cerebral hypothermia, for example, found that the efficacy of cooling was progressively lost the longer the initiation of treatment was delayed and that there was no significant protection if cooling was started after the onset of delayed seizures [9]. Based on these experimental data, clinical trials of hypothermia have required that infants are recruited within 6 hours of resuscitation [13,14].

Why Is Treatment within 6 Hours of Birth Not Always Effective?

In real life, unlike the laboratory, insults are not always clearly defined. First, injury may begin many hours before birth [15] and often involves repeated or prolonged exposure to asphyxia [16]. Thus injury may already be evolving at the time of birth, leading to a very short or even no latent phase when hypothermia could be of benefit. Indeed, some infants may enter labor already injured from an insult much earlier in gestation [17,18]. However, most cases of acute, evolving encephalopathy are associated with acute cerebral changes on magnetic resonance imaging (MRI) and therefore are potentially treatable [19]. Finally, and critically, there is evidence that the more severe the insult, the more rapid is the transition from injury to irreversible death [10,11,20]. Indeed, some cells are so injured that they will never fully restore mitochondrial function [21]. Thus, although we cannot yet define this group with precision, it is highly likely that a proportion of infants are too severe to treat [22].

Has an Infant Been Exposed to Acute Asphyxia?

The most "classic" biomarkers are those for exposure to asphyxia. Exposure to asphyxia around the time of birth may be inferred from some combination of the presence of nonreassuring fetal heart changes, an oxygen debt (increased base deficit (BD) and blood lactate values) on cord blood gases, and need for resuscitation (i.e., Apgar score), all of which are easily and routinely documented [13–15]. Unfortunately, nonreassuring heart rate changes are well known to have a very low positive predictive value for neural injury [23]. For example, Murray et al. have shown that among infants who develop encephalopathy after birth, those with initially normal fetal heart rate tracings followed by acute "sentinel" events before birth developed more severe encephalopathy than infants with other patterns such as a progressive deterioration

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in heart rate patterns [24]. However, only 11.5% of infants with encephalopathy showed this pattern.

Total oxygen debt, including BD, and lactate concentrations should be a direct measure of anaerobic metabolism. In practice, they show a rather broad, imprecise relationship with neonatal encephalopathy. For example, profound acidosis (BD >18 mmol/L at 30 minutes of life) was associated with moderate to severe encephalopathy in nearly 80% of patients [25], and no cases occurred with BD below approximately 10–12 mmol/L [25,26]. Between these extremes, however, outcomes are rather variable. Low et al., for example, found that fewer than half of babies born with cord blood BDs over 16 mmol/L (and pH < 7.0) developed significant encephalopathy and that encephalopathy still occurred, although at low frequency (~10% of cases), in babies with moderate metabolic acidosis of between 12 and 16 mmol/L [26]. Thus infants at either extreme are correctly identified with reasonable precision (i.e., no versus severe encephalopathy), but not the intermediate group. Consistent with these observations, although lactate measurements have a better sensitivity and negative predictive value than BD, the specificity of a plasma lactate value of more than 7.5 mmol/L for moderate to severe encephalopathy in term infants is just 67% [27].

More recently, there has been interest in whether plasma glucose also may be a good predictor of outcomes with variability in glucose, both low and high, associated with adverse outcomes [28–30]. Post hoc analysis of the CoolCap Trial showed that in infants with moderate to severe encephalopathy, both hypo- and hyperglycemia were independently associated with unfavorable outcomes [31]. Significant further work is required to determine whether glucose levels provide material diagnostic or prognostic utility.

The aforementioned findings indicate that while exposure to lack of oxygen is necessary to cause injury, the healthy fetus has a remarkable ability to adapt to profound and often prolonged asphyxia and can often adapt to such insults without brain damage [7]. This is due in large part to the far greater anaerobic neural and cardiac tolerance of the fetuses of all mammalian species studied compared with adults [32,33], coupled with the ability to mount a timely and coordinated cardiovascular and metabolic defense to hypoxia [7,34]. Thus both physiologic adaptation that allowed the fetus to survive uninjured and failure of that adaptation that ultimately leads to injury may be accompanied by a substantial oxygen debt [15].

The Apgar score, a measure of the need for resuscitation at birth, is bedeviled by similar limitations. The NICHD Neonatal Research Network hypothermia trial has recently demonstrated, for example, that severely depressed Apgar scores (scores of 0–2) at 10 minutes of age can identify infants at high risk (76–82%) of disability or death well before more specific evaluations are available for infants with encephalopathy [35]. However, only 27% of infants who were recruited to the NICHD trial with moderate or severe encephalopathy had Apgar scores of 0 to 2. More recently, it was reported that low Apgar scores at 10 minutes correlate well with adverse outcomes in 6- to 7-year-old children but, remarkably, that approximately 20% of children with Apgar scores of 0 at 10 minutes survived without disability [36].

Alternatively, increased nucleated red blood cells (NRBCs) in umbilical venous blood may be a marker of perinatal asphyxia [37]. A recent cohort study of infants with encephalopathy who underwent therapeutic hypothermia showed that both elevated absolute NRBC counts and number of NRBCs per 100 white blood cells within 6 hours of birth correlated with adverse outcomes at 2 years of age and abnormal MRIs [38]. Increased NRBCs largely reflect stimulation of erythropoietin release, which leads to erythropoiesis and then release of immature red blood cells into the fetal circulation [39]. It takes time for NRBCs to be produced after release of erythropoietin, so it is postulated that elevated levels during the first 24 hours after birth likely reflect a hypoxic insult occurring some 20–30 hours before birth [39].

From this perspective, NRBCs may be useful in helping to determine when an insult may have occurred and thus provide a better understanding of which phase of injury may be occurring. However, the correlation between erythropoietin levels and numbers of NRBCs in cord blood is relatively weak, suggesting that other hypoxia-related factors are also involved [40]. Consistent with this, in a large population-based study of preterm and term deliveries, placental abruption, intra-amniotic infection, and being small for gestational age were all associated with higher NRBC counts [41], strongly suggesting that both acute and prenatal hypoxia and infection affect NRBCs. Thus it is important to be cautious in using NRBCs as a marker of the presence or timing of hypoxia or injury.

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Table 21.1 Potential Biomarkers for Asphyxia, Neonatal Encephalopathy, Evolution of Injury, and Neurodevelopmental Outcome after Perinatal Hypoxia-Ischemia

Strong clinical evidence	Preliminary clinical evidence or preclinical evidence only
Evidence of exposure to asphyxia	
Nonreassuring fetal heart rate [24], lactate [135–137], base deficit [138], need for resuscitation (Apgar scores) [139,140], NRBCs [37,141], S100B [142]	Micro-RNAs [57], activin A [143], VEGF [144], cord blood metabolites (e.g., acetone, betaine, creatinine, glucose-3-hydroxybutyrate, and O-phosphocholine) [145]
Predict presence and severity of neonatal encephalopathy	
EEG [146]	Combined analyses of pH, base deficit, spontaneous activity and PCO_2 [147], metabolite profile [145], CK-BB [62], NRBCs [148], NSE [44], GFAP [45], UCH-L1 [45], S100B [62,64], activin A [143], micro-RNAs [57], VEGF [45], TIMPs and MMP-9 [149], glucose [31], cytokines (IL-1β, IL-6, and IL-8) [44], MDA [150]
Identify evolving injury in latent phase	
None	EEG [89], NIRS [89,90]
Predict long-term outcomes	
EEG at 48–72 hours [75,84,151–154], MRS within the first 15–30 days [105,151,154], MRI at 1–2 weeks [108,151,155]	GFAP [45], UCH-L1 [45], S100B, MBP [156], VEGF [45], cytokines (IL-1, IL-6, and IL-8) [44,45], glucose [29,31], NRBC [38]

Note: CK-BB, creatine kinase BB isoenzyme; GFAP, glial fibrillary acidic protein; IL, interleukin; MBP, myelin basic protein; MDA, malondialdehyde; MMP-9, matrix-metalloproteinase 9; NIRS, near-infrared spectroscopy; NRBCs, nucleated red blood cells; NSE, neuron-specific enolase; S100B, S100 calcium-binding protein B; TIMP, tissue inhibitor of metalloproteinases; UCH-L1, ubiquitin carboxyl-terminal hydrolase; VEGF, vascular endothelial growth factor.

Possible Laboratory Markers of Neural Injury

During and after exposure to HI, a number of biochemical markers are elevated in body fluids and are reasonably easy to access and measure [42]. Given that many are activated within the brain by hypoxia, a number have been suggested to be useful as sentinel biomarkers for encephalopathy (Table 21.1), including S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), activin A, adrenomedullin, and interleukin 1β (IL-1β), and IL-6 [43–45]. All these biochemical candidates are induced after asphyxia. However, it is important to note that they can be elevated in other settings. S100B levels, for example, are markedly increased by intrauterine growth restriction or chronic hypoxia [46], central and peripheral hypoperfusion (which are common during recovery from HI) [47], perinatal infection/inflammation [48,49], traumatic delivery [50], preexisting neural injury [51], treatments such as prenatal or maternal glucocorticoids and anesthetics [52,53], and preterm gestational age [54], as well as being affected by the sex of the infant [52,53]. Further, S100B and NSE, for example, may also be released from a variety of tissues, including the umbilical cord and placenta [55].

In a meta-analysis, serum IL-1β and IL-6 and cerebrospinal fluid IL-1β and NSE measured before 96 hours of age were significantly predictive of long-term neurodevelopmental outcome [44]. In single studies, urine lactate, first urine S100B, cord blood IL-6, serum non-protein-bound iron, serum CD14 cell NF-κβ, serum IL-8, and serum ionized calcium also appeared to predict death or abnormal outcomes [44]. More recently, Chalak et al. have shown that abnormal neurologic outcomes at 15–18 months of age were associated with elevated plasma concentrations of glial fibrillary acidic protein (GFAP), IL-1, IL-6, IL-8, tumor necrosis factor, interferon, and vascular endothelial growth factor at 6–24 hours [45]. Further, the serial values were unaffected by hypothermia and rewarming. In this study, the severity of encephalopathy correlated well with concentration changes in

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GFAP, a cytoskeleton intermediate filament protein that is specific to astrocytes. Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), a neuron-specific cytoplasmic enzyme, also increased as a function of the severity of the insult. Whether the predictive value of these changes was better than lactate was not evaluated. However, not all studies observe this relationship. Zaigham et al. found no differences in cord blood UCH-L1 and GFAP concentrations between neonates with encephalopathy and controls and no evidence that these makers had prognostic utility [56].

More recently, micro-RNA (miRNA) levels in umbilical cord blood have been reported to be differentially expressed in infants who developed encephalopathy compared with either asphyxia without encephalopathy or normal controls [57]. Even the most suppressed miRNA in this study, hsa-miR-374a, did not show any significant difference between grades of encephalopathy. However, other miRNAs may prove to have greater discriminatory power in future larger studies. A recent clinical study showed that the combined expression of hypoxia-induced miRNAs 20 and 21 in maternal blood before delivery was threefold higher in women delivering fetuses with high lactate (cord blood lactate > 6mmol/L). Such tests have a potential to be used before birth to screen babies at risk of developing encephalopathy [58]. Further, given the emerging evidence in neonatal rodents that miRNA expression can modulate evolving brain injury after perinatal hypoxia-ischemia [59], such studies may also provide important insights into potential therapeutic targets.

Limitations of Studies of Biochemical Biomarkers

Several key limitations need to be kept in mind. First, there have been few long-term follow-up studies (>12 months of age) to assess neurodevelopmental disability [44]. This is a particular concern for infants with moderate (stage II) encephalopathy, who have rather variable outcomes [14]. Many studies assess outcome based on birth asphyxia criteria (Apgar scores or pH and lactate) or neurodevelopment at 1 week using the Sarnat and Sarnat Assessment Scale [60], and they all have limited discrimination for long-term outcome [61]. This is not a theoretical concern; Nadgyman et al. demonstrated that S100B and creatine kinase (CK-BB) measured at 2 hours after birth correlated well with encephalopathy indices at birth [62] but that there was no significant correlation with neurodevelopmental outcome at 20 months of age [63].

Second, a delay of up to 96 hours before samples are taken is meaningless for selection of infants with encephalopathy for acute neuroprotective treatment, where early treatment is important. The majority of studies of biochemical markers have been based on samples taken after 24 hours, that is, well after the latent phase. Even when early samples were taken, the apparent time course has been rather variable. For example, Nadyman et al. reported that S100B, an astroglial protein that leaks from damaged cells, peaked by 2–6 hours after birth asphyxia [62]. In contrast, others reported that levels remained elevated for 1–2 days [64–66]. Bashir et al. reported that S100B levels in urine were elevated at the first measurement at 4 hours and that levels reached a plateau at 12 hours, which was sustained for at least a week [67]. There are similar data in preterm infants, in whom serum levels were elevated at 3 hours in all infants, including those with mild encephalopathy; values stayed relatively constant in the mild group but increased over time in the severe group [68]. In experimental studies in fetal sheep, moderate hypoxia, which does not cause injury, significantly elevates S100B, and these values are sustained for an hour after the insult [69]. In contrast, after asphyxia that produced mild, moderate, or severe brain injury, there were no early changes, and elevated levels were found only in two fetuses with moderate and severe changes at 24 hours after the insult [70]. Collectively, these studies suggest that S100B is actually a marker of impaired oxidative metabolism in the primary or secondary phase and is not a marker of the latent phase, when cerebral metabolism is typically near normal. Thus elevated levels late in recovery may provide good prediction of adverse outcomes. This interpretation is consistent with studies of traumatic brain injury in older children [71,72].

Finally, while many of the biochemical markers do appear to distinguish between no or mild injury and moderate to severe injury [44,45], it is not clear that they are any better at predicting outcome for infants with moderate (Sarnat stage II) encephalopathy than either acid-base values or the neurologic examination. In many of these studies, there was considerable overlap in values between groups, and babies could have low levels and yet have adverse outcomes, and vice versa. Further experimental studies are needed to relate time-course changes to the evolution of injury and to final outcome before we can conclude that

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any of these parameters can improve prediction of evolving injury in a timely manner. Equally, there needs to be a much more systematic approach to when and how samples are taken and stored, particularly as we move forward to more intensively dissecting the metabolic changes that may tell us more about timing and outcomes [73].

Electrophysiology: Electroencephalography

Like blood sampling, the electroencephalogram (EEG) can be readily measured at the bedside. There is evidence that the combination of EEG amplitude or pattern assessment with clinical assessment of neurologic abnormalities may improve specificity for adverse outcomes [74]. Of particular promise, in the CoolCap Trial, infants with the most severe EEG changes, as shown by the combination of seizures and severe suppression of background activity at the time of recruitment, did not appear to improve after cooling [14]. However, this finding needs to be replicated in further studies.

There are experimental and clinical data that severe suppression of EEG amplitude in the first 6 hours after HI can occur in subjects with both good and bad outcomes [75–78]. Van Rooij et al. showed, for example, that some infants with early severe abnormal amplitude-integrated EEG (aEEG) background patterns went on to have a near-normal EEG within 24 hours, and more than 60% survived with no or only mild injury [75]. This is also observed in experimental studies. In fetal sheep, EEG amplitude was suppressed in the first 6 hours after asphyxia induced by complete umbilical cord occlusion regardless of neural outcomes (normal or severely injured) [78]. Both groups then showed a progressive improvement in EEG amplitude, but for different reasons. In the fetuses that sustained no injury, EEG returned to normal, baseline values. In the fetuses that developed severe brain injury, the EEG remained highly abnormal, but mean amplitude increased prior to the onset of frank electrographic and clinical seizures. Thus suppression of EEG amplitude alone is insufficient to discriminate between the injured and uninjured brain. Suppression likely reflects a combination of injury-induced impairment of brain function associated with severe damage and active suppression of brain activity by increased release of neuroinhibitors such as neurosteroids and norepinephrine after moderate insults that helps to improve recovery [42].

Importantly, therapeutic hypothermia itself alters the predictive value of aEEG [79]. In the TOBY hypothermia trial it was observed that the predictive value of the 6-hour aEEG for adverse outcome at 18 months is reduced, albeit not significantly, in infants who undergo therapeutic hypothermia [80]. A number of studies suggest that the predictive value of aEEG in infants with hypothermia is effectively delayed until around 48 hours [81–83]. Abnormal aEEG patterns correlate well with later MRI analysis in noncooled babies, but this predictive utility is lost after hypothermia [84].

Other features of the EEG may also have prognostic value. For example, variation of the power spectrum [85] and evaluation of nonlinear quantitative EEG (qEEG) measures of frequency [86] and long-range correlations in sub-band EEG signals by detrended fluctuation analysis (DFA) may be predictive of outcome and the phase of injury [87]. Critically, the diagnostic and prognostic capacity of the EEG may be improved when it is combined with other markers, such as measures of cerebral oxidative metabolism (as discussed below) [88]. Such analyses require us to move away from dependence on aEEG and toward analysis of the raw record. One element of the aEEG record that is overlooked is frequency of EEG waveforms that drive changes in frequency changes [42].

Experiments in preterm fetal sheep have demonstrated that while early EEG amplitude changes during recovery from asphyxia did not reliably predict outcome, spectral edge frequency (SEF) seemed to have predictive value [78]. In the first 3 hours after asphyxia, there was a rise in SEF that was associated with a small fall in relative cerebral oxygenation measured with near-infrared spectroscopy [89] and a modest increase in cytochrome oxidase activity similar to that seen during hypoxia [90]. This combination of findings is consistent with a genuine, albeit small, relative increase in brain activity and metabolism. Analysis of the continuous raw record demonstrated marked EEG transient activity superimposed on a profoundly suppressed background [78,91]. This abnormal EEG activity was epileptiform in nature, not the stereotypic evolving seizures seen during the secondary phase of recovery but rather subtle discrete, fast, sharp, and slow-wave spikes, typically high-frequency, low-amplitude events with a duration of 70 to 400 ms [42,92]. Their incidence is greatest in the latent phase [91,93–96] and in several studies correlated closely with the severity of neuronal loss in

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the hippocampus and basal ganglia [78,94,95]. In the human newborn, epileptiform transients are also documented but not fully characterized and can be associated with adverse neurodevelopmental outcomes [97,98].

Transients are altered by treatment. Experimentally, cerebral hypothermia has been shown to reduce or eliminate transients [94]. Clinically, during hypothermia, such transients may be masked by or mistaken as EEG artifacts. High-frequency artifacts that often lead to the conclusion of normality are common during cooling likely secondary to shivering [99]. Other treatments such as steroids have also been shown to alter the morphometry of background EEG activity, transients, and seizures [100,101]. In conclusion, further work is required to examine whether these EEG events occur in term infants with encephalopathy and how they are affected by treatment [42].

Magnetic Resonance Spectroscopy

MRI is the "gold standard" for diagnosis of injury, and advances in recent years with approaches such as diffusion MRI (dMRI) and blood oxygen level–dependent (BOLD) functional MRI (fMRI) have improved clinical assessment of structural and functional changes over time [102]. Magnetic resonance spectroscopy (MRS) adds the potential to estimate recovery of oxidative metabolism and thus of mitochondrial function after birth [102,103].

Early studies of infants with encephalopathy found that measures of oxidative metabolism such as the ratio of phosphocreatine (PCr) to inorganic phosphate (Pi) fall dramatically during HI, are restored during reperfusion and the latent phase, and then progressively decline in the secondary phase [20]. The severity of the final fall in oxidative metabolism is highly predictive of neurodevelopmental outcomes [12,104]. The central limitation of these findings is that while the fall is predictive as early as 6–18 hours after birth [105], it again represents a measure of secondary deterioration and developing cell death [106], well after the realistic window of opportunity for treatment. Cady et al. reported in a piglet model of encephalopathy that an increase in the ratio between [Pi] and [EPP] (the exchangeable high-energy phosphate pool), intracellular pH, and intracellular Mg approximately 2 hours after intrapartum HI was associated with severe injury, whereas increased [PCr]/[EPP] was associated with mild damage [107]. It is unknown whether these parameters predict response to treatment. Nevertheless, these data raise the possibility that in specialist centers [^{31}P]-MRS may have potential to help select infants for trials of neuroprotection.

In neonates examined in the first week after birth, a poor outcome was associated with a lower apparent diffusion coefficient (ADC) in the basal ganglia and thalamus and a higher lactate (Lac)-*N*-acetylaspartate (NAA) ratio in the basal ganglia [108]. The authors also observed that a combination of MRI and MRS better predicts outcome than MRI alone and that while early MRI is good at detecting injury to areas such as the basal ganglia, thalamus, cortex, and cerebellum, it may underestimate injury to the hippocampus, cerebral white matter, and the brainstem [109]. Specificity of MRI may be improved by attention to the MRI patterns of injury during recovery described by National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) investigators, which have been shown to correlate well with outcomes at 6 years of age [110].

Most MRI and MRS studies do not provide clear guidelines for decision making and are limited by the size of cohorts, diffuse outcome measures, and other methodologic considerations that have led to erroneous data assumptions [103,105,111]. Further, there is a need to determine the effect of therapeutic hypothermia on MRS measurements, but to date, there are very limited data. In a cohort study of 31 infants with moderate to severe encephalopathy, serial [^{1}H]-MRS showed that phosphocreatine concentrations were around 20% higher during hypothermia than during rewarming, whereas levels of free creatine, NAA, glutamate, and other excitatory neurotransmitters were reduced [112].

One of the limitations of MRI and MRS is that they are expensive technologies. While many centers have access to MRI, fewer have MRS, so at present this technique is not immediately available for use within the intensive care unit. Thus, in practice, its use is hampered by the need to transport sick, sedated infants. Further, now that therapeutic hypothermia is standard care, modern studies can no longer compare with contemporaneous uncooled controls and so either rely on historical data or are uncontrolled.

Near-Infrared Spectroscopy (NIRS)

NIRS is a safe, noninvasive bedside technology that uses light in the near-infrared region of the spectrum that is absorbed by oxygenated and deoxygenated hemoglobin from which cerebral oxygenation can be

assessed along with calculated measurements of cerebral blood volume and blood flow [113,114]. It also has the capacity to measure cytochrome oxidase (CytOx) [89,100,115–118]. Modern-day monitors do not include this measurement because CytOx sampled on only four wavelengths can lead to potential errors in CytOx calculations [119]. However, the loss of this measurement is unfortunate because CytOx is a measure of the terminal complex of the mitochondrial respiratory chain and thus generation of ATP [117,120]. Changes in CytOx over time offers insight into cerebral metabolism that can help to delineate the phases of injury [89]. Changes in the redox state of the brain correlate with delayed cerebral energy failure [121]. Such metabolic changes are the drivers of the neural biochemical factors measured in blood and urine such as S100B and GFAP. Recent advances in broadband technology may overcome the calculation issues [115,118]. Advances using time-resolved approaches (such as frequency-domain NIRS) also help to address limitations, such as measuring relative rather than absolute changes, and help to define the areas of tissue being interrogated and improve the contrast-to-noise ratio [113]. Recent generations of devices now seek to combine NIRS with imaging diffuse optical imaging, for example, allows regional assessment of cerebral oximetry and function.

Despite these advances and the appearance of NIRS machines in most Western NICUs, there is a surprising lack of experimental and clinical data looking at the time-course changes in oxygenation and CytOx in different types of encephalopathy. Animal studies show that NIRS can be used to monitor the different stages of the evolution of injury. For example, during recovery from severe asphyxia, there is a brisk restoration of blood volume, oxygenation, and oxidative metabolism [89,90]. During the latent phase, there is a modest fall in oxygenation associated with epileptiform transients and reduced cerebral perfusion [89], which can be modified by exposure to glucocorticoids [100]. Overall cerebral metabolism is suppressed during this phase, and this is associated with suppression of cerebral metabolic rate for oxygen ($CMRO_2$) [122]. Consistent with this finding, there is evidence from recent studies combining NIRS with MRS in newborn piglets after HI that the fall $CMRO_2$ in the latent phase was mediated by a mixture of impaired mitochondrial function and reduced energy demand [123]. The reduction in $CMRO_2$ is observed to persist after profound hypoxia. Similarly, cerebral oxygen saturation has also been shown to remain suppressed in animals that were exposed to longer durations of asphyxia but is restored rapidly after shorter durations of asphyxia [124]

Measurements of oxygenated hemoglobin show that levels rise significantly in the secondary phase [89,100]. This is associated with a progressive fall in CytOx consistent with secondary metabolic deterioration. Increased oxygenation thus likely reflects a condition of luxury perfusion where there is normal oxygenation but failure of mitochondrial function [125,126]. Increased perfusion may also accompany this phase, and, clinically, greater perfusion or vasoparalysis is associated with adverse outcomes [127,128]. Inhibiting this perfusion, however, increases rather than decreases injury [129]. Further information is needed to determine whether modifying the hypo- or hyper-oxygenation seen on NIRS is beneficial, and caution is warranted [126].

Further, it is now clear that as for EEG, hypothermia alters how we may interpret NIRS signals. Hypothermia was associated with increased oxygen saturation and perfusion, but infants did not have radiologically detectable injury, suggesting that these changes were not associated with luxury perfusion [130]. In contrast to earlier studies of normothermic infants [127], hypothermic infants who had severe encephalopathy had lower cerebral blood flow (CBF) than newborns with moderate encephalopathy and higher cerebral tissue oxygen saturation than newborns who did not develop brain injury [130]. When NIRS is combined with aEEG during hypothermia, aEEG provided good short-term prognostic capacity consistent with earlier studies [83]; cerebral saturation did not [131]. However, reduced variability of the cerebral oxygen saturation signal did predict worse outcomes [131]. Finally, Ancora et al. reported that the total oxygen index derived from NIRS was better at predicting neurologic outcomes at 24 hours than aEEG [132].

Impaired cerebral autoregulation may also be associated with evolving brain injury, which potentially may be assessed by spectral coherence between blood pressure and NIRS-derived delta hemoglobin (oxygenated-deoxygenated hemoglobin). There is preliminary evidence from small studies that the duration and magnitude of cerebral pressure passivity can help to distinguish moderate to severe encephalopathy from mild to no injury [133] and are associated with

motor and cognitive impairments at 21–32 months of age [134].

Conclusions

The purpose of this chapter was to highlight the key attributes needed for any measure or combination of measures to aid in the selection of infants for treatment. Biomarkers should be able to tell us whether an infant needs treatment and, if so, whether brain cells can still be saved – are we in time to treat? This overview of the literature shows that at present none of the proposed biomarkers has been established to be clearly better than clinical evaluation of encephalopathy. Many of these biomarkers show good correlations with outcomes well after the onset of secondary deterioration, at relatively late time points (e.g., 12 or 24 hours or later), and so are of little use for determining whether an infant should be treated. There is a strong need both for detailed studies of the time courses of potential measures after HI and for studies that discriminate between the effects of exposure to asphyxia per se and neural injury. We speculate that a combination of multiple bedside measures may be needed to detect the critical transition from reversible to irreversible injury and thus allow us to reliably detect infants who are likely to benefit from treatment at an early enough time that their brain cells can still be saved.

References

1. Reid SM, Carlin JB, Reddihough DS. Rates of cerebral palsy in Victoria, Australia, 1970 to 2004: has there been a change? *Dev Med Child Neurol* 2011; **53**: 907–12.
2. Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. Washington, DC: Institute of Medicine of the National Academies, 2007 Available at http://books.nap.edu/openbook.php?record_id=11622&page=1.
3. McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869–77.
4. Himmelmann K, Hagberg G, Beckung E, et al. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatr* 2005; **94**: 287–94.
5. Centers for Disease Control and Prevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment–United States, 2003. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 57–9.
6. Kruse M, Michelsen SI, Flachs EM, et al. Lifetime costs of cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 622–8.
7. Gunn AJ, Bennet L. Timing of injury in the fetus and neonate. *Curr Opin Obstet Gynecol* 2008; **20**: 175–81.
8. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013; **1**: CD003311.
9. Gunn AJ, Thoresen M. Hypothermic neuroprotection. *NeuroRx* 2006; **3**: 154–69.
10. Beilharz EJ, Williams CE, Dragunow M, et al. Mechanisms of delayed cell death following hypoxic-ischemic injury in the immature rat: evidence for apoptosis during selective neuronal loss. *Brain Res Mol Brain Res* 1995; **29**: 1–14.
11. Geddes R, Vannucci RC, Vannucci SJ. Delayed cerebral atrophy following moderate hypoxia-ischemia in the immature rat. *Dev Neurosci* 2001; **23**: 180–5.
12. Roth SC, Baudin J, Cady E, et al. Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. *Dev Med Child Neurol* 1997; **39**: 718–25.
13. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–84.
14. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**: 663–70.
15. Westgate JA, Wibbens B, Bennet L, et al. The intrapartum deceleration in center stage: a physiological approach to interpretation of fetal heart rate changes in labor. *Am J Obstet Gynecol* 2007; **197**: e1–e11.236.
16. de Haan HH, Gunn AJ, Williams CE, Gluckman PD. Brief repeated umbilical cord occlusions cause sustained cytotoxic cerebral edema and focal infarcts in near-term fetal lambs. *Pediatr Res* 1997; **41**: 96–104.
17. Graham EM, Ruis KA, Hartman AL, et al. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008; **199**: 587–95.
18. MacLennan A, International Cerebral Palsy Task Force, et al. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999; **319**: 1054–9.
19. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.
20. Iwata O, Iwata S, Bainbridge A, et al. Supra- and sub-baseline phosphocreatine recovery in developing brain

after transient hypoxia-ischaemia: relation to baseline energetics, insult severity and outcome. *Brain* 2008; **131**: 2220–6.

21. Szeto HH. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. *Antioxid Redox Signal* 2008; **10**: 601–19.
22. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 2010; **340**: c363.
23. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. *N Engl J Med* 1996; **334**: 613–8.
24. Murray DM, O'Riordan MN, Horgan R, et al. Fetal heart rate patterns in neonatal hypoxic-ischemic encephalopathy: relationship with early cerebral activity and neurodevelopmental outcome. *Am J Perinatol* 2009; **26**: 605–12.
25. Wayenberg JL. Threshold of metabolic acidosis associated with neonatal encephalopathy in the term newborn. *J Matern Fetal Neonatal Med* 2005; **18**: 381–5.
26. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol* 1997; **177**: 1391–4.
27. Shah S, Tracy M, Smyth J. Postnatal lactate as an early predictor of short-term outcome after intrapartum asphyxia. *J Perinatol* 2004; **24**: 16–20.
28. Boardman JP, Hawdon JM. Hypoglycaemia and hypoxic-ischaemic encephalopathy. *Dev Med Child Neurol* 2015; **57**: 29–33.
29. Nadeem M, Murray DM, Boylan GB, et al. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischaemic encephalopathy. *BMC Pediatr* 2011; **11**: 10.
30. Chouthai NS, Sobczak H, Khan R, et al. Hyperglycemia is associated with poor outcome in newborn infants undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy. *J Neonatal Perinatal Med* 2015; **8**: 125–31.
31. Basu SK, Kaiser JR, Guffey D, et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. *Arch Dis Child Fetal Neonatal Ed* 2016; **101**: F149–55.
32. Shelley HJ. Glycogen reserves and their changes at birth and in anoxia. *Br Med Bull* 1961; **17**: 137–43.
33. Dawes GS, Mott JC, Shelley HJ. The importance of cardiac glycogen for the maintenance of life in foetal lambs and newborn animals during anoxia. *J Physiol* 1959; **146**: 516–38.
34. Wassink G, Bennet L, Booth LC, et al. The ontogeny of hemodynamic responses to prolonged umbilical cord occlusion in fetal sheep. *J Appl Physiol* 2007; **103**: 1311–7.
35. Laptook AR, Shankaran S, Ambalavanan N, et al. Outcome of term infants using Apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. *Pediatrics* 2009; **124**: 1619–26.
36. Natarajan G, Shankaran S, Laptook AR, et al. Apgar scores at 10 min and outcomes at 6–7 years following hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F473–9.
37. Bayram F, Ozerkan K, Cengiz C, et al. Perinatal asphyxia is associated with the umbilical cord nucleated red blood cell count in pre-eclamptic pregnancies. *J Obstet Gynaecol* 2010; **30**: 383–6.
38. Li J, Kobata K, Kamei Y, et al. Nucleated red blood cell counts: an early predictor of brain injury and 2-year outcome in neonates with hypoxic-ischemic encephalopathy in the era of cooling-based treatment. *Brain Dev* 2014; **36**: 472–8.
39. Christensen RD, Lambert DK, Richards DS. Estimating the nucleated red blood cell 'emergence time' in neonates. *J Perinatol* 2014; **34**: 116–9.
40. Ferber A, Fridel Z, Weissmann-Brenner A, et al. Are elevated fetal nucleated red blood cell counts an indirect reflection of enhanced erythropoietin activity? *Am J Obstet Gynecol* 2004; **190**: 1473–5.
41. Christensen RD, Henry E, Andres RL, Bennett ST. Reference ranges for blood concentrations of nucleated red blood cells in neonates. *Neonatology* 2011; **99**: 289–94.
42. Bennet L, Booth L, Gunn AJ. Potential biomarkers for hypoxic-ischemic encephalopathy. *Semin Fetal Neonatal Med* 2010; **15**: 253–60.
43. Gazzolo D, Abella R, Marinoni E, et al. New markers of neonatal neurology. *J Matern Fetal Neonatal Med* 2009; **2**(Suppl 3): 57–61.
44. Ramaswamy V, Horton J, Vandermeer B, et al. Systematic review of biomarkers of brain injury in term neonatal encephalopathy. *Pediatr Neurol* 2009; **40**: 215–26.
45. Chalak LF, Sanchez PJ, Adams-Huet B, et al. Biomarkers for severity of neonatal hypoxic-ischemic encephalopathy and outcomes in newborns receiving hypothermia therapy. *J Pediatr* 2014; **164**: 468–74.
46. Loukovaara M, Teramo K, Alfthan H, et al. Amniotic fluid S100B protein and erythropoietin in pregnancies at risk for fetal hypoxia. *Eur J Obstet Gynecol Reprod Biol* 2009; **142**: 115–8.
47. Routsi C, Stamataki E, Nanas S, et al. Increased levels of serum S100B protein in critically ill patients without brain injury. *Shock* 2006; **26**: 20–4.

48. Garnier Y, Frigiola A, Li Volti G, et al. Increased maternal/fetal blood S100B levels following systemic endotoxin administration and periventricular white matter injury in preterm fetal sheep. *Reprod Sci* 2009; **16**: 758–66.
49. Friel LA, Romero R, Edwin S, et al. The calcium binding protein, S100B, is increased in the amniotic fluid of women with intra-amniotic infection/ inflammation and preterm labor with intact or ruptured membranes. *J Perinat Med* 2007; **35**: 385–93.
50. Schulpis KH, Margeli A, Akalestos A, et al. Effects of mode of delivery on maternal-neonatal plasma antioxidant status and on protein S100B serum concentrations. *Scand J Clin Lab Invest* 2006; **66**: 733–42.
51. Bokesch PM, Appachi E, Cavaglia M, et al. A glial-derived protein, S100B, in neonates and infants with congenital heart disease: evidence for preexisting neurologic injury. *Anesth Analg* 2002; **95**: 889–92.
52. Bruschettini M, van den Hove DL, Gazzolo D, et al. A single course of antenatal betamethasone reduces neurotrophic factor S100B concentration in the hippocampus and serum in the neonatal rat. *Brain Res Dev Brain Res* 2005; **159**: 113–8.
53. Vicente E, Tramontina F, Leite MC, et al. S100B levels in the cerebrospinal fluid of rats are sex and anaesthetic dependent. *Clin Exp Pharmacol Physiol* 2007; **34**: 1126–30.
54. Gazzolo D, Vinesi P, Marinoni E, et al. S100B protein concentrations in cord blood: correlations with gestational age in term and preterm deliveries. *Clin Chem* 2000; **46**: 998–1000.
55. Wijnberger LD, Nikkels PG, van Dongen AJ, et al. Expression in the placenta of neuronal markers for perinatal brain damage. *Pediatr Res* 2002; **51**: 492–6.
56. Zaigham M, Lundberg F, Hayes R, et al. Umbilical cord blood concentrations of ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) in neonates developing hypoxic-ischemic encephalopathy. *J Matern Fetal Neonatal Med* 2015:**1**–7.
57. Looney AM, Walsh BH, Moloney G, et al. Downregulation of umbilical cord blood levels of miR-374a in neonatal hypoxic ischemic encephalopathy. *J Pediatr* 2015; **167**: 269–73.
58. Whitehead CL, Teh WT, Walker SP, et al. Circulating microRNAs in maternal blood as potential biomarkers for fetal hypoxia in-utero. *PloS One* 2013; **8**: e78487.
59. Qu Y, Wu J, Chen D, et al. MiR-139-5p inhibits HGTD-P and regulates neuronal apoptosis induced by hypoxia-ischemia in neonatal rats. *Neurobiol Dis* 2014; **63**: 184–93.
60. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; **33**: 696–705.
61. Wyatt JS, Gluckman PD, Liu PY, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 2007; **119**: 912–21.
62. Nagdyman N, Komen W, Ko HK, et al. Early biochemical indicators of hypoxic-ischemic encephalopathy after birth asphyxia. *Pediatr Res* 2001; **49**: 502–6.
63. Nagdyman N, Grimmer I, Scholz T, et al. Predictive value of brain-specific proteins in serum for neurodevelopmental outcome after birth asphyxia. *Pediatr Res* 2003; **54**: 270–5.
64. Thorngren-Jerneck K, Alling C, Herbst A, et al. S100 protein in serum as a prognostic marker for cerebral injury in term newborn infants with hypoxic ischemic encephalopathy. *Pediatr Res* 2004; **55**: 406–12.
65. Martins RO, Rotta NT, Portela LV, Souza DO. S100B protein related neonatal hypoxia. *Arq Neuropsiquiatr* 2006; **64**: 24–9.
66. Murabayashi M, Minato M, Okuhata Y, et al. Kinetics of serum S100B in newborns with intracranial lesions. *Pediatr Int* 2008; **50**: 17–22.
67. Bashir M, Frigiola A, Iskander I, et al. Urinary S100A1B and S100BB to predict hypoxic ischemic encephalopathy at term. *Front Biosci (Elite Ed)* 2009; **1**: 560–7.
68. Giuseppe D, Sergio C, Pasqua B, et al. Perinatal asphyxia in preterm neonates leads to serum changes in protein S-100 and neuron specific enolase. *Curr Neurovasc Res* 2009; **6**: 110–6.
69. Giussani DA, Thakor AS, Frulio R, Gazzolo D. Acute hypoxia increases S100beta protein in association with blood flow redistribution away from peripheral circulations in fetal sheep. *Pediatr Res* 2005; **58**: 179–84.
70. Fujii EY, Kozuki M, Mu J, et al. Correlation of neuron-specific enolase and S100B with histological cerebral damage in fetal sheep after severe asphyxia. *Brain Res* 2004; **1018**: 136–40.
71. Nylen K, Ost M, Csajbok LZ, et al. Serum levels of S100B, S100A1B and S100BB are all related to outcome after severe traumatic brain injury. *Acta Neurochir* 2008; **150**: 221–7.
72. Berger RP, Adelson PD, Pierce MC, et al. Serum neuron-specific enolase, S100B, and myelin basic protein concentrations after inflicted and noninflicted traumatic brain injury in children. *J Neurosurg* 2005; **103**: 61–8.
73. Denihan NM, Boylan GB, Murray DM. Metabolomic profiling in perinatal asphyxia: a promising new field. *Biomed Res Int* 2015; **2015**: 254076.

74. Shalak LF, Laptook AR, Velaphi SC, Perlman JM. Amplitude-integrated electroencephalography coupled with an early neurologic examination enhances prediction of term infants at risk for persistent encephalopathy. *Pediatrics* 2003; **111**: 351–7.

75. van Rooij LG, Toet MC, Osredkar D, et al. Recovery of amplitude integrated electroencephalographic background patterns within 24 hours of perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F245–51.

76. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. *Pediatrics* 2009; **124**: e459–67.

77. Pezzani C, Radvanyi-Bouvet MF, Relier JP, Monod N. Neonatal electroencephalography during the first twenty-four hours of life in full-term newborn infants. *Neuropediatrics* 1986; **17**: 11–8.

78. George S, Gunn AJ, Westgate JA, et al. Fetal heart rate variability and brainstem injury after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R925–33.

79. Gunn AJ, Wyatt JS, Whitelaw A, et al. Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. *J Pediatr* 2008; **152**: 55–8.

80. Azzopardi D. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**: F80–2.

81. Cseko AJ, Bango M, Lakatos P, et al. Accuracy of amplitude-integrated electroencephalography in the prediction of neurodevelopmental outcome in asphyxiated infants receiving hypothermia treatment. *Acta Paediatr* 2013; **102**: 707–11.

82. Hallberg B, Grossmann K, Bartocci M, Blennow M. The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment. *Acta Paediatr* 2010; **99**: 531–6.

83. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* 2010; **126**: e131–9.

84. Padden B, Scheer I, Brotschi B, et al. Does amplitude-integrated electroencephalogram background pattern correlate with cerebral injury in neonates with hypoxic-ischaemic encephalopathy? *J Paediatr Child Health* 2015; **51**: 180–5.

85. Wong FY, Barfield CP, Walker AM. Power spectral analysis of two-channel EEG in hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2007; **83**: 379–83.

86. Doyle OM, Greene BR, Murray DM, et al. The effect of frequency band on quantitative EEG measures in neonates with hypoxic-ischaemic encephalopathy. In *Conference Proceedings of the IEEE Engineering in Medicine and Biology Society* (Piscataway, NJ: IEEE, 2007): 717–21.

87. Jiang D, Wu W, Jia X, et al. Scaling exponents of EEG are related to the temporal process of the therapeutic hypothermia following ischemic brain injury. In *Conference Proceedings of the IEEE Engineering in Medicine and Biology Society*, vol. 1 (Piscataway, NJ: IEEE, 2009): 2192–5.

88. Tichauer KM, Elliott JT, Hadway JA, Lee TY, St Lawrence K. Cerebral metabolic rate of oxygen and amplitude-integrated electroencephalography during early reperfusion after hypoxia-ischemia in piglets. *J Appl Physiol* 2009; **106**: 1506–12.

89. Bennet L, Roelfsema V, Pathipati P, et al. Relationship between evolving epileptiform activity and delayed loss of mitochondrial activity after asphyxia measured by near-infrared spectroscopy in preterm fetal sheep. *J Physiol* 2006; **572**: 141–54.

90. Bennet L, Roelfsema V, Dean J, et al. Regulation of cytochrome oxidase redox state during umbilical cord occlusion in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2007; **292**: R1569–76.

91. Dean JM, George SA, Wassink G, et al. Suppression of post hypoxic-ischemic EEG transients with dizocilpine is associated with partial striatal protection in the preterm fetal sheep. *Neuropharmacology* 2006; **50**: 491–503.

92. Scher MS. Controversies regarding neonatal seizure recognition. *Epileptic Disord* 2002; **4**: 139–58.

93. Dean JM, George S, Naylor AS, et al. Partial neuroprotection with low-dose infusion of the 2-adrenergic receptor agonist clonidine after severe hypoxia in preterm fetal sheep. *Neuropharmacology* 2008; **55**: 166–74.

94. Bennet L, Dean JM, Wassink G, Gunn AJ. Differential effects of hypothermia on early and late epileptiform events after severe hypoxia in preterm fetal sheep. *J Neurophysiol* 2007; **97**: 572–8.

95. Dean JM, Gunn AJ, Wassink G, et al. Endogenous alpha(2)-adrenergic receptor-mediated neuroprotection after severe hypoxia in preterm fetal sheep. *Neuroscience* 2006; **142**: 615–28.

96. Dean JM, Gunn AJ, Wassink G, Bennet L. Transient NMDA receptor-mediated hypoperfusion following umbilical cord occlusion in preterm fetal sheep. *Exp Physiol* 2006; **91**: 423–29.

97. Scher MS, Bova JM, Dokianakis SG, Steppe DA. Physiological significance of sharp wave transients on EEG recordings of healthy pre-term and full-term

neonates. *Electroencephalogr Clin Neurophysiol* 1994; **90**: 179–85.

98. Vecchierini-Blineau MF, Nogues B, Louvet S, Desfontaines O. Positive temporal sharp waves in electroencephalograms of the premature newborn. *Neurophysiol Clin* 1996; **26**: 350–62.
99. Marics G, Cseko A, Vasarhelyi B, et al. Prevalence and etiology of false normal aEEG recordings in neonatal hypoxic-ischaemic encephalopathy. *BMC Pediatr* 2013; **13**: 194.
100. Lear CA, Koome MM, Davidson JO, et al. The effects of dexamethasone on post-asphyxial cerebral oxygenation in the preterm fetal sheep. *J Physiol* 2014; **592**: 5493–505.
101. Davidson JO, Quaedackers JS, George SA, et al. Maternal dexamethasone and EEG hyperactivity in preterm fetal sheep. *J Physiol* 2011; **589**: 3823–35.
102. Counsell SJ, Ball G, Edwards AD. New imaging approaches to evaluate newborn brain injury and their role in predicting developmental disorders. *Curr Opin Neurol* 2014; **27**: 168–75.
103. Robertson NJ, Thayyil S, Cady EB, Raivich G. Magnetic resonance spectroscopy biomarkers in term perinatal asphyxial encephalopathy: from neuropathological correlates to future clinical applications. *Curr Pediatr Rev* 2014; **10**: 37–47.
104. Martin E, Buchli R, Ritter S, et al. Diagnostic and prognostic value of cerebral ^{31}P magnetic resonance spectroscopy in neonates with perinatal asphyxia. *Pediatr Res* 1996; **40**: 749–58.
105. Thayyil S, Chandrasekaran M, Taylor A, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics* 2010; **125**: e382–95.
106. Vannucci RC, Towfighi J, Vannucci SJ. Secondary energy failure after cerebral hypoxia-ischemia in the immature rat. *J Cereb Blood Flow Metab* 2004; **24**: 1090–7.
107. Cady EB, Iwata O, Bainbridge A, et al. Phosphorus magnetic resonance spectroscopy 2 h after perinatal cerebral hypoxia-ischemia prognosticates outcome in the newborn piglet. *J Neurochem* 2008; **107**: 1027–35.
108. Alderliesten T, de Vries LS, Benders MJ, et al. MR imaging and outcome of term neonates with perinatal asphyxia: value of diffusion-weighted MR imaging and ^{1}H MR spectroscopy. *Radiology* 2011; **261**: 235–42.
109. Alderliesten T, Nikkels PG, Benders MJ, et al. Antemortem cranial MRI compared with postmortem histopathologic examination of the brain in term infants with neonatal encephalopathy following perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F304–9.
110. Shankaran S, McDonald SA, Laptook AR, et al. Neonatal magnetic resonance imaging pattern of brain injury as a biomarker of childhood outcomes following a trial of hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 2015; **167**: 987–93.
111. Wilkinson D. MRI and withdrawal of life support from newborn infants with hypoxic-ischemic encephalopathy. *Pediatrics* 2010; **126**: e451–8.
112. Wisnowski JL, Wu TW, Reitman AJ, et al. The effects of therapeutic hypothermia on cerebral metabolism in neonates with hypoxic-ischemic encephalopathy: an in vivo ^{1}H-MR spectroscopy study. *J Cereb Blood Flow Metab* 2016; **36**:1075–86.
113. Liao SM, Culver JP. Near infrared optical technologies to illuminate the status of the neonatal brain. *Current Pediatr Rev* 2014; **10**: 73–86.
114. Liu P, Chalak LF, Lu H. Non-invasive assessment of neonatal brain oxygen metabolism: a review of newly available techniques. *Early Hum Dev* 2014; **90**: 695–701.
115. Bale G, Mitra S, Meek J, et al. A new broadband near-infrared spectroscopy system for in-vivo measurements of cerebral cytochrome-c-oxidase changes in neonatal brain injury. *Biomed Optics Express* 2014; **5**: 3450–66.
116. Drury PP, Bennet L, Booth LC, et al. Maturation of the mitochondrial redox response to profound asphyxia in fetal sheep. *PLoS One* 2012; **7**: e39273.
117. van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. *Neonatology* 2008; **94**: 237–44.
118. Bainbridge A, Tachtsidis I, Faulkner SD, et al. Brain mitochondrial oxidative metabolism during and after cerebral hypoxia-ischemia studied by simultaneous phosphorus magnetic-resonance and broadband near-infrared spectroscopy. *Neuroimage* 2014; **102**: 173–83.
119. Matcher SJ, Elwell CE, Cooper CE, et al. Performance comparison of several published tissue near-infrared spectroscopy algorithms. *Anal Biochem* 1995; **227**: 54–68.
120. Cooper CE, Cope M, Springett R, et al. Use of mitochondrial inhibitors to demonstrate that cytochrome oxidase near-infrared spectroscopy can measure mitochondrial dysfunction noninvasively in the brain. *J Cereb Blood Flow Metab* 1999; **19**: 27–38.
121. Peeters-Scholte C, van den Tweel E, Groenendaal F, van Bel F. Redox state of near infrared spectroscopy-measured cytochrome aa(3) correlates with delayed cerebral energy failure following perinatal hypoxia-ischaemia in the newborn pig. *Exp Brain Res* 2004; **156**: 20–6.

122. Jensen EC, Bennet L, Hunter CJ, et al. Post-hypoxic hypoperfusion is associated with suppression of cerebral metabolism and increased tissue oxygenation in near-term fetal sheep. *J Physiol* 2006; **572**: 131–9.

123. Winter JD, Tichauer KM, Gelman N, et al. Changes in cerebral oxygen consumption and high-energy phosphates during early recovery in hypoxic-ischemic piglets: a combined near-infrared and magnetic resonance spectroscopy study. *Pediatr Res* 2009; **65**: 181–7.

124. Kurth CD, McCann JC, Wu J, et al. Cerebral oxygen saturation-time threshold for hypoxic-ischemic injury in piglets. *Anesth Analg* 2009; **108**: 1268–77.

125. Perlman JM. Summary proceedings from the neurology group on hypoxic-ischemic encephalopathy. *Pediatrics* 2006; **117**: S28–33.

126. Greisen G. Cerebral blood flow and oxygenation in infants after birth asphyxia: clinically useful information? *Early Hum Dev* 2014; **90**: 703–5.

127. Meek JH, Elwell CE, McCormick DC, et al. Abnormal cerebral haemodynamics in perinatally asphyxiated neonates related to outcome. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F110–15.

128. Pryds O, Greisen G, Lou H, Friis-Hansen B. Vasoparalysis associated with brain damage in asphyxiated term infants. *J Pediatr* 1990; **117**: 119–25.

129. Marks KA, Mallard CE, Roberts I, et al. Nitric oxide synthase inhibition attenuates delayed vasodilation and increases injury after cerebral ischemia in fetal sheep. *Pediatr Res* 1996; **40**: 185–91.

130. Wintermark P, Hansen A, Warfield SK, et al. Near-infrared spectroscopy versus magnetic resonance imaging to study brain perfusion in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *Neuroimage* 2014; **85**: 287–93.

131. Shellhaas RA, Thelen BJ, Bapuraj JR, et al. Limited short-term prognostic utility of cerebral NIRS during neonatal therapeutic hypothermia. *Neurology* 2013; **81**: 249–55.

132. Ancora G, Maranella E, Locatelli C, et al. Changes in cerebral hemodynamics and amplitude integrated EEG in an asphyxiated newborn during and after cool cap treatment. *Brain Dev* 2009; **31**: 442–4.

133. Massaro AN, Govindan RB, Vezina G, et al. Impaired cerebral autoregulation and brain injury in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *J Neurophysiol* 2015; **114**: 818–24.

134. Burton VJ, Gerner G, Cristofalo E, et al. A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia. *BMC Neurol* 2015; **15**: 209.

135. Wiberg-Itzel E, Lipponer C, Norman M, et al. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomized, controlled multicentre trial. *BMJ* 2008; **336**: 1284–7.

136. Borruto F, Comparetto C, Treisser A. Prevention of cerebral palsy during labour: role of foetal lactate. *Arch Gynecol Obstet* 2008; **278**: 17–22.

137. Ramanah R, Martin A, Clement MC, et al. Fetal scalp lactate microsampling for non-reassuring fetal status during labor: a prospective observational study. *Fetal Diagn Ther* 2010; **27**: 14–9.

138. Wiberg N, Kallen K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. *Acta Obstet Gynaecol Scand* 2010; **89**: 1263–9.

139. Hogan L, Ingemarsson I, Thorngren-Jerneck K, Herbst A. How often is a low 5-min Apgar score in term newborns due to asphyxia? *Eur J Obstet Gynecol Reprod Biol* 2007; **130**: 169–75.

140. Thorngren-Jerneck K, Herbst A. Low 5-minute Apgar score: a population-based register study of 1 million term births. *Obstet Gynecol* 2001; **98**: 65–70.

141. Kovalak EE, Dede FS, Gelisen O, et al. Nonreassuring fetal heart rate patterns and nucleated red blood cells in term neonates. *Arch Gynecol Obstet* 2011; **283**: 1005–9.

142. Gazzolo D, Marinoni E, Di Iorio R, et al. Urinary S100B protein measurements: a tool for the early identification of hypoxic-ischemic encephalopathy in asphyxiated full-term infants. *Crit Care Med* 2004; **32**: 131–6.

143. Florio P, Luisi S, Moataza B, et al. High urinary concentrations of activin A in asphyxiated full-term newborns with moderate or severe hypoxic ischemic encephalopathy. *Clin Chem* 2007; **53**: 520–2.

144. Aly H, Hassanein S, Nada A, et al. Vascular endothelial growth factor in neonates with perinatal asphyxia. *Brain Dev* 2009; **31**: 600–4.

145. Reinke SN, Walsh BH, Boylan GB, et al. ^{1}H NMR derived metabolomic profile of neonatal asphyxia in umbilical cord serum: implications for hypoxic ischemic encephalopathy. *J Proteome Res* 2013; **12**: 4230–9.

146. Thoresen M. Patient selection and prognostication with hypothermia treatment. *Semin Fetal Neonatal Med* 2010; **15**: 247–52.

147. Ambalavanan N, Carlo WA, Shankaran S, et al. Predicting outcomes of neonates diagnosed with hypoxemic-ischemic encephalopathy. *Pediatrics* 2006; **118**: 2084–93.

148. Haiju Z, Suyuan H, Xiufang F, et al. The combined detection of umbilical cord nucleated red blood cells and lactate: early prediction of neonatal hypoxic ischemic encephalopathy. *J Perinat Med* 2008; **36**: 240–7.

149. Bednarek N, Svedin P, Garnotel R, et al. Increased MMP-9 and TIMP-1 in mouse neonatal brain and plasma and in human neonatal plasma after hypoxia-ischemia: a potential marker of neonatal encephalopathy. *Pediatr Res* 2012; **71**: 63–70.

150. Kirimi E, Peker E, Tuncer O, et al. Increased serum malondialdehyde level in neonates with hypoxic-ischaemic encephalopathy: prediction of disease severity. *J Int Med Res* 2010; **38**: 220–6.

151. van Laerhoven H, de Haan TR, Offringa M, et al. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review. *Pediatrics* 2013; **131**: 88–98.

152. Horn AR, Swingler GH, Myer L, et al. Early clinical signs in neonates with hypoxic ischemic encephalopathy predict an abnormal amplitude-integrated electroencephalogram at age 6 hours. *BMC Pediatr* 2013; **13**: 52.

153. Jose A, Matthai J, Paul S. Correlation of EEG, CT, and MRI brain with neurological outcome at 12 months in term newborns with hypoxic ischemic encephalopathy. *J Clin Neonatol* 2013; **2**: 125–30.

154. Ancora G, Soffritti S, Lodi R, et al. A combined a-EEG and MR spectroscopy study in term newborns with hypoxic-ischemic encephalopathy. *Brain Dev* 2010; **32**: 835–42.

155. Twomey E, Twomey A, Ryan S, et al. MR imaging of term infants with hypoxic-ischaemic encephalopathy as a predictor of neurodevelopmental outcome and late MRI appearances. *Pediatr Radiol* 2010; **40**: 1526–35.

156. Garcia-Alix A, Cabanas F, Pellicer A, et al. Neuron-specific enolase and myelin basic protein: relationship of cerebrospinal fluid concentrations to the neurologic condition of asphyxiated full-term infants. *Pediatrics* 1994; **93**: 234–40.

Chapter 22

Congenital Malformations of the Brain

Jin S. Hahn and Ronald J. Lemire

Introduction

This chapter focuses on some of the more common brain malformations that are encountered early in life. Tremendous advances in neuroimaging with MRI in the past two decades have significantly improved our ability to diagnose brain malformations. In conjunction, there have been rapid advances in neurobiology that have led to better understanding of how the brain develops and what disturbances to the development lead to malformation. Each year more and more genes responsible for malformations are being discovered, leading to a greater understanding of how mutations in the genes perturb the molecules and structures involved in the developing brain and lead to the malformations. Furthermore, modern fetal ultrasonography and fetal MRI have increased the ability to detect a large variety of CNS malformations in utero. Prenatal detection and anatomic diagnosis of the malformations will better allow medical caregivers to provide prognosis and management counseling.

Normal Brain Development

A brief overview of normal embryonic and fetal brain development will help to clarify the timing and etiology of brain malformations. Normal human brain development occurs in a highly defined spatial and temporal sequence of events in utero (Table 22.1). The temporal sequence consists of several overlapping phases. During the *induction* phase, signals sent to the ectoderm cause it to develop into neural tissue. The neural plate, a sheet of cells that will ultimately develop into the nervous system, develops by the seventeenth to twentieth day of gestation. *Neurulation* occurs next, where the neural plate begins to fold into the neural tube, a process that begins by day 21. Toward the rostral end, cephalic enlargement and vesicle formation start to occur by day 23. By day 27, the ends of the neural tube, the neuropores, close.

After 3 weeks of gestation, at the cephalic end the brain has developed into the three primary vesicles: prosencephalon, mesencephalon, and rhombencephalon. By the end of the sixth week, these vesicles will develop further into five vesicles: telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon. By the fifth week, *ventral induction* (or *patterning*) causes the telencephalic vesicle to bifurcate (or cleave) into the two hemispheres.

Cell proliferation and *neuronal generation* peak between the second and fifth month. During this phase, neuronal precursor cells in the germinal layer of the ventricular zone undergo rapid proliferation, resulting in a large number of neurons that will migrate to the cortex.

Cell migration occurs between the sixth and twentieth weeks. Cells that will become neurons exit the cell cycle and move out through the ventricular and subventricular zones along the fibers of radial glial cells. In the neocortex, there is an inside-out migration pattern. Newer neurons migrate past older neurons to occupy the more exterior layer.

Cell process and synapse formation begins around the fifth month of gestation, peaks around the seventh month, and continues after birth. During this phase, neuronal processes must extend locally, and at times, long distances, to find their targets in other neurons. Neurons also undergo differentiation into specific neuronal subtypes.

Etiologies and Timing of Malformations

Various disturbances in any of the developmental stages just described will result in specific brain malformations depending on the timing and nature of the perturbation. A useful concept in assessing the timing of human brain malformation is that of a *termination period*, a point in time beyond which a specific malformation cannot occur. For example, in humans, the

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Table 22.1 Selected Features in the Development of the Human Embryonic Brain

Stage	Age (days)	Features of brain development
7–8	16–18	Neural plate/groove
9	20	Neural folds, three rhombomeres
10	22	Optic primordium; fusion of rhombencephalic folds; cranial flexure
11	24	Rostral neuropore closes; acousticofacial complex; optic vesicle; primordium of corpus striatum
12	26	Caudal neuropore closes; hindbrain roof thins; cerebellar plate
13	28	Three divisions of trigeminal nerve; pontine flexture; olfactory placode
14	32	Oculomotor nerve; hypothalamic sulcus; roots of CN5–10 formed
15	33	Cerebral vesicles appear; striatal ridge; CN4 decussate
16	37	Infundibulum; subthalamic nucleus
17	41	Frontal and parietal lobe areas; choroid fissure closes; posterior commissure
18	44	Choroid plexus in fourth ventricle; superior and inferior colliculi; caudate nucleus
19	48	Choroid plexus in lateral ventricle; putamen; occipital pole area present; first fibers in internal capsule
20	50	Tentorium begins laterally; nerve fiber layer in retina
21	52	Choroid plexus in third ventricle
22	54	Anlage of dentate nucleus; superior colliculus
23	56	Temporal pole area present

ventral patterning process that leads to bifurcation of the cerebral hemispheres from the telencephalon occurs by the fifth week of gestation. Holoprosencephaly is thought to arise when there is failure of ventral patterning, and therefore suspected genetic mutations or teratogenic agents acting at a later time would not likely be the cause of this anomaly.

The general principle underlying brain malformations is that the same anomaly may arise from genetic or environmental causes. Genetic etiologies include chromosomal abnormalities as well as gene mutations. Some complex malformations can be due to multiple unrelated genes. Exogenous or environmental etiologies include congenital infections (especially rubella, toxoplasmosis, and cytomegalovirus), radiation, chemical agents, drugs, vitamin deficiencies or excesses, and nutritional deficiencies. Ischemia occurring at various stages of development also can lead to several different types of malformations.

Disorders of Neural Tube Formation and Related Events

Neural Tube Defects

The neurulation process completes with the closure of the neural tube between the third and fourth weeks of gestation. Failure of the closure of the neural tube at either end causes neural tube defects (NTDs). Rostral nonclosure results in anencephaly, and caudal nonclosure results in myelomeningocele. Until recently, the prevalence of NTDs has averaged about 1/1,000 deliveries, but a wide geographic variation exists [1]. The highest rates have been found in Ireland (4.6–6.7/1,000), South Wales (3.55), and Scotland (2.59). Low prevalence rates occurred in Columbia (0.1), Norway (0.2), and France (0.5). Prenatal screenings with serum α-fetoprotein (AFP) and ultrasound are used to detect NTDs early.

Anencephaly

Anencephaly is one of the most severe malformations of the brain and arises from failure of closure of the rostral neuropore. This results in a large defect of the cranial vault, meninges, and scalp. The cerebral hemispheres are absent or rudimentary, and tissue is softened with blood infiltration. The brainstem has variable preservation of nuclei. Some infants with anencephaly are born alive but usually expire within several days. Prenatal screenings with maternal serum AFP and fetal ultrasound enable relatively straightforward

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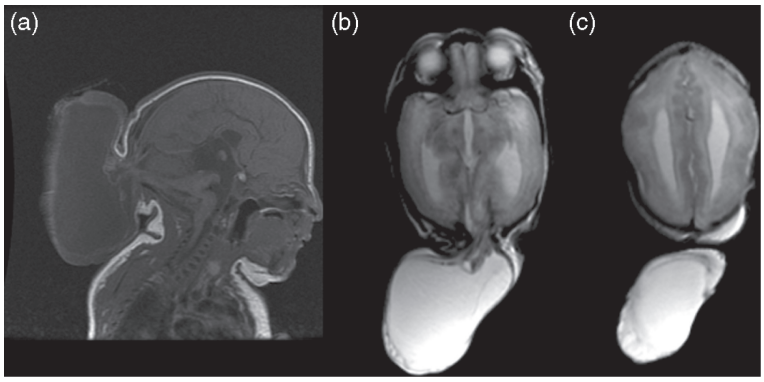


Figure 22.1 MRI of a term newborn with occipital encephalocele. (a) Sagittal T1-weighted image shows herniation of brain tissue through the defect in the skull posteriorly. (b,c) Axial T2-weighted images demonstrate the large encephalocele and cobblestone lissencephaly in the cerebral cortex. The corpus callosum is also dysplastic in appearance. This child was diagnosed with Walker-Warburg syndrome with congenital muscular dystrophy.

detection of anencephaly. Ultrasound detection of anencephaly is possible from 12 weeks' gestation.

The prevalence of anencephaly is approximately 1.2/10,000 live births, and the recurrence risk is approximately 4%. Some studies show as much as a 100-fold increase in risk of recurrence among mothers who have had a previous child with this condition.

Encephalocele

Encephaloceles occur when there is herniation of intracranial structures through a midline defect in the skull to form a sac covered by intact skin. When the prolapse involves meninges only, the term *meningocele* is used. When neural tissue is present, it is called *encephalocele*. Most commonly, encephaloceles are located in the occipital region at or below the inion (Figure 22.1). They may also be found in a frontal or nasofrontal location. In the United States, the frontal-to-occipital ratio is 1:6. Compared with anencephaly, which occurs during primary neurulation (neural tube formation), encephaloceles occur later (after 4 weeks). The prevalence is between 1/2,000 and 1/5,000 live births [2].

Children with *occipital encephalocele* are at risk for visual problems, microcephaly, mental retardation, and seizures. The nature and severity of disabilities depend on location and the amount of cerebral tissue involved in the defect. When the ventricular systems are involved or there are associated anomalies, such as aqueductal stenosis or Dandy-Walker malformation, hydrocephalus may be a complication.

Anterior encephaloceles may be visible, located around the root of the nose or in the superomedial aspect of the orbital cavity. *Basal encephaloceles* are not visible externally and are often located in the orbit, nasal fossae, or sphenoid sinuses. These types of encephaloceles are less common than occipital encephaloceles and may have a more favorable neurodevelopmental prognosis.

Myelomeningocele

Although myelomeningoceles are not a brain malformation per se, they represent a neural tube defect due to failure of closure of the caudal neuropore (which normally occurs by day 26). They are almost always associated with brain malformations such as Chiari II malformation and hydrocephalus. Pathology shows failure of closure of the posterior vertebral arches (spina bifida) most commonly in the lumbosacral region and protrusion of the dura and leptomeninges through the spinal defect. In addition, myelomeningoceles entail protrusion of nerve roots and malformed spinal cord. Clinically, affected children have lower motor neuron paralysis of the lower limbs, cutaneous sensory deficits below the level of the lesion, and bowel and bladder dysfunction.

Maternal serum AFP level is elevated in myelomeningoceles, and this provides a method of screening for open NTDs. Ultrasound can detect spina bifida from 16 to 20 weeks of gestation.

Chiari II Malformation

Chiari II malformation (Arnold-Chiari malformation) consists of caudal displacement of the posterior lobe of the cerebellar vermis into the foramen magnum and upper cervical spinal canal, beaked tectum, fusion of the colliculi, kinking of the medulla, and small, shallow posterior fossa. Associated spinal cord abnormalities include myelomeningocele, hydromyelia, syringomyelia, and diastematomyelia.

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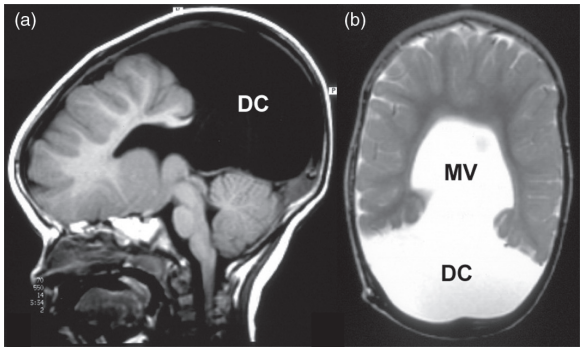


Figure 22.2 MRI of a child with alobar holoprosencephaly. (a) Sagittal T1-weighted and (b) axial T2-weighted images show failure of separation of the two hemispheres and thalami, a monoventricle (MV), and a large dorsal cyst (DC) that communicates with the MV.

Hydrocephalus is a major complication of Chiari II malformation, and postnatally, about 80% of these infants require a ventriculoperitoneal shunt to decrease intracranial pressure and provide a route for adequate CSF drainage. Some patients require surgical bony decompression of suboccipital bones and high cervical laminectomies if they develop apnea, cranial nerve palsies, and dysphagia.

There is nearly a constant association of hydrocephalus in patients with myelomeningocele and Chiari II malformation. Several hypotheses have been advanced regarding the pathogenesis of Chiari II, but none has been universally accepted because they do not adequately explain all the findings. There is also a temporal dissociation of the onset of myelomeningocele (before 26 days) and Chiari II, which occurs later.

Disorders of Ventral Patterning (Prosencephalic Cleavage)

Holoprosencephaly

Holoprosencephaly (HPE) is a complex brain malformation characterized by failure of the forebrain to bifurcate into two hemispheres. This ventral patterning process is normally complete by the fifth week of gestation [3]. It is the most common developmental defect of the forebrain and midface in humans, occurring in 1/250 pregnancies [4]. Because only 3% of fetuses with HPE survive to delivery [5], the live-birth prevalence is only about 1/10,000 [6–8].

Holoprosencephaly traditionally has been classified according to DeMyer's classification into three grades of severity: alobar, semilobar, and lobar. In addition to these classic forms, there is another milder subtype of HPE called the *middle interhemispheric variant* (MIH) or *syntelencephaly* [9,10]. The sine qua non feature of HPE is an incomplete separation of the cerebral hemispheres. In the most severe form, *alobar* HPE, there is complete or nearly complete lack of separation of the cerebral hemispheres with a single midline forebrain ventricle (monoventricle), which often communicates with a dorsal cyst (Figure 22.2). The interhemispheric fissure and corpus callosum are completely absent. The thalami and basal ganglia are often fused in appearance. In *semilobar* HPE, there is a failure of separation of the anterior hemispheres, while some portions of the posterior hemispheres show separation. The frontal horns of the lateral ventricle are absent, but posterior horns are present (Figure 22.3). The corpus callosum is absent anteriorly, but the splenium of the corpus callosum is present. In *lobar* HPE, the mildest form, the cerebral hemispheres are fairly well separated, while only the most rostral/ventral aspects are nonseparated. The splenium and body of the corpus callosum are present, although the genu may be poorly developed. Rudimentary formation of the frontal horns may be present. In contrast to classic HPE, in the middle interhemispheric variant of HPE (MIH) there is failure of separation of the posterior frontal and parietal lobes, while the poles of the frontal and occipital lobes are well separated [9,10].

Patients with HPE have various midline craniofacial and facial malformations, and the severity in general correlates with the severity of the brain malformation. Very severe abnormalities, such as cyclopia, ethmocephaly (a proboscis between severely hypoteloric eyes), and cebocephaly (hypotelorism with a single nostril), are rare (~2%) [11]. Severe defects, including midline cleft lip (premaxillary agenesis) and cleft palate and flat nose, are seen in 16%. Moderate defects, including midface hypoplasia and moderate hypotelorism, occur in 14%. Mild malformations, including single maxillary central incisors and iris colobomas, are seen in 36%.

Children with HPE experience many medical and neurologic problems, including mental retardation, epilepsy, weakness, spasticity, dystonia, choreoathetosis, and endocrine disorders, particularly diabetes insipidus [11,12]. Developmental disability affects virtually all patients with HPE. The degrees of disability and neurologic problems generally correlate with the severity of the brain malformation. Abnormalities of

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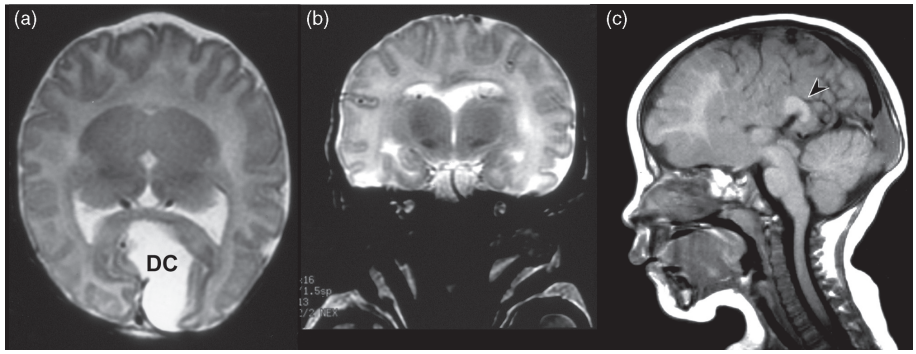


Figure 22.3 MRI of a child with semilobar holoprosencephaly. (a) Axial T2-weighted image shows that posterior portions of the hemispheres are well separated, but the anterior cerebral hemispheres are not cleaved. A dorsal cyst (DC) is present. The posterior horns of the lateral ventricles are well formed. The frontal horns are poorly developed (b), and posteriorly, there is a monoventricle demonstrated on a coronal T2-weighted image. (c) A sagittal T1-weighted image of another patient demonstrates that the splenium of corpus callosum is formed (arrowhead), but the genu and body are not developed (arrowhead). This latter finding is highly suggestive of semilobar or lobar HPE.

tone and movement are present in all forms of HPE [11–13]. The pituitary gland may be absent, dysplastic, or heterotopic. Diabetes insipidus, owing to posterior pituitary dysfunction, is a common problem in HPE. Anterior pituitary dysfunctions, such as growth hormone deficiency, hypocortisolism, and hypothyroidism, are also seen, but less frequently.

HPE is etiologically heterogeneous, and both environmental and genetic causes have been identified. *Chromosomal anomalies* including trisomies (13 and 18), duplications, deletions (e.g., 18p), and ring arrangements have played an important role in HPE. Approximately 40% of live births with HPE have a chromosomal anomaly, and trisomy 13 accounts for over half these cases [6]. Of infants born with trisomy 13, 70% have holoprosencephaly [14]. The prognosis in HPE is much worse for those with cytogenetic abnormalities, with only 2% surviving beyond 1 year, compared with 30–54% for those without cytogenetic anomalies [6]. Familial HPE also occurs, with both autosomal dominant and autosomal recessive inheritance.

Several multiple-malformation syndromes have been associated with HPE, with as many as 25% of HPE patients having a recognizable monogenic syndrome [6,15]. These include pseudotrisomy 13 and Pallister-Hall, Meckel, and velocardiofacial syndromes. In addition, there is an increased incidence of HPE (~5%) in patients with Smith-Lemli-Opitz syndrome, in which affected children have a defect in 7-dehydrocholesterol reductase, the enzyme that catalyzes the final step of cholesterol biosynthesis. Defective cholesterol synthesis may have a role in the pathogenesis of HPE through the sonic hedgehog (SHH) signaling pathway because cholesterol is required for activation of SHH.

Mutations in several genes have been associated with HPE in humans: *SHH, PATCHED1* (*PTCH*), *TGIF, TDGF1, ZIC2, SIX3, GLI2, FAST1*, and *DISPATCHEDA* [16]. Two of these genes (*SHH* and *PTCH*) encode members of the SHH signaling pathway, which regulates ventral development in both the forebrain and spinal cord. Human mutations have been discovered in *SHH* [17], which encodes a secreted signaling ligand localized at early stages to ventral domains in the developing neural tube, and *PATCHED1* (*PTCH*) [18], which encodes a receptor for *SHH*. The currently known mutations have been identified in only 15–20% of HPE cases in a cohort with normal karyotypes [16].

Maternal diabetes, including gestational diabetes, is a well-established risk factor [19]. A diabetic mother's risk of having a child with HPE is approximately 1%, a greater than 100-fold increase over that of the general population. Prenatal exposures to alcohol, antiepileptic medications, retinoic acid, and cytomegalovirus infection have also been reported in cases of HPE.

Absence of Septum Pellucidum and Septo-optic Dysplasia

Absence of the septum pellucidum (ASP) is associated with various congenital brain malformations, including HPE, septo-optic dysplasia (SOD), schizencephaly, and agenesis of the corpus callosum. One study of fetal ultrasounds indicated that the two most common

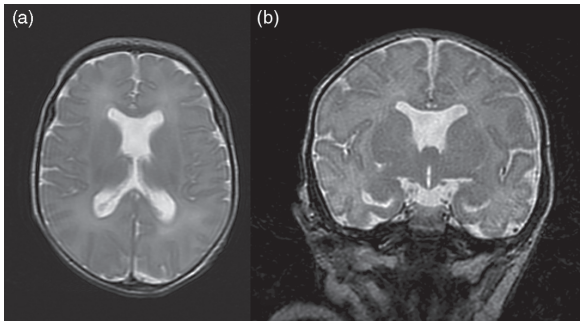


Figure 22.4 (a) Axial T2-weighted and (b) coronal T2-weighted MRIs of a term infant with isolated absence of septum pellucidum. The corpus callosum was intact.

conditions associated with ASP were HPE (including the MIH variant) and hydrocephalus that causes a disruption of the septum pellucidum [20]. When seen in isolation with an intact corpus callosum (Figure 22.4), it may indicate a syndrome of SOD. SOD is a midline anomaly characterized by a triad of (1) ASP, (2) optic nerve hypoplasia, and (3) pituitary dysfunction. It is a rare condition with an estimated incidence of 1–10/100,000. SOD has a wide range of clinical presentations, including decreased visual acuity (from optic nerve hypoplasia), endocrine dysfunctions (from anterior pituitary maldevelopment), cholestatis, and mental retardation/developmental delay [20]. SOD may also be associated with cortical malformations (polymicrogyria and schizencephaly), HPE, callosal agenesis or hypogenesis, and hippocampal abnormalities. Known genetic etiologies contribute to only a small percentage of cases; a small number of patients with SOD have mutations of homeobox gene *HESX1* or transcription factor gene *SOX2*.

Disorders of Cell Proliferation and Neuronal Generation

Microcephaly and Microencephaly

Microcephaly is a term that applies to heads in which the circumference is smaller than 2 standard deviations (SD) below the mean for age and sex, although some studies have used smaller than 3 SD. The measurement should be corrected for prematurity and intrauterine growth retardation. *Microcephaly* (small skull) goes hand in hand with *microencephaly* (small brain) and can be associated with mental retardation.

In primary microcephaly, no other malformations are present. It may be familial or associated with a specific genetic syndrome (microcephaly vera). In autosomal recessive primary microcephaly (MCPH), individuals are born with a small brain, which subsequently grows but always remains relatively small, whereas the rest of the body grows normally [21]. MCPH is thought to be a disorder of neuronal proliferation (mitosis) resulting in a reduced number of neurons. Many genes have been identified for this disorder, including *ASPM* and *MCPH1*. In severe primary microcephaly, MRI may show a simplified gyral pattern.

Secondary microcephaly results from a large number of insults that affect the fetus in utero or in infancy during periods of rapid brain growth (first 2 years of life). Chromosomal and gene aberrations are often associated with small brains. Environmental factors include prenatal radiation (during the first two trimesters), drugs, other chemicals, and congenital infections including rubella, cytomegalovirus, toxoplasmosis, and type 2 herpes simplex virus (HSV). In utero ischemia to the developing brain also can lead to secondary microcephaly.

Megalencephaly

The terms *megalencephaly* and *macrencephaly* are synonymous and imply large brains, in contrast to the term *macrocephaly*, which denotes a large head from various causes (e.g., hydrocephalus). In megalencephaly, there is diffuse neuroepithelial proliferation and an increased number of cells in the brain. To standardize the definition, the head circumference must be over 2.5 SD above the mean for age and sex.

Megalencephaly may be primary. Familial megalencephaly has an autosomal dominant inheritance, and affected individuals have normal or near-normal intelligence. There are a number of syndromes associated with megalencephaly, including Soto syndrome (cerebral gigantism), fragile-X syndrome, autism, and various neurocutaneous disorders. Mutations of *PTEN* involved in the PI3 K-AKT-mTOR pathway have been identified in various megalencephaly syndromes, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and megalencephaly with autism [22]. Numerous storage diseases, such as Tay–Sachs disease, Canavan disease, and Alexander disease, are associated with megalencephaly, which is not usually present at birth but develops during infancy and beyond.

The clinical manifestations depend on the etiology. Familial megalencephalies can be associated with learning disabilities, neurologic abnormalities, and epilepsy.

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Hemimegalencephaly

Hemimegalencephaly (HME) is a rare malformation of cortical development in which there is unilateral enlargement of one side of the brain. Diffuse pachygyria and areas of polymicrogyria may be present in the affected hemisphere [23]. It may affect one hemisphere or some of its lobes with macroscopic enlargement due to abnormal proliferation of anomalous cells similar to those in focal cortical dysplasia type 2. Mutations of the PI3 K-AKT-mTOR pathway have also been implicated in HME [22]. Clinical manifestation of HME is dominated by early onset refractory epilepsy but also includes developmental delay and hemiparesis. HME can occur alone or in association with neurocutaneous disorders such as linear sebaceous nevus syndrome, hypomelanosis of Ito, and neurofibromatosis. Surgical hemispherectomy is the most effective treatment for medically refractory epilepsy.

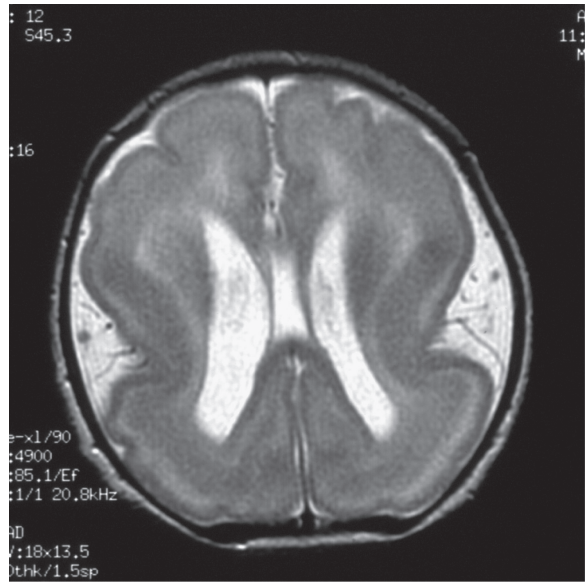


Figure 22.5 Nine-day-old male infant with type 1 lissencephaly. Axial T2-weighted MRI shows a smooth cortical surface (agyria/lissencephaly) that is prominent posteriorly. Frontal pachygyria is present. The Sylvian fissure is poorly formed.

Disorders of Neuronal Migration

Neuronal migration is characterized by an inside-out migration pattern into six distinct layers in which the successive waves of newer postmitotic neurons in the ventricular zone migrate past the older neurons to occupy a more exterior layer in the neocortex [21]. Neuronal migration begins at days 40–41 of gestation. Disturbances in the migration process will cause failure of neurons to reach their intended destination in the cerebral cortex and lead to disorganization of the cortical cytoarchitecture. This abnormality may be focal or diffuse.

Failure of neurons to leave the ventricular zone would result in periventricular heterotopias. Failure to complete their migration into the cortex would cause lissencephaly. Finally, failure of a subpopulation of neurons to complete their migration while others finish their migration could result in nodular or band heterotopias [23]. An updated classification of the cortical malformations based on genetic knowledge and developmental stages has been published by Barkovich et al. [24].

Lissencephaly/Agyria and Pachygyria

Lissencephaly is defined as a smooth brain without gyri. *Pachygyria* describes a reduced number of broad and flat gyri, shallow sulci, and fewer than normal foldings of the cortex. Both lissencephaly and pachygyria may be seen in the same brain. Affected infants have failure to thrive, microcephaly, marked developmental delay, and severe epilepsy.

Type 1 Lissencephaly

The brain is small in type 1 lissencephaly, with only the primary and sometimes a few secondary gyri (Figure 22.5). There is lack of opercularization, resulting in abnormal Sylvian fissure formation. The cortex is thick, with white matter forming a thin rim along the ventricles. Twelve gene mutations account for approximately 90% of cases, the most common being a mutation of the *LIS1* gene. In Miller-Dieker syndrome, there are also dysmorphic facial features and deletion of 17p13.3, a region that includes the *LIS1* gene. A mutation in the doublecortin gene *DCX* also causes lissencephaly in males. For a review, see Kerjan and Gleeson [25].

Cobblestone Lissencephaly (Type 2)

Type 2 lissencephaly is also known as *cobblestone lissencephaly* because the smooth cortex has a granular surface and is covered with meninges that are thickened [23]. Abnormal migration of neurons through the defective glia limitans and into the leptomeningeal space results in disruption of cortical organization. This is seen in a group of rare autosomal recessive disorders characterized by

congenital muscular dystrophy, severe brain malformations, and ocular abnormalities. Walker-Warburg syndrome, which is the most severe phenotype of cobblestone lissencephaly (Figure 22.1), can result from mutations in Fukutin (*FCMD*), Fukutin-related protein (*FKRP*), *POMT1*, or *POMT2* [21]. Fukuyama congenital muscular dystrophy resulting from different *FCMD* mutations also is associated with cobblestone lissencephaly.

Heterotopias

Heterotopia is a term used to describe ectopic neurons in white matter or neuronal malorientation. Periventricular heterotopias are abnormal collections of neurons in the subependymal region. They may be clinically silent or associated with epilepsy and neurodevelopmental dysfunction. Bilateral periventricular nodular heterotopia (BPNH) is an X-linked dominant disorder that is caused by a mutation in the filamin gene *FLNA*.

Subcortical band heterotopias are also known as *laminar heterotopias* or *double cortex*. Most cases in females are due to a mutation in the doublecortin gene *DCX*, which in males causes type 1 lissencephaly.

Abnormal Cortical Organization or Late Migration

Polymicrogyria

Polymicrogyria is characterized by an abundance of small gyral convolutions. The etiology is not well understood. It may be a genetic neuronal migration disorder or due to midcortical ischemic laminar necrosis affecting primarily the fifth cortical layer. The onset of the disorder is after 20 weeks (fifth month of gestation). It may be associated with genetic and chromosomal disorders. *Bilateral perisylvian syndrome* (or anterior operculum syndrome) consists of bilateral opercular abnormalities that include polymicrogyria visible on MRI. Patients have dysarthria, dysphagia, and pseudobulbar palsy.

Schizencephaly

Schizencephaly is characterized by unilateral or bilateral clefts within the cerebral hemispheres in which the borders of the cleft are surrounded by abnormal heterotopic gray matter, particularly *microgyria*. On MRI, the cleft has the appearance of an irregular surface with polymicrogyria. Because this disorder is thought to be due to an ischemic lesion of the cerebrum, it is discussed later in the section on encephaloclastic lesions.

Cortical Dysplasia and Microdysgenesis

Cortical microdysgeneses are microscopic abnormalities of cortical arrangement that may lead to epilepsy and other neurodevelopmental syndromes. Focal cortical dysplasias are larger than microdysgenesis and can usually be detected by high-resolution MRI. Focal cortical dysplasia are classified into three major types [26]. Type I involves disruption of cortical architecture due to radial or tangential migration of neurons. Type II is marked by the presence of dysmorphic neurons with or without balloon cells. Type III refers to various dysplasias associated with hippocampal sclerosis. Surgical resection of the dysplasias in affected patients may lead to significant improvement in seizure control.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by cortical tubers, subependymal nodules, and retinal hamartomas. Children often develop epilepsy and neurodevelopmental delay and may also have involvement of other organs (cardiac rhabdomyomas and renal angiomyolipomas and cysts). Mutations in the *TSC1* (hamartin) and *TSC2* (tuberin) genes leading to activation of the mTOR pathway lead to tuber formation in TSC [27]. The diagnosis can be made clinically based on neurocutaneous features (hypopigmented macules, facial angiofibromas, or a shagreen patch), neuroimaging findings, and clinical picture. Prenatal diagnosis is sometimes made on fetal MRI when there is a high index of suspicion for this disorder. Mothers carrying a fetus with TSC are often referred to a prenatal diagnostic center because of detection of a cardiac tumor (usually rhabdomyomas) on prenatal ultrasound. When images of the fetal brain are carefully examined, subependymal nodules can be seen.

Combined and Overlapping Cerebral Malformations

Agenesis of the Corpus Callosum

The corpus callosum is a fiber-tract bridge that connects neurons between the two hemispheres. Its

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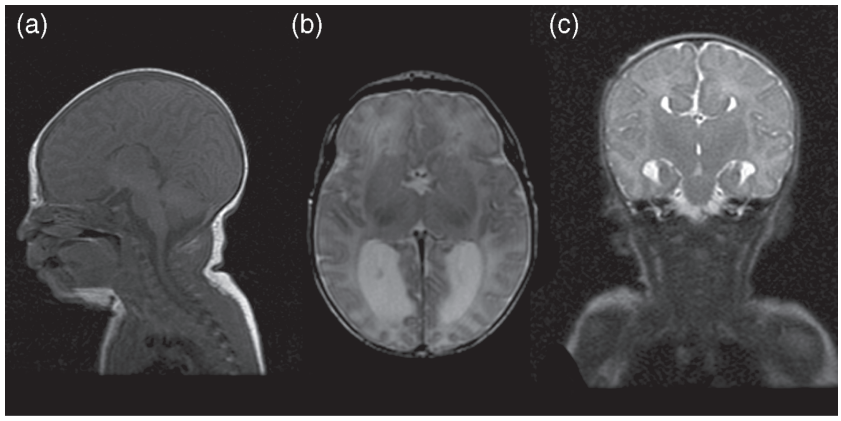


Figure 22.6 MRI of a term newborn with isolated agenesis of the corpus callosum. (a) Sagittal T1-weighted image shows absence of the corpus callosum and cingulate gyrus. There is radial orientation of the mesial gyri. (b) T2-weighted axial image shows dilated posterior horn of the lateral ventricles, colpocephaly. (c) T2-weighted coronal image shows absence of callosal fibers across the midline and continuity of the third ventricle with the interhemispheric fissure superiorly.

function is to coordinate communication of information between the left and right cerebral hemispheres. The corpus callosum begins to develop from the lamina reunions of His between 6 and 8 weeks of gestation. The last of the commissural fibers cross at 18–20 weeks [28].

Agenesis of the corpus callosum (ACC) can result from many causes, including infections, environmental exposures, inherited errors of metabolism, and genetic syndromes. ACC occurs in a large number of congenital syndromes and may also be associated with specific chromosomal abnormalities such as trisomy 8 and 18, subtle copy-number variations, and single-gene mutations [29]. Some ACC syndromes have autosomal or X-linked inheritance but do not have identified gene defects. The prevalence of ACC is between 0.1% and 0.7% in the general population and 2.3% in the developmentally disabled population [28].

The agenesis may be complete or partial. When partial, the defect is usually in the posterior portion of the corpus callosum. When the agenesis is complete, the cingulate gyrus fails to form, and a radial orientation of the mesial gyri is seen on sagittal MRI (Figure 22.6). The enlargement of the occipital horns of the lateral ventricles associated with ACC is known as *colpocephaly*. Although the lateral ventricles in colpocephaly appear enlarged (*ventriculomegaly*), they should not be mistaken for hydrocephalus. "True" callosal agenesis should be distinguished from secondary agenesis, which is associated with major brain malformation of the embryonic forebrain such as holoprosencephaly.

Children with isolated ACC may appear and function normally. However, as they grow older, they often function in the low-borderline to normal range. With testing, difficulties in higher cortical function, language, perception, behavior, and integration of hemispheric functions may be demonstrated. Some patients have mental retardation, cerebral palsy, and epilepsy. ACC may be associated with several other CNS malformations. The most common coexisting malformations include Dandy-Walker malformation, interhemispheric cysts, hydrocephalus, midline lipoma of the corpus callosum, and Chiari II malformation. Cortical anomalies associated with ACC include heterotopias, microgyria, and pachygyria. When other CNS malformations are associated with ACC, the outcomes are often less favorable than in the isolated type.

MRI is the neuroimaging technique of choice because the brain can be imaged in three orthogonal planes. MRI tractography can help to identify aberrant connections. This provides a better assessment of the extent of corpus callosal hypogenesis. In fetal MRI, direct visualization of the corpus callosum is possible by 20 weeks of gestation. Mothers with suspected ACC are often referred for fetal MRI because of lack of visualization of the cavum septum pellucidum on fetal ultrasound. The fetal MRI offers the ability to assess for associated CNS anomalies, and in one study using fetal MRI, additional anomalies were seen in over half the cases [28]. The additional malformations included diffuse or focal cortical malformations, delayed sulcal development, dysplastic deep gray nuclei, and brainstem anomalies.

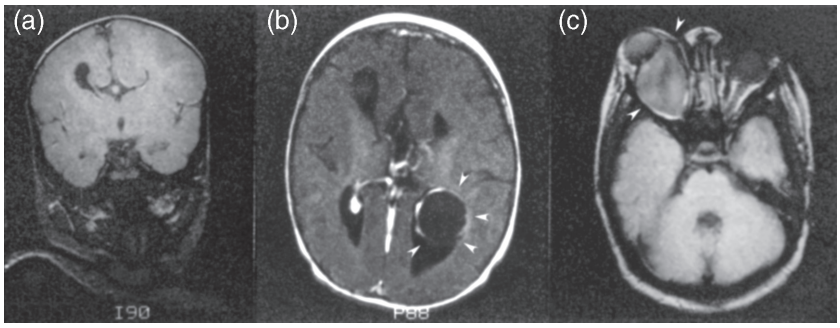


Figure 22.7 MRI images of an infant girl with Aicardi syndrome demonstrate absence of the corpus callosum on (a) T1-weighted coronal and (b) axial images. The arrowheads in panel (b) outline an intraventricular cystic mass. (c) A retro-orbital mass (optic nerve coloboma) is noted (arrowheads) in the axial image through the orbits.

Aicardi Syndrome

Aicardi syndrome (AS) is a complex disorder defined as a triad of abnormalities: (1) total or partial agenesis of the corpus callosum, (2) chorioretinal "lacunae," and (3) infantile spasms (Figure 22.7) [30]. Other associated findings include eye defects (colobomas of the optic disc), cortical polymicrogyria, periventricular heterotopia, and cysts of the choroid plexus and/or the pineal or periventricular interhemispheric regions. Other brain abnormalities, such as intracranial cysts or tumors, represent a specific malformation complex of AS. It is an X-linked dominant disorder that affects and is lethal in males with only a single X chromosome.

Recognition of this complex on fetal MRI is sometimes possible due to the associated brain and eye malformation. This is important because AS carries a much more severe prognosis than that of isolated ACC.

Encephaloclastic Lesions

A number of conditions can lead to destruction of the fetal brain that, in turn, will develop into a congenital brain malformation. These conditions include maternal hypoxia, congenital infections, toxins, and pregnancies at risk of brain damage [31]. Examples of cerebrovascular causes of ischemia to the brain include cord accidents, twin-to-twin transfusion, embolic events, and cocaine exposure. During fetal neuroimaging, one usually observes the fetal responses to injuries that are chronic in nature. A mild form of a chronic response may be slight ventriculomegaly with irregular ventricular wall or nodular and irregular germinal matrix [31]. White matter gliosis and ependymal abrasions are not visible on fetal MRI but can be found at autopsy. A more severe response may result in parenchymal cystic cavities or hydranencephaly. Calcifications and malformation of the cortex are most likely seen in congenital infections but also can be seen in antenatal hypoxic-ischemic injury.

Hydranencephaly

Hydranencephaly is considered to be an encephaloclastic lesion of the brain in which most of the cortical plate and hemispheric white matter has been damaged or resorbed. The cerebral hemispheres are replaced by thin-walled sacs containing CSF (Figure 22.8). Remnants of a thin cortical rim may be present. The thalami, brainstem, and cerebellum are usually relatively preserved. The meninges are intact, and the skull appears normal. The presence of the falx is important in distinguishing hydranencephaly from alobar holoprosencephaly.

Hydranencephaly develops as a result of an in utero destructive process of a brain that has been previously normally formed. The insult to the brain occurs at a time when the brain reacts by liquefaction necrosis (weeks 20–27). This insult could result from ischemia, hemorrhage, infection, or vasculopathies. Infectious causes such as toxoplasmosis, syphilis, mucormycosis, cytomegalovirus, and herpes simplex virus have been found in some cases. The vascular insult must occur within a relatively narrow window of time to produce hydranencephaly. Similar injuries after 27 weeks tend to cause multicystic encephalomalacia with astroglial reaction.

Because the injury occurs late in gestation, infants can appear completely normal at birth. Transillumination of the head results in a striking positive sign. Newborns may develop epilepsy, extensor rigidity, and respiratory failure. The outcome is unfavorable, with global delays, but some children may live many years with these deficits.

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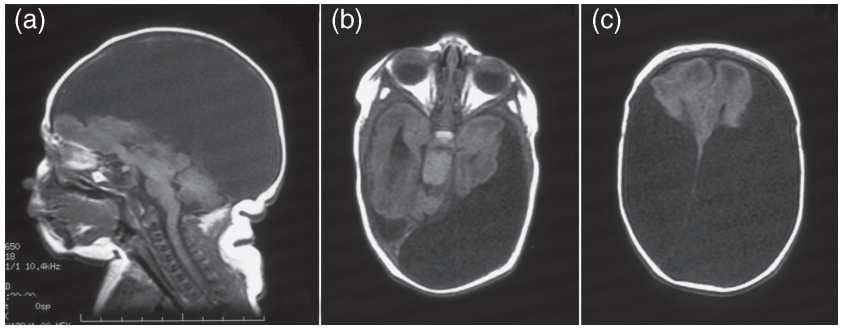


Figure 22.8 T1-weighted MRI images of 1-day-old newborn female with hydranencephaly and history of twin-to-twin transfusion syndrome. Midsagittal image shows that most of the cerebral hemispheres are replaced by a large CSF-containing sac. (a) There is preservation of brainstem, cerebellum, and inferior frontal lobes. The cranial vault is intact. (b) Low axial image shows relative preservation of the temporal lobes with enlargement of the temporal horns. (c) High axial image shows preservation of part of the frontal lobes and presence of a falx.

Schizencephaly

Schizencephaly is a brain malformation that is characterized by infolding of the cortical gray matter along a hemispheric cleft near the primary cerebral fissures. The cleft traverses the full thickness of the hemisphere, connecting the ventricle to the subarachnoid space. The clefts are often bilateral and lined with an irregular surface and polymicrogyria. Schizencephaly is classified as closed lip or separated lip depending on whether or not there is an open gap between the edges of the cleft (Figure 22.9). Frequently, patients with schizencephaly have severe mental retardation and refractory epilepsy, language delay, and motor dysfunction.

The etiology of schizencephaly is not well understood. Typically, schizencephaly occurs sporadically, accompanying an insult to the brain, often following hypoperfusion or disruption of blood flow in the developing fetus. The injury is thought to occur before 26 weeks of gestation. Because of limited astroglial response in early fetal life, the necrotic tissue becomes reabsorbed and leaves fluid-filled cavities. Genetic factors are likely to play a role in some cases of schizencephaly. A small percentage of cases of schizencephaly occur in familial clusters [32]. Familial and sporadic cases of schizencephaly have been associated with mutations in the homeobox gene *EMX2* [33].

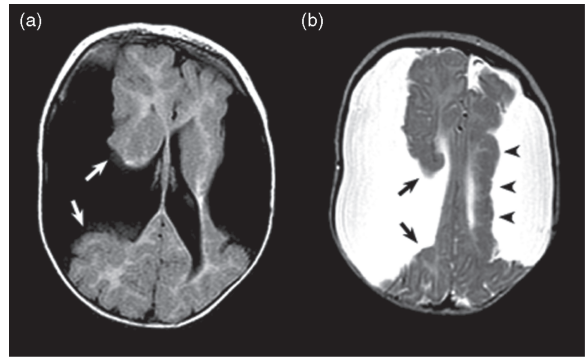


Figure 22.9 (a) Axial fluid inversion recovery and (b) T2-weighted MRI images obtained at 7 months of an infant who at birth had a hamartomatous umbilical cord mass containing multiple vessels. The cord mass is presumed to have caused hypoperfusion. The images show separated-lip schizencephaly in the right hemisphere with a cleft that is lined by gray matter (arrows). The cleft communicates with the right lateral ventricle. The cortex around the cleft appears dysplastic. In the left hemisphere, the cleft does not communicate with the lateral ventricle (b). The cortex lining the cleft appears polymicrogyric (arrowheads).

Porencephaly

Porencephaly is a term used for cavities within the cerebral hemispheres that communicate with the subarachnoid space (*external* porencephaly), the ventricle (*internal* porencephaly), neither (*central* porencephaly), or both. There is an overlap between porencephaly, hydranencephaly, and schizencephaly. At times, porencephaly and schizencephaly can coexist in the same brain. Porencephaly can be due to a developmental defect or acquired lesions, including in utero infarction of tissue. Injury occurring during late second trimester (24–26 weeks) leads to encephaloclastic porencephalies with smooth walls but lacking gray matter–lined clefts. Injury during the third trimester is likely to result in encephalomalacia with shaggy-walled cavities and astroglial reaction [30]. Children with these lesions may have hemiparesis, focal seizures, or mental retardation.

Defects of Midbrain and Hindbrain Organization and Patterning

Dandy-Walker Malformation

The classic Dandy-Walker malformation (DWM) includes three features: (1) cerebellar vermis agenesis

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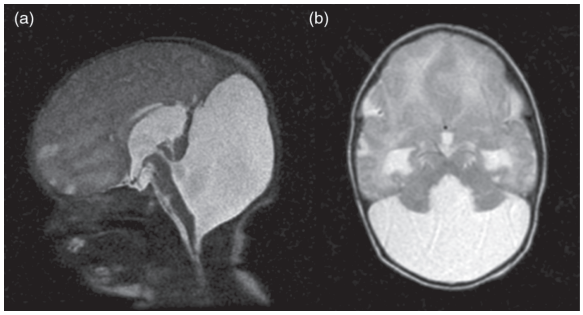


Figure 22.10 (a) Midsagittal and (b) axial MRI images of Dandy-Walker malformation with agenesis of the vermis, elevated tentorium, and enlargement of the posterior fossa with a fluid-filled cyst that communicates with the fourth ventricle. The brainstem also appears dysplastic, and the anterior hemispheres are not separated, indicating coexisting holoprosencephaly.

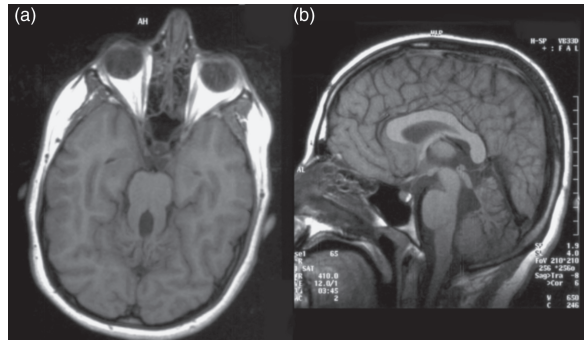


Figure 22.11 Eighteen-year-old female with Joubert syndrome. (a) Axial T1-weighted MRI at the level of midbrain shows typical molar tooth anomaly of the midbrain and cerebellar peduncles. (b) Midsagittal T1-weighted image shows expansion of the fourth ventricle.

(complete or partial), (2) cystic dilation of the posterior fossa communicating with the fourth ventricle, and (3) abnormally high tentorium with enlargement of the posterior fossa (Figure 22.10). DWM is thought to occur due to arrest of vermian development, failure of adequate fenestration of the fourth ventricular outflow foramina, or both, leading to an enlarged posterior fossa cyst and uplifted and compressed vermis [34]. Pathologically, DWM is sometimes, but not always, associated with atresia of the foramina of Luschka or Magendie. The incidence is 1/25,000–30,000 births.

Children with DWM often have motor delay, hypotonia, and mental deficiency [34]. Clinical presentation also depends on the severity of the associated hydrocephalus and other brain malformations that occur in over half the patients. These anomalies include microcephaly, encephalocele, syringomyelia, gyral malformation, and ACC. Total or partial absence of the corpus callosum is seen is 60%. They may also have a variety of extracerebral anomalies.

DWM may be seen in genetic disorders (e.g., Meckel syndrome), chromosomal disorders, or sporadic defects (e.g., holoprosencephaly). Other causal associations include environmental toxins (e.g., rubella, alcohol) or multifactorial etiology (e.g., congenital heart defect, neural tube defects). Some cases of DWM have been linked to heterozygous loss of *ZIC1* and *ZIC4* genes in individuals with a 3q2 deletion [35].

Cerebellar Vermis Hypoplasia

Several terms are used for disorders of cerebellar vermis hypoplasia. The *Dandy-Walker variant* is an older term that consists of (1) variable hypoplasia of the cerebellar vermis that is rotated and (2) absence of elevated tentorium and enlargement of the posterior fossa. *Inferior vermian hypoplasia* is a more recent, preferred term that describes similar abnormalities. The severity of the neurodevelopmental problems associated with the cerebellar vermian hypoplasia may be less than those of classic DWM, but outcome depends on the presence or absence of associated anomalies [36]. Mega-cisterna magna consists of a large cisterna magna without cerebellar abnormalities, and it seems to carry a more benign prognosis.

Joubert Syndrome

Joubert syndrome (JS) is an autosomal recessive disorder characterized by the *molar tooth malformation*, which is a complex brainstem malformation of hypoplasia of the vermis, thickened and elongated superior cerebellar peduncles, and a deepened interpeduncular fossa that is apparent on axial MRI (Figure 22.11) [37]. JS presents with neonatal hypotonia and neonatal tachypnea/apnea. As children get older, they may have psychomotor retardation, ataxia, nystagmus, and oculomotor apraxia.

Molar tooth malformation has been reported in several distinct syndromes that are known collectively as *JS-related disorders*. The phenotype includes the neurologic features of JS plus variable multiorgan involvement (primarily retinal dystrophy and nephronophthisis). Over 20 causative genes have been identified. These genes encode for proteins of the primary cilium or its apparatus [37].

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Pontocerebellar Hypoplasia

Pontocerebellar hypoplasia (PCH) is a heterogeneous group of inherited disorders characterized by prenatal onset of microcephaly and hypoplasia of the cerebellum, pons, and olivary nucleus [38]. PCH types 1 and 2 are autosomal recessive disorders. In type 1, spinal anterior horn cells undergo degeneration, leading to hypotonia, muscle atrophy and arthrogryposis. Type 2 is notable for chorea, dystonia, and progressive cortical atrophy (with microcephaly). Oromotor, respiratory, and swallowing difficulties are noted in the newborn period. Motor and intellectual disabilities are severe, and epilepsy is frequent. Several other types of PCH in addition to types 1 and 2 have been classified and are reviewed by Rudnik-Schöneborg et al. [38].

Hydrocephalus

Hydrocephalus has been defined in many ways, and clinicians are familiar with the terms *communicating* versus *noncommunicating* (depending on whether the CSF flow is contiguous from the ventricular system to the subarachnoid spaces). When cerebral hypoplasia or atrophy is present with enlarged ventricles, the term *hydrocephalus ex vacuo* is often used. When hydrocephalus results in ventricular enlargement, there is centifugal atrophy of the white matter and thinning of the cortical mantle. In infancy, clinical manifestations of hydrocephalus include macrocephaly, accelerated rate of head growth, bulging fontanel, separated cranial sutures, and downward deviation of the eyes (*setting-sun sign*). The infants may display irritability, lethargy, vomiting, and papilledema. After closure of sutures, the intracranial pressure may increase rapidly.

Communicating Hydrocephalus

In communicating hydrocephalus there is free communication between the cerebral ventricles and the lumbar subarachnoid space. The problem arises from impaired CSF reabsorption due to arachnoiditis or defective reabsorption into cerebral venous sinuses. Etiologies include earlier meningitis or other meningeal inflammation, meningeal infiltration, prior subarachnoid hemorrhage, intraventricular hemorrhage, and sinovenous thrombosis.

Noncommunicating Hydrocephalus

In noncommunicating (obstructive) hydrocephalus there is a block in the flow of CSF within the ventricular system or at the exit foramina. CSF accumulates proximal to the block and causes dilation of the proximal ventricles. This type tends to produce higher intracranial pressures and a more acute clinical picture than communicating hydrocephalus.

Common causes of noncommunicating hydrocephalus include aqueductal stenosis, congenital malformation, congenital infections (toxoplasmosis and cytomegalovirus), ependymitis, intraventricular hemorrhage, compression, Dandy-Walker malformation, Chiari II malformation (medulla and cerebellar tonsils displaced downward through the foramen magnum), and neoplasm or other mass obstructing the flow of CSF.

Genetic forms of hydrocephalus exist. The X-linked recessive form of inherited hydrocephalus is often accompanied by aqueductal stenosis; it results from mutations in the *L1CAM* gene [39]. Affected males demonstrate enlargement of the lateral and third ventricles.

Vascular Malformations

Malformations involving blood vessels include arteriovenous malformations, malformations of the vein of Galen, hemangioblastoma of the cerebellum, congenital aneurysms of the circle of Willis, and anomalies of the carotid artery system. Of these, vein of Galen malformations are most likely to present in the newborn period. The other vascular malformations will not be discussed here.

Vein of Galen Malformations

In this malformation, the vein of Galen is dilated, and branches of the posterior cerebral, superior cerebellar, and middle cerebral arteries communicate with it (Figure 22.12). When the vein of Galen enlarges, it can compress the quadrigeminal plate and aqueduct, causing hydrocephalus. Because of the arterial-venous shunting to the malformation, bypassing the capillary network, ischemic damage can occur to cerebral tissue.

In the neonatal period, infants with cyanosis and respiratory distress who are in congestive heart failure can have blood abnormally shunted to the venous system by this malformation. This *steal phenomenon* may cause cerebral ischemia. Intracranial bruits, seizures, and intracranial hemorrhage also may be present. In contrast, patients presenting during infancy

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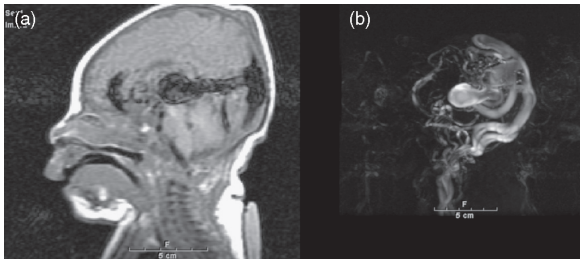


Figure 22.12 One-day-old boy with vein of Galen malformation. (a) Sagittal T1-weighted MRI shows a dilated, round Galenic varix communicating posteriorly through the falx to the venous sinuses. (b) 2D phase-contrast MR venogram shows the large midline Galenic varix and vein draining into dilated venous sinuses.

usually have progressive hydrocephalus along with intracranial bruits and seizures. Upgaze paralysis is frequent, and proptosis may be found. Subarachnoid hemorrhage occurs in one-third of cases.

Cranial ultrasound with Doppler studies in the newborn period can be diagnostic. MRI with magnetic resonance angiogram and venogram will delineate the extent of the malformation. Prenatal detection with fetal ultrasound and MRI has also been reported. These are usually treated with endovascular techniques (embolization) by an interventional radiologist or clipping of feeders by a neurosurgeon. Hydrocephalus often requires ventriculoperitoneal shunting [40].

Diagnostic Approaches

Modern fetal ultrasonography has facilitated the ability to detect a large variety of CNS malformations in utero. The widespread use of fetal ultrasonography makes it also more likely that severe malformations will be detected early (by 20 weeks of gestation) and that appropriate counseling can be given to the parents about management of the pregnancy. In addition, when anomalies of the CNS are detected by fetal ultrasound, fetal MRI has increased our ability to provide a more accurate diagnosis of the malformation [41,42]. Fetal MRI is becoming an increasingly important tool in diagnosis and management.

There are limitations to the resolution, however, even with fetal MRI. While it is relatively easy to detect overt anomalies such as severe hydrocephalus, agenesis of the corpus callosum, alobar or semilobar holoprosencephaly, anencephaly, and spina bifida, it is challenging at times to detect subtle lesions such as microdysgenesis, heterotopias, and gyral malformations. This is particularly true because the imaging is done on immature fetal brains, which are small, have poor gray-white matter signal contrast, and often have smooth-appearing cortical surfaces.

Neuroimaging studies after birth depend on the extent of prenatal imaging studies. If abnormalities are detected in the CNS on fetal ultrasound or MRI, then another MRI after birth may be indicated. This is not always the case; for example, in a neonate who has had isolated ACC diagnosed prenatally with fetal MRI and who is otherwise doing well in the newborn period, postnatal MRI can be deferred. If there are neurologic symptoms and signs, it may be worthwhile repeating the MRI because more subtle lesions that are associated with ACC may be easier to detect in a postnatal MRI. If the newborn has not had any prenatal studies, there are often other clinical indications as to why the neuroimaging study is being done. MRI is favored over CT because of its higher resolution, as well as its ability to scan in three orthogonal planes.

After a neuroanatomic diagnosis is made on the neuroimaging studies, it is important to determine whether the child has a genetic syndrome. Careful investigation for extracerebral malformations should be undertaken as well as a genetic evaluation. Consultation with neurologists, geneticists, ophthalmologists, and other specialists should be considered. High-resolution chromosome studies are also often carried out.

This chapter has highlighted several brain malformations, many of which have a genetic basis. With certain malformations, gene mutational analysis is appropriate. However, many of the malformations may be due to environmental causes. Thus it is important to ascertain a careful history of any complications during the pregnancy (e.g., drug exposure, infections, trauma, and bleeding) and to try to correlate the timing of those events, if any, with the stage of embryonic/fetal brain development. A careful evaluation of the placenta and cord may also provide clues to in utero encephaloclastic lesions.

Providing prognostic evaluation prenatally can be quite challenging. This is due in part to the lower resolution of neuroimaging studies in fetuses. The outcomes for many disorders, such as ACC, can be quite varied. Therefore, it is difficult to give a precise prognosis to expectant parents. After the birth, having postnatal MRI study information and clinical examination enables clinicians to provide a more specific diagnosis and precise prognosis.

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References

1. Elwood JM, Little J, Elwood JH. *Epidemiology and Control of Neural Tube Defects*. Oxford University Press, 1992.
2. Warkany J, Lemire RJ, Cohen MM. *Mental Retardation and Congenital Malformations of the Central Nervous System*. Chicago: Year Book, 1981.
3. Golden JA. Towards a greater understanding of the pathogenesis of holoprosencephaly. *Brain Dev* 1999; **21**: 513–21.
4. Matsunaga E, Shiota K. Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. *Teratology* 1977; **16**: 261–72.
5. Cohen MM. Perspectives on holoprosencephaly: Part III. Spectra, distinctions, continuities, and discontinuities. *Am J Med Genet* 1989; **34**: 271–88.
6. Croen LA, Shaw GM, Lammer EJ. Holoprosencephaly: epidemiologic and clinical characteristics of a California population. *Am J Med Genet* 1996; **64**: 465–72.
7. Rasmussen SA, Moore CA, Khoury MJ, et al. Descriptive epidemiology of holoprosencephaly and arhinencephaly in metropolitan Atlanta, 1968–1992. *Am J Med Genet* 1996; **66**: 320–33.
8. Bullen PJ, Rankin JM, Robson SC. Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the North of England. *Am J Obstet Gynecol* 2001; **184**: 1256–62.
9. Barkovich AJ, Quint DJ. Middle interhemispheric fusion: an unusual variant of holoprosencephaly. *AJNR Am J Neuroradiol* 1993; **14**: 431–40.
10. Simon EM, Hevner RF, Pinter JD, et al. The middle interhemispheric variant of holoprosencephaly. *AJNR Am J Neuroradiol* 2002; **23**: 151–5.
11. Plawner LL, Delgado MR, Miller VS, et al. Neuroanatomy of holoprosencephaly as predictor of function: beyond the face predicting the brain. *Neurology* 2002; **59**: 1058–66.
12. Barr M, Cohen MM. Holoprosencephaly survival and performance. *Am J Med Genet* 1999; **89**: 116–20.
13. Lewis AJ, Simon EM, Barkovich AJ, et al. Middle interhemispheric variant of holoprosencephaly: a distinct cliniconeuroradiologic subtype. *Neurology* 2002; **59**: 1860–5.
14. Taylor AI. Autosomal trisomy syndromes: a detailed study of 27 cases of Edwards' syndrome and 27 cases of Patau's syndrome. *J Med Genet* 1968; **5**: 227–52.
15. Olsen CL, Hughes JP, Youngblood LG, et al. Epidemiology of holoprosencephaly and phenotypic characteristics of affected children: New York State, 1984–1989. *Am J Med Genet* 1997; **73**: 217–26.
16. Ming JE, Muenke M. Multiple hits during early embryonic development: digenic diseases and holoprosencephaly. *Am J Hum Genet* 2002; **71**: 1017–32.
17. Roessler E, Belloni E, Gaudenz K, et al. Mutations in the human *Sonic Hedgehog* gene cause holoprosencephaly. *Nat Genet* 1996; **14**: 357–60.
18. Ming JE, Kaupas ME, Roessler E, et al. Mutations in *PATCHED-1*, the receptor for SONIC HEDGEHOG, are associated with holoprosencephaly. *Hum Genet* 2002; **110**: 297–301.
19. Barr M, Jr., Hanson JW, Currey K, et al. Holoprosencephaly in infants of diabetic mothers. *J Pediatr* 1983; **102**: 565–8.
20. Malinger G, Lev D, Kidron D, et al. Differential diagnosis in fetuses with absent septum pellucidum. *Ultrasound Obstet Gynecol* 2005; **25**: 42–9.
21. Carmichael J, Woods C. Genetic defects of human brain development. *Curr Neurol Neurosci Rep* 2006; **6**: 437–46.
22. Mirzaa GM, Poduri A. Megalencephaly and hemimegalencephaly: breakthroughs in molecular etiology. *Am J Med Genet C Semin Med Genet* 2014; **166C**: 156–72.
23. Guerrini R, Dobyns WB. Malformations of cortical development: clinical features and genetic causes. *Lancet Neurol* 2014; **13**: 710–26.
24. Barkovich AJ, Guerrini R, Kuzniecky RI, et al. A developmental and genetic classification for malformations of cortical development: update 2012. *Brain* 2012; **135**: 1348–69.
25. Kerjan G, Gleeson JG. Genetic mechanisms underlying abnormal neuronal migration in classical lissencephaly. *Trends Genet* 2007; **23**: 623–30.
26. Prayson RA. Classification and pathologic characteristics of the cortical dysplasias. *Childs Nerv Sys* 2014; **30**: 1805–12.
27. Lim KC, Crido PB. Focal malformations of cortical development: new vistas for molecular pathogenesis. *Neurosciences* 2013; **252**: 262–76.
28. Glenn OA, Goldstein RB, Li KC, et al. Fetal magnetic resonance imaging in the evaluation of fetuses referred for sonographically suspected abnormalities of the corpus callosum. *J Ultrasound Med* 2005; **24**: 791–804.
29. Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. *Brain* 2014; **217**: 1579–613.
30. Aicardi J. Aicardi syndrome. *Brain Dev* 2005; **27**: 164–71.

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31. Girard N, Chaumoitre K, Confort-Gouny S, et al. Magnetic resonance imaging and the detection of fetal brain anomalies, injury, and physiologic adaptations. *Curr Opin Obstet Gynecol* 2006; **18**: 164–76.
32. Haverkamp F, Zerres K, Ostertun B, et al. Familial schizencephaly: further delineation of a rare disorder. *J Med Genet* 1995; **32**: 242–4.
33. Brunelli S, Faiella A, Capra V, et al. Germline mutations in the homeobox gene EMX2 in patients with severe schizencephaly. *Nat Genet* 1996; **12**: 94–6.
34. Robinson AJ. Inferior vermian hypoplasia: preconception, misconceptions. *Ultrasound Obstet Gynecol* 2014; **43**: 123–36.
35. Grinberg I, Northrup H, Ardinger H, et al. Heterozygous deletion of the linked genes *ZIC1* and *ZIC4* is involved in Dandy-Walker malformation. *Nat Genet* 2004; **36**: 1053–5.
36. Ecker JL, Shipp TD, Bromley B, et al. The sonographic diagnosis of Dandy-Walker and Dandy-Walker variant: associated findings and outcomes. *Prenat Diagn* 2000; **20**: 328–32.
37. Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with "molar tooth." *Lancet Neurol* 2013; **12**: 894–905.
38. Rudnik-Schöneborg S, Barth PG, Zerres K. Pontocerebellar hypoplasia. *Am J Med Genet C Semin Med Genet* 2014; **166C**: 173–83.
39. Kanemura Y, Okamoto N, Sakamoto H, et al. Molecular mechanisms and neuroimaging criteria for severe L1 syndrome with X-linked hydrocephalus. *J Neurosurg* 2006; **105**: 403–12.
40. Alvarez H, Garcia Monaco R, Rodesch G, et al. Vein of Galen aneurysmal malformations. *Neuroimag Clin North Am* 2007; **17**:189–206.
41. Glenn OA, Barkovich AJ. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis, part 1. *AJNR Am J Neuroradiol* 2006; **27**: 1604–11.
42. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. *AJNR Am J Neuroradiol* 2006; **27**: 1807–14.

Chapter 23

Neurogenetic Disorders of the Brain

Jonathan A. Bernstein and Louanne Hudgins

Introduction

A number of genetic disorders share clinical features with fetal and neonatal brain injury. Although these conditions are individually rare, collectively they should be expected encounters in the neonatal intensive care setting. This chapter aims to familiarize readers with select inherited conditions that may clinically mimic neonatal brain injury. Most of the genetic conditions with clinical resemblance to neonatal brain injury discussed here present with hypotonia. Other syndromes can result in central nervous system (CNS) hemorrhage, findings similar to congenital infection, hydrocephalus, and central hypoventilation.

Conditions included in this chapter do not ordinarily present with overt malformations or minor anomalies. Such conditions should be readily distinguishable from the sequelae of fetal and neonatal injury. Several inborn errors of metabolism have clinical findings similar to hypoxic-ischemic encephalopathy (HIE). These disorders are reviewed in Chapter 34.

The following discussion of inherited disorders with features similar to those of fetal and neonatal brain injury begins with an overview of the clinical genetics evaluation and its rationale. Subsequently, the chapter is organized by clinical presentation: hypotonia, apparent congenital infection, intracranial hemorrhage, hydrocephalus, and central hypoventilation. Information regarding clinical findings, diagnostic approach, and management is provided. References are included for additional reading.

The Clinical Genetics Evaluation

The goal of the clinical genetics evaluation in the setting of suspected brain injury is to determine a specific diagnosis. Identifying the genetic etiology of a patient's condition enables the care team to better provide guidance regarding prognosis and recurrence risk. Additionally, a specific genetic diagnosis can have important implications for therapy.

In evaluating a patient for a genetic disorder, the clinician should draw on history, physical examination, clinical imaging, diagnostic procedures, and laboratory testing as indicated. Evaluating a patient from a genetics perspective additionally should include review of the family history in the form of a three-generation pedigree. This portion of the family history allows the identification of consanguinity as well as evidence of a specific mode of inheritance. Such information can have a significant impact on the differential diagnosis for a patient.

Determination of a diagnosis by molecular DNA studies is by its nature a more central component of genetic medicine than of many other specialties. The NIH Genetic Testing Registry (GTR), an online resource available at www.ncbi.nlm.nih.gov/gtr/, includes a database of laboratories able to perform the molecular and biochemical tests mentioned in this chapter and many others. The GeneReviews site at www.genereviews.org hosts regularly updated review articles on many of the conditions discussed in this chapter.

Conditions Presenting with Hypotonia

General Approach

Low muscle tone in the newborn period can result from an inborn or acquired defect at any or multiple levels of the neuraxis from brain to spine, to neuromuscular junction, to muscle. Hypotonia as a manifestation of vascular accident, infection, or other acquired cause is addressed elsewhere in this book. The diagnostic approach to the infant with a suspected genetic disorder can be stepwise or, alternatively, multiple investigations can be pursued in parallel. Efforts should be made to perform less invasive testing before undertaking procedures such as muscle or nerve biopsy, nerve conduction studies, or electromyogram, unless dictated otherwise by clinical decision making or genetic-counseling imperatives.

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Elements of the prenatal history relevant to the investigation of neonatal hypotonia include fetal movement, positioning, and amniotic fluid levels. History should also include noninvasive prenatal testing, first- and/or second-trimester biochemical and ultrasound screening, and diagnostic testing by amniocentesis or chorionic villus sampling, if performed.

Physical examination findings that are helpful in the diagnosis of hypotonic infants include involvement of facial musculature, presence and quality of deep tendon reflexes, and presence or absence and location of contractures and flexion creases. Hypotonia with increased reflexes suggests cortical or upper motor neuron disease. Hypotonia accompanied by weakness or decreased reflexes is consistent with lower motor neuron or muscular disease. Congenital contractures or decreased evidence of flexion creases, which form by 11–12 weeks of gestation, provide evidence of decreased movement in utero [1]. The presence of organomegaly should increase suspicion for a storage disease.

Eye examination, preferably performed by a pediatric ophthalmologist, can be useful in examining for anterior chamber defects, cataracts, and retinal anomalies. Radiologic evaluation should include ultrasound and preferably MRI to define brain anatomy. Ideally, these studies should be reviewed by a pediatric neuroradiologist with experience in evaluating congenital malformations. Abnormalities of the CNS can be seen in several of the conditions described in this chapter, but specific brain malformation syndromes such as holoprosencephaly and neuronal migration defects are covered elsewhere in this book.

Measurement of serum creatine kinase (CK) can be useful in identifying muscular disease. Laboratory screening for inborn errors of metabolism also should be considered in the evaluation of infantile hypotonia, as discussed in Chapter 34. Multiorgan dysfunction can be suggestive of metabolic disease. When sufficient clinical information has been gathered to narrow the differential diagnosis, molecular DNA studies or biochemical assays can be selected to confirm a diagnosis.

The following sections describe selected inherited conditions known to present in infancy with moderate to severe hypotonia. In planning a diagnostic workup, a central consideration is whether to initiate testing for a specific condition or to pursue a panel test or whole-exome sequencing.

The clinical availability of whole-exome sequencing [2–5] and next-generation sequencing panels allows the use of molecular diagnostic testing to pursue a specific diagnosis even when the differential diagnosis remains broad. This testing takes advantage of high-throughput sequencing methods that allow evaluation of thousands of genes simultaneously [6]. Exome sequencing as offered by many clinical laboratories offers near-comprehensive coverage of the coding regions of genes known to be associated with genetic disorders. Current disadvantages of whole-exome sequencing include relatively long test turnaround time (weeks to months), limited ability to detect whole or partial gene deletions, and relatively high cost. Patients or families being offered exome sequencing should be offered pretest genetic counseling because of the possibility of identifying genetic variants of unknown significance as well as findings unrelated to the primary indication for testing. Importantly and as noted later, several common causes of neonatal hypotonia are not readily diagnosed by currently available exome sequencing tests.

Table 23.1 presents the disorders in two diagnostic groups. Disorders in group 1 can generally be diagnosed without invasive testing; disorders in group 2 can sometimes be diagnosed without invasive testing but often require or are corroborated by biopsy or neurophysiologic studies. In the following text, conditions that can be diagnosed by less invasive methods are presented first, followed by those requiring more invasive testing such as muscle or nerve biopsy and nerve conduction studies or electromyogram. An overview of conditions presented can be found in Table 23.1.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetically complex disorder resulting from loss of paternal gene expression from an imprinted region on chromosome 15q11. For recent review, see Driscoll et al. [7]. Incidence is estimated to be approximately 1/25,000 [8,9]. Although most commonly associated with the features of compulsive eating, obesity, and behavioral difficulties that develop in childhood, manifestations of PWS are frequently evident at birth. Newborns with PWS often feed poorly and are hypotonic; there can be a history of decreased movement prenatally. Neonatal respiratory distress is generally not observed as a result of PWS. Physical findings of PWS evident in the newborn period include characteristic facial features such as bitemporal narrowing, almond-shaped eyes, and downturned mouth. Cryptorchidism is almost universal among affected males.

Table 23.1 Approach to Neonatal Hypotonia

Group	Condition	Characteristic clinical features	Inheritance	Initial diagnostics	Diagnosed by whole exome sequencing
1	Prader-Willi syndrome	Absence of respiratory distress, cryptorchidism in males	AD	Methylation study	No
	Spinal muscular atrophy I	Tongue fasiculations, arreflexia	AR	PCR for recurrent deletion	No
	Myotonic dystrophy type 1	Positive maternal history, respiratory distress	AD	PCR or Southern blot for trinucleotide repeat expansion	No
	MECP2-related encephalopathy	Poor head growth, central hypoventilation	XD	DNA sequencing	Yes
	Pompe disease	Cardiomegaly, elevated CK	AR	Dried blood spot or fibroblast enzyme assay	Yes
2	Syndromic congenital muscular dystrophies	Structural brain anomalies, elevated CK, eye anomalies	AR	DNA sequencing or muscle biopsy	Yes
	Congential myopathies	Often nonprogressive	Varies	Muscle biopsy	Yes
	Nonsyndromic congenital muscular dystrophies	Elevated CK	Varies	Muscle biopsy	Yes
	Congenital myasthenia	Fatiguability	Varies	Electromyography	Yes
	Congenital neuropathies	Arreflexia	Varies	Nerve conduction studies	Yes

Note: AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant.

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A number of diagnostic studies can be pursued in the evaluation of suspected PWS. Currently, the most sensitive tests are DNA methylation studies [10]. More than 99% of affected patients demonstrate an exclusively maternal methylation pattern at 15q11, which can arise by multiple mechanisms including chromosomal deletions, translocations, uniparental disomy, and imprinting center defects. At present, whole-exome sequencing will not detect the vast majority of cases of PWS.

Management of infants with PWS requires an interdisciplinary approach and should be coordinated by a clinical geneticist or other practitioner familiar with the condition. In early infancy, feeding difficulties are the most common management issue and can necessitate gastrostomy tube placement. Detailed recommendations regarding the management of individuals with PWS have been published [11].

Spinal Muscular Atrophy (SMA Type I)

Spinal muscular atrophy (SMA) is an autosomal recessive condition that can present at any time between the prenatal period and adulthood. For review, see Arnold [12] and Prior and Russman [13]. The overall incidence in the United States is estimated at approximately 1/10,000 births. SMA results from homozygous loss of function of the *SMN1* gene. Weakness develops due to the progressive loss of lower motor neurons. The prenatal form of disease features congenital contractures as the result of decreased movement in utero. SMA type I presents between birth and 6 months of age, most commonly with hypotonia and weakness. Reflexes are generally absent or diminished, and tongue fasiculations are often present. Mild contractures are seen at the knees more commonly than at the elbows. In severe cases, difficulty with feeding and respiration will develop.

Molecular diagnosis of SMA includes polymerase chain reaction (PCR) or Southern blot studies of the *SMN1* gene to detect a recurrent intragenic deletion responsible for approximately 95% of cases. *SMN1* sequencing is also available on a clinical basis and is most commonly useful when the diagnosis of SMA is suspected but a deletion is found on only one allele. At present, whole-exome sequencing will not detect the vast majority of cases of SMA.

Predicted life expectancy for infants diagnosed with SMA type I is less than 2 years. However, long-term survival has been observed and is much more common when assisted ventilation is elected. Management in the newborn period is interdisciplinary and focuses on feeding and respiration.

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 is an autosomal dominant condition resulting from trinucleotide expansion within the *DM1* gene. For review, see Scriver [14] and Bird [15]. It presents most commonly in adulthood, with myotonia and weakness of distal leg muscles. The adult-onset form of disease is associated with between 100 and 1,000 repeats in *DM1* (the normal allele contains between 5 and 34 repeats). Congenital myotonic dystrophy has been observed in infants with especially large intragenic expansions. The incidence of myotonic dystrophy varies widely according to the population studied; 1/8,000 is a frequently cited estimate [16]. Features of congenital myotonic dystrophy include hypotonia, clubfeet, and respiratory insufficiency. Facial muscles are affected, which results in a tented appearance to the upper lip. MRI findings including cortical atrophy, and ventriculomegaly can mimic HIE. Subcortical white matter lesions can also be seen [17].The majority of infants with congenital myotonic dystrophy type 1 experience developmental delay/intellectual disability, in contrast to later-onset forms of the disease. There is an increased risk of cardiac conduction defects in all forms of myotonic dystrophy.

Trinucleotide repeats in *DM1* are known to expand in succeeding generations. For reasons that are incompletely understood, expansions within *DM1* more commonly enlarge in the maternal germ line. Because the expansions in congenital myotonic dystrophy are large, mothers of congenitally affected infants often manifest the condition. Maternal symptomatology can be mild, and may include myopathic facies, cataracts, and myotonia.

Molecular diagnosis of myotonic dystrophy is widely available on a clinical basis. Polymerase chain reaction (PCR) and Southern blot methods are used to determine *DM1* allele size, and these are predicted to detect all cases. At present, whole-exome sequencing will not detect the vast majority of cases of myotonic dystrophy type 1.

Serum CK may be mildly elevated in myotonic dystrophy. Electromyogram (EMG) is less useful in demonstrating electrical myotonia in infants than in older patients. Muscle biopsy may demonstrate characteristic changes, but molecular diagnosis is preferable because it is less invasive and more sensitive and specific.

Management of infants with myotonic dystrophy is supportive. An interdisciplinary approach is recommended to maximize developmental progress and overall health status. Notably, patients with neonatal

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presentation can demonstrate significant improvement in motor function during childhood. However, they remain at risk for longer-term complications.

MECP2-Related Congenital Encephalopathy

The *MECP2* gene encoding methyl CpG binding protein 2 is known for its causative role in Rett syndrome, an X-linked progressive developmental disorder affecting girls. For many years, Rett syndrome was felt to be lethal in males because it was diagnosed exclusively in females. However, wider availability of molecular testing facilitated recognition that loss of *MECP2* function in males can result in a severe congenital encephalopathy [18].

The diagnosis of *MECP2*-related congenital encephalopathy should be considered in male infants with severe neurologic impairment. For recent review, see Christodoulou and Ho [19]. In this condition, hypotonia is frequently noted in the first days of life, although it may not be as prominent as in other conditions described in this chapter. Other recurring features of this congenital encephalopathy are microcephaly or poor head growth, difficulty with suck and swallow, gastroesophageal reflux, and episodic apnea or central hypoventilation. With time, seizures and movement disorders often become evident.

DNA sequence analysis of *MECP2* is clinically available in several laboratories. The gene is also well covered on many whole-exome sequencing tests. Molecular genetic testing is the only means of definitively diagnosing a *MECP2*-related congenital encephalopathy. Electroencephalogram (EEG) demonstrating generalized slowing or seizure activity may be supportive of the diagnosis. Apparent brain atrophy has been observed on MRI in a minority of cases.

Management of infants with congenital encephalopathy is supportive. The condition is associated with profound developmental delay and a severely shortened lifespan. Diagnosis of the condition can be beneficial for both prognosis and estimation of recurrence risk.

Pompe Disease (Infantile Type)

Pompe disease is an autosomal recessive glycogen storage condition resulting from deficiency of the enzyme acid α-glucosidase. For review, see Leslie and Tinkle [20]. Most commonly it manifests with weakness and cardiomyopathy. The age at presentation can range from the prenatal period to adulthood. Overall incidence in the United States is estimated at approximately 1/40,000 births [21]. The infantile form of Pompe disease classically presents in the first months of life with delayed motor development secondary to weakness and cardiomyopathy [22]. However, symptoms may be evident at birth. Classically, the cardiac silhouette is enlarged on chest x-ray, and a shortened PR interval is seen on electrocardiogram (ECG). Moderate elevation of serum CK is a common feature of infantile Pompe disease.

The diagnostic standard for Pompe disease is assay of acid α-glucosidase performed on cultured fibroblasts. Dried blood spot and leukocyte enzyme testing is also available but may be less sensitive and specific. Sequencing of the *GAA* gene encoding acid α-glucosidase is available clinically as a single-gene test and via whole-exome analysis. The sensitivity of molecular testing is incomplete. The diagnosis can also be suggested by muscle biopsy demonstrating lysosomal glycogen accumulation.

The management of Pompe disease includes the use of enzyme-replacement therapy (ERT). ERT currently requires weekly infusions. Response to therapy is variable but can be dramatic in some cases. In some patients the duration of response to therapy is limited by the development of neutralizing antibodies. Guidelines for the management of Pompe disease have been published [23]. Interdisciplinary care includes attention to nutrition and feeding, cardiac disease, and motor development.

Congenital Myopathies

Congenital disorders of muscle are referred to as *myopathies* when there appears to be a primary defect in muscle fiber assembly. The term *dystrophy* refers to the degeneration of existing muscle fibers due to an intrinsic defect. As these conditions are increasingly understood on a molecular basis, the distinction between myopathy and dystrophy is sometimes blurred. In recent years, several conditions historically recognized as myopathies or dystrophies have been found to be due to mutations in the same gene or allelic. This section provides an overview of the congenital myopathies. Congenital muscular dystrophies are addressed in the next section.

A large clinically, histopathologically, and genetically diverse group of disorders is collectively referred to as the *congenital myopathies*. For review, see Goebel [24]. These disorders can demonstrate autosomal dominant, recessive, and X-linked inheritance. Major histopathologic categories include nemaline myopathy,

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central core disease, and myotubular myopathy. The neonatal presentation of congenital myopathies can feature hypotonia, decreased or absent reflexes, contractures, and respiratory insufficiency. Facial muscles are generally affected. There can be a history of decreased movement in utero. Although symptoms can be severe, they are generally nonprogressive. Cardiomyopathy can occur in the congenital myopathies.

In contrast to the congenital muscular dystrophies, it is unusual to detect significant elevations of serum CK in a congenital myopathy. Historically, muscle biopsy has been the primary method for diagnosis. Whole-exome sequencing now provides a noninvasive alternative to biopsy. However, a genetic etiology is not identified in approximately one-third of cases of congenital myopathy, and the interpretation of DNA testing results can be aided by the presence of a tissue diagnosis [25]. The pathologic findings in a congenital myopathy may not be evident on routine light microscopic examination. Therefore, it is recommended that investigation of this family of disorders be pursued with the assistance of a pathologist with special expertise in the area. This collaboration ideally should begin prior to biopsy to be sure appropriate tissue is obtained for evaluation. Although diagnostic, histopathologic categorization of a congenital myopathy is not always predictive of its underlying genetic defect or prognosis.

Among the congenital myopathies that may present in the newborn period, X-linked myotublar myopathy has several features that may aid in diagnosis. By nature of its inheritance, this condition affects male infants. A family history of affected maternal male relatives is present in approximately one-third of cases. Affected infants tend to be relatively long and macrocephalic for gestational age. Long fingers and toes, as well as cryptorchidism, may also be noted. DNA analysis of the *MTM1* gene is available clinically. Causative mutations are identified in 60–90% of cases. Molecular testing is more likely to be positive in more severe disease. For additional discussion of the clinical spectrum of congenital myopathies, see North et al. [26].

Specific therapy is not currently available for the congenital myopathies. Therefore, treatment is supportive.

Congenital Muscular Dystrophies

The congenital muscular dystrophies (CMDs) are a genetically diverse group of conditions that characteristically present at birth with elevations of serum CK due to muscle breakdown and associated weakness and hypotonia. For recent reviews, see Sparks et al. [27] and Mendell et al. [28].With rare exceptions, they are inherited in an autosomal recessive manner. Estimates of the combined incidence of all forms of congenital muscular dystrophy are imprecise but are reported as approximately 1/20,000 [29].

Syndromic and nonsyndromic forms of CMD are recognized. In syndromic disease (e.g., Walker-Warburg syndrome, Fukuyama CMD, muscle-eye-brain disease), there are characteristically anomalies of brain and eye development in addition to muscular pathology. Eye anomalies in syndromic CMDs include anterior chamber defects such as Peters anomaly, cataracts, and retinal degeneration. The characteristic brain appearance in syndromic congenital muscular dystrophies is *cobblestone lissencephaly*. Significant cognitive and motor developmental impairment is associated with the syndromic CMDs, although the degree of disability varies widely between the disorders in this group.

In general, the cognitive difficulties seen in syndromic CMDs are not present in nonsyndromic forms. However, brain malformations and developmental delay have been observed, highlighting limitations of the current nomenclature. As in syndromic CMD, motor function can be severely affected in nonsyndromic disease. Consequently, complications of disease include contractures and respiratory insufficiency. Creatine kinase is not consistently elevated in some forms of nonsyndromic CMD.

Ophthalmologic evaluation and head imaging are potentially useful in the evaluation of any infant with an undiagnosed neuromuscular condition. They are specifically indicated in the evaluation of suspected CMD in order to distinguish syndromic from nonsyndromic forms.

Molecular DNA diagnosis for syndromic and some forms of nonsyndromic CMD is available on a clinical basis, and the relevant genes are well covered on at least several whole-exome sequencing tests. Because the eye findings and brain malformations of syndromic disease are distinctive, selection of genes for DNA analysis is more straightforward in these conditions. Although nonsyndromic disease can be highly suspected on the basis of hypotonia, weakness, and elevated CK levels, muscle biopsy historically has been necessary to define the subtype of disease. At present, whole-exome sequencing provides a

noninvasive alternative to biopsy. It should be noted that in many cases biopsy findings may be helpful in interpreting the results of molecular testing including whole-exome sequencing. For additional discussion of the clinical spectrum of CMD see Peat et al. [30]. The management of patients with CMD is supportive because specific therapy is not available.

Congenital Neuropathies

Congenital neuropathies presenting in the newborn period represent the severest manifestations of hereditary nerve dysfunction. They have been reported only rarely. Congenital neuropathies presenting in the neonatal period are characterized by extremely slow conduction. Clinical manifestations include hypotonia, arreflexia, ptosis, difficulty with suck and swallow, and respiratory insufficiency. Increased CSF protein has been noted in a minority of cases. Although controversy exists in the literature regarding the appropriate nomenclature for these conditions, they are frequently referred to as *Dejerine-Sottas syndrome* (DSS) or *congenital hypomyelinating neuropathy* [31]. Both autosomal dominant and recessive inheritance of this phenotype has been described.

Dominant mutations in a number of genes, including *PMP22, MPZ*, and *PRX*, have been reported to result in the DSS phenotype. Dominant and recessive mutations in *EGR2* have also been observed [32]. Some authors distinguish DSS from congenital hypomyelinating neuropathy (CHN) on the basis of histologic features seen on nerve biopsy. However, because findings historically described as DSS or CHN can result from allelic mutations, the distinction is not consistently observed.

DNA analysis of *PMP22, MPZ, PRX*, and *EGR2* is available on a clinical basis. These genes are also assessed by whole-exome sequencing. Based on one case series [24], the yield of DNA analysis in cases demonstrating neonatal onset appears low, although the yield was higher in a more recent study [32]. The diagnosis of a congenital neuropathy is established primarily by nerve conduction studies and biopsy.

Congenital Myasthenia

Congenital myasthenia can result from inherited defects in a number of components of the neuromuscular junction. Most commonly, autosomal recessive inheritance is observed, although dominant forms have been documented. This family of conditions presents most commonly in the first year of life, although prenatal and neonatal onsets have been described. For recent reviews, see Abicht and Lochmüller [33] and Engel et al. [34]. Collectively, the congenital myasthenias are very rare, but estimates of incidence are uncertain. As is the case for many of the disorders covered in this section, prenatal onset of symptoms can lead to presentation with arthrogryposis rather than hypotonia or weakness. Clinical features that may be useful in distinguishing myasthenia from other neuromuscular conditions include fatigability and eyelid ptosis. Additionally, congenital myasthenias often worsen with fever or infection.

The clinical symptoms of congenital myasthenia are very similar to those of myasthenia gravis and seronegative myasthenia gravis, but these conditions have not been observed in the first year of life. Transient neonatal myasthenia as the result of placental transfer of maternal antibody may closely mimic congenital myasthenia but should be distinguishable by the presence of antibodies in maternal or infant serum.

EMG can be useful in establishing the diagnosis of myasthenia. Repeated muscle stimulation demonstrates a characteristically decreasing response over time. Presently, molecular DNA diagnostics are available on a clinical basis for the evaluation of at least 12 components of the neuromuscular junction [33]. Exome sequencing or DNA panel testing may also be employed to pursue this diagnosis.

Therapy for infants with congenital myasthenia should be directed by or in consultation with a pediatric neurologist familiar with these conditions. In many cases, pharmacologic therapy with acetylcholinesterase inhibitors or other agents can be helpful. However, in other cases, symptoms may be unchanged or worsen with treatment. Identification of the causative mutation(s) may aid in the choice of therapeutic agents. Because respiratory status can deteriorate acutely in congenital myasthenia, apnea monitors and CPR training of caretakers may be indicated. Since symptoms can worsen during acute illness, patients should be managed closely during such periods.

Apparent TORCH Infection

Congenital infection with a TORCH agent (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and others) is often considered in the evaluation of the ill-appearing newborn. These infections are discussed in detail in Chapter 32. A group of genetic disorders

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collectively referred to as *Aicardi-Goutières syndrome* can mimic several features of these conditions, particularly thromobocytopenia, hepatitis, intracranial calcifications, chorioretinitis, and meningoencephalitis.

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is most commonly an autosomal recessive condition that can clinically resemble toxoplasmosis and cytomegalovirus (CMV) infection. An autosomal dominant form has also been characterized. For recent review of AGS, see Crow [35] and Rice et al. [36]. AGS is a very rare but likely underdiagnosed condition. Mutations in at least six genes, *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1*, and *ADAR*, can result in the AGS phenotype, which includes basal ganglia calcifications, leukodystrophy, recurrent fevers, and a chronic CSF lymphocytosis. Neurologic findings include hypotonia, dystonia, and occasionally seizures. Vasculitic skin lesions with associated swelling of the fingers and toes are less frequently observed. Most cases of AGS present with developmental delay and/or loss of previously acquired milestones, abnormal neurologic findings, and recurrent fevers after several months of normal development. However, CNS calcifications have been observed prenatally, as have microcephaly and intrauterine growth restriction at birth and neurologic findings in the first week of life. Therefore, the diagnosis of AGS should be considered when evidence of congenital infection is present but diagnostic studies are negative.

Molecular DNA testing is available on a clinical basis for AGS; this includes single-gene tests and multigene panels. In many cases, the condition can also be diagnosed by whole-exome sequencing. In addition to CSF lymphocytosis, mentioned earlier, elevated interferon α levels are supportive of the diagnosis of AGS. It is important to also consider prenatal infections such as CMV, toxoplasmosis, rubella, and herpes simplex virus (HSV), as well as other genetic conditions that can result in leukodystrophy, in evaluating for AGS.

The outcome of AGS diagnosed in early infancy is severe. Treatment is supportive.

Bleeding

The primary considerations in the evaluation of unexplained bleeding in the newborn are infectious and hematologic disorders. Although frequently genetic in origin, disorders of platelet function and the coagulation cascade are outside the scope of this chapter. Glutaric academia is rarely symptomatic in the newborn period. However, it can predispose to subdural hemorrhage due to macrocephaly and extra-axial hydrocephalus. Bleeding in early infancy has also been described in congenital disorders of glycosylation [37].

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition featuring multiple arteriovenous malformations (AVMs). For recent review, see McDonald and Pyeritz [38]. Estimated incidence has been reported as approximately 1/10,000 [39]. Although the condition most commonly presents in midchildhood or adulthood with recurrent epistaxis and multiple mucocutaneous telangiectasias, presentation in the newborn with catastrophic CNS bleeding is documented [40]. HHT is known to result from mutations in *ENG, ACVRL1*, *SMAD4*, and *GDF2*. Additional loci are under investigation. In the vast majority of cases, HHT is inherited from a parent, and therefore, assessment of family history is important in determining this diagnosis in an infant. Minimally affected parents may only report a history of epistaxis after specific questioning.

Clinical criteria for the diagnosis of HHT have been published [41]. In older children and adults, the diagnosis should be considered in the presence of recurrent epistaxis associated with mucocutaneous telangiectasias or AVMs. DNA sequencing of *ENG, ACVRL1*, *SMAD4*, and *GDF2* is available on a clinical basis. A pathogenic mutation is identified in up to 85% of cases meeting clinical criteria [42]. Whole-exome sequencing can also be used to establish this diagnosis, although most cases are due to mutations in *ENG* or *ACVRL1*. Therefore, if the diagnosis is suspected on clinical grounds or family history, panel testing may be most appropriate.

Detailed age-specific protocols for the identification, monitoring, and management of AVMs in patients with HHT have been developed [38,43]. Components of the initial evaluation of the newly diagnosed infant include pulse oximetry, head MRI, and hepatic ultrasound to screen for AVMs.

Hydrocephalus

Hydrocephalus and ventriculomegaly are frequently encountered in the neonatal intensive care setting. Hydrocephalus can result from excessive CSF

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production, obstruction of CSF flow, and decreased CSF absorption. Frequently recognized causes include intraventricular bleeds, hypoxic injury, and congenital brain malformations. As discussed below, hydrocephalus can also result from metabolic disease and mutations in the X-linked gene *L1CAM*.

Cobalamin Disorders and MTHFR Deficiency

Hydrocephalus and ventriculomegaly have also been reported in a number of inborn errors of metabolism involving vitamin B_{12} and folate metabolism: cblC disease, cblD disease, and homozygous methylene tetrahydrofolate reductase (MTHFR) deficiency [44,45]. Preliminary screening for these conditions can be accomplished by measurement of a total plasma homocysteine level. These disorders are currently included in the list of disorders evaluated for by tandem mass spectrometry–based newborn screening programs in the United States.

X-Linked Hydrocephalus with Stenosis of the Aqueduct of Sylvius (HSAS)

An X-linked recessive form of inherited hydrocephalus, often accompanied by aqueductal stenosis, results from mutations in the *L1CAM* gene. Affected males characteristically demonstrate enlargement of the lateral and third ventricles. Approximately one-half of affected males demonstrate persistently adducted thumbs. Other frequent features include spasticity and severe developmental disability. Notably, hydrocephalus can occur without aqueductal stenosis. In recent years it has been recognized that HSAS is one of several phenotypes resulting from *L1CAM* mutations. Collectively, they are referred to as *L1 syndrome*. For review, see Stumpel and Vos [46]. In some individuals, only spastic paraplegia and mild developmental difficulties are observed. The incidence of HSAS has been estimated at approximately 1/30,000 births[47]. *L1CAM* mutations are believed to explain up to 10% of cases of nonsyndromic hydrocephalus in males.

The diagnosis of HSAS traditionally has been based on clinical findings, including family history of affected male maternal relatives, hydrocephalus, adducted thumbs, and spasticity. The finding on MRI of absent pyramids is felt to be highly specific for HSAS and other forms of L1 syndrome [48]. *L1CAM* DNA sequencing and deletion/duplication analysis is available in several laboratories on a clinical basis. However, the sensitivity of molecular testing has not been precisely determined. The condition can also be diagnosed by whole-exome sequencing.

Management of L1 syndrome is symptomatic. Recommended participants in the care team include pediatricians, neurologists, neurosurgeons, developmental specialists, and geneticists.

Central Hypoventilation

Hypoventilation and apnea are frequently encountered in hospitalized infants. Recognized causes include prematurity, infection, and neuromuscular disease. In the absence of another recognizable cause, persistent hypoventilation, especially during sleep, should raise the possibility of congenital central hypoventilation syndrome. As noted earlier, central hypoventilation has also been reported in *MECP2*-related congenital encephalopathy.

Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is an autosomal dominant condition resulting from disruption of the *PHOX2B* gene. For review, see Weese-Mayer et al. [49]. Most CCHS cases occur as the result of trinucleotide expansion within *PHOX2B*, leading to polyalanine repeats. Precise estimates of incidence are not available, but several cases are diagnosed each month in the United States [49]. Infants with CCHS typically maintain adequate ventilation while awake but hypoventilate when asleep sometimes with a normal respiratory rate. In severely affected infants, hypoventilation can occur during wakefulness. At the other end of the spectrum, a number of individuals have been diagnosed later in childhood or adulthood with milder hypoventilation. CCHS is believed to be the result of autonomic nervous system dysfunction because abnormal regulation of heart rate and blood pressure has been observed in affected individuals. CCHS has also been described as a disorder of neural crest development because Hirschsprung disease and tumors of neural crest origin are seen with increased frequency. Mild facial dysmorphism has also been reported in individuals with CCHS [50]. Affected individuals have been found to have relatively broad and flat facies.

PCR-based molecular testing for *PHOX2B* expansions is clinically available and is diagnostic in over 90% of cases. Other *PHOX2B* mutations have been found in the remainder of confirmed cases [49,51]. Sequence variants in a number of other genes have been reported

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in patients with features of CCHS, but the role of other genes in this condition is currently debated. Given the prominent role of trinucleotide repeats in the pathogenesis of this condition, whole-exome sequencing should not be relied on to establish this diagnosis.

The primary focus of treatment in CCHS is the provision of adequate respiratory support to avoid hypoventilation. Thorough cardiac evaluation is also recommended for children diagnosed with CCHS. Individuals with large polyalanine repeats or mutations not involving trinucleotide expansion are at greater risk of neural crest–derived tumors such as neuroblastoma [52]. Screening for this condition is recommended in this population. Trinucleotide expansion length of 27 or greater repeats and mutations not involving expansions also confer an increased risk of Hirschsprung disease; therefore, screening is recommended in these cases [49,51].

Conclusion

The possibility of a genetic etiology to the apparent sequelae of fetal and neonatal brain injury should be kept in mind when evaluating infants presenting with hypotonia, congenital infection, intracranial hemorrhage, hydrocephalus, and central hypoventilation. More common causes of these signs and symptoms can be difficult to distinguish from rarer hereditary etiologies. Obtaining a detailed family history is essential in evaluating newborns for the possibility of a genetic disorder. In cases where a specific genetic diagnosis is not determined but continues to be suspected, follow-up evaluation with a clinical geneticist is worthwhile. This provides the best chance of ultimately identifying a diagnosis with potentially significant impact on medical management and estimates of recurrence risk. Whole-exome sequencing is capable of establishing or confirming a diagnosis of many, but not all, conditions discussed in this chapter. It is a powerful diagnostic tool, but consideration of its cost, turnaround time, and inability to detect the mutation types responsible for certain disorders must be given before it is employed. Prenatal genetic counseling should be routinely recommended to the families of children with significant congenital illness of unclear origin as well as those of known genetic cause.

References

1. Jones K.L., Jones MC, Campo MD. *Smith's Recognizable Patterns of Human Malformation*, 7th edn. Philadelphia: Elsevier Saunders, 2013: xiii.
2. Yang Y, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA* 2014; **312**(18): 1870–9.
3. Lee H, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA* 2014; **312**(18): 1880–7.
4. Iglesias A, et al. *The usefulness of whole-exome sequencing in routine clinical practice. Genet Med* 2014; **16**(12): 922–31.
5. Yang Y, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med* 2013; **369**(16): 1502–11.
6. Reuter JA, Spacek DV, Snyder MP. High-throughput sequencing technologies. *Mol Cell* 2015; **58**(4): 586–97.
7. Driscoll DJ, et al. Prader-Willi syndrome. *GeneReviews*. Seattle: University of Washington, 1998. Available from www.ncbi.nlm.nih.gov/books/NBK1330/.
8. Smith A, et al. Birth prevalence of Prader-Willi syndrome in Australia. *Arch Dis Child* 2003; **88**(3): 263–4.
9. Vogels A, et al. Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. *Eur J Hum Genet* 2004; **12**(3): 238–40.
10. Kubota T, et al. Methylation-specific PCR simplifies imprinting analysis. *Nature Genet* 1997; **16**(1): 16–17.
11. Cassidy SB, McCandless SE. Prader-Willi syndrome. In *Management of Genetic Syndromes*. Hoboken, NJ: Wiley-Liss, 2010:xvii.
12. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve* 2015; **51**(2): 57–67.
13. Prior TW, Russman BS. Spinal muscular atrophy. *GeneReviews*. Seattle: University of Washington, 2000. Available from www.ncbi.nlm.nih.gov/books/NBK1352/.
14. Scriver CR. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: xlvii, I–140.
15. Bird TD. Myotonic dystrophy type 1. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
16. Harper PS. Myotonic dystrophy. In *Major Problems in Neurology*, vol. **21**, 2nd edn. London: Saunders, 1989: xi.
17. Bachmann G, et al. The clinical and genetic correlates of MRI findings in myotonic dystrophy. *Neuroradiology* 1996; **38**(7): 629–35.
18. Wan M, et al. Rett syndrome and beyond: recurrent spontaneous and familial *MECP2* mutations at CpG hotspots. *Am J Hum Genet* 1999; **65**(6): 1520–9.
19. Christodoulou J, Ho G. MECP2-related disorders. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.

20. Leslie N, Tinkle BT. Glycogen storage disease type II (Pompe disease). In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
21. Martiniuk F, et al. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. *Am J Med Genet* 1998; **79**(1): 69–72.
22. Kishnani PS, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 2006; **148**(5): 671–6.
23. Kishnani PS, et al. Pompe disease diagnosis and management guideline. *Genet Med* 2006; **8**(5): 267–88.
24. Goebel HH. Congenital myopathies in the new millennium. *J Child Neurol* 2005; **20**(2): 94–101.
25. Maggi L, et al. Congenital myopathies–clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. *Neuromus Disord: NMD* 2013; **23**(3): 195–205.
26. North KN, et al. Approach to the diagnosis of congenital myopathies. *Neuromusc Disord NMD* 2014; **24**(2): 97–116.
27. Sparks S, et al. Congenital muscular dystrophy overview. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
28. Mendell JR, Boue DR, Martin PT. The congenital muscular dystrophies: recent advances and molecular insights. *Pediatr Dev Pathol* 2006; **9**(6): 427–43.
29. Mostacciuolo ML, et al. Genetic epidemiology of congenital muscular dystrophy in a sample from north-east Italy. *Hum Genet* 1996; **97**(3): 277–9.
30. Peat RA, et al. Diagnosis and etiology of congenital muscular dystrophy. *Neurology* 2008; **71**(5): 312–21.
31. Plante-Bordeneuve V, Said G. Dejerine-Sottas disease and hereditary demyelinating polyneuropathy of infancy. *Muscle Nerve* 2002; **26**(5): 608–21.
32. Baets J, et al. Genetic spectrum of hereditary neuropathies with onset in the first year of life. *Brain: A Journal of Neurology* 2011; **134**(Pt 9): 2664–76.
33. Abicht A, Muller JS, Lochmuller H. Congenital myasthenic syndromes. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
34. Engel AG, et al. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *Lancet. Neurol* 2015; **14**(5): 461.
35. Crow YJ. Aicardi-Goutieres syndrome. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
36. Rice G, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. *Am J Hum Genet* 2007; **81**(4): 713–25.
37. Cohn RD, et al. Intracranial hemorrhage as the initial manifestation of a congenital disorder of glycosylation. *Pediatrics* 2006; **118**(2): e514–21.
38. McDonald J, Pyeritz RE. Hereditary hemorrhagic telangiectasia. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
39. Marchuk DA, et al. Report on the workshop on hereditary hemorrhagic telangiectasia, July 10–11, 1997. *Am J Med Genet* 1998; **76**(3): 269–73.
40. Morgan T, et al. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). *Pediatrics* 2002; **109**(1): e12.
41. Shovlin CL, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000; **91**(1): 66–7.
42. McDonald J, et al. Molecular diagnosis in hereditary hemorrhagic telangiectasia: findings in a series tested simultaneously by sequencing and deletion/duplication analysis. *Clin Genet* 2011; **79**(4): 335–44.
43. Porteous ME, Berg JN. *Hereditary hemorrhagic telangiectasia*. In *Management of Genetic Syndromes*. Hoboken, NJ: Wiley-Liss, 2005: xvii.
44. Baethmann M, et al. Hydrocephalus internus in two patients with 5,10-methylenetetrahydrofolate reductase deficiency. *Neuropediatrics* 2000; **31**(6): 314–7.
45. Longo D, et al. MRI and 1H-MRS findings in early-onset cobalamin C/D defect. *Neuropediatrics* 2005; **36**(6): 366–72.
46. Stumpel C, Vos YJ., L1 syndrome. *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
47. Halliday J, et al. X linked hydrocephalus: a survey of a 20 year period in Victoria, Australia. *J Med Genet* 1986; **23**(1): 23–31.
48. Chow CW, et al. Congenital absence of pyramids and its significance in genetic diseases. *Acta Neuropathol* 1985; **65**(3–4): 313–7.
49. Weese-Mayer DE, et al. Congenital central hypoventilation syndrome. In *GeneReviews*, Pagon RA, et al., eds. Seattle: University of Washington, 1993.
50. Todd ES, et al. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. *Pediatr Res* 2006; **59**(1): 39–45.
51. Berry-Kravis EM, et al. Congenital central hypoventilation syndrome: PHOX2B mutations and phenotype. *Am J Respir Crit Care Med* 2006; **174**(10): 1139–44.
52. Trochet D, et al. *PHOX2B* genotype allows for prediction of tumor risk in congenital central hypoventilation syndrome. *Am J Hum Genet* 2005; **76**(3): 421–6.

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Chapter

24 Hemorrhagic Lesions of the Central Nervous System

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Introduction

In this chapter, attention is paid to intracranial hemorrhage in preterm and full-term infants. While germinal matrix intraventricular hemorrhage is the most common problem in preterm infants, choroid plexus hemorrhage and extra-axial hemorrhage are more common in full-term infants. Hemorrhages are now more accurately diagnosed due to improvements in neonatal brain imaging, from only having access to cranial ultrasound (cUS) and computed tomography (CT) in the early 1980s to increased use of magnetic resonance imaging (MRI) at present. This has resulted in a more accurate diagnosis of smaller hemorrhagic lesions and especially the diagnosis of cerebellar hemorrhage, which occur most often in the extremely preterm infant. Incidence, risk factors, and management, including preventive methods, are discussed.

Intracranial Hemorrhage in Preterm Infants

During the last decade, attention has increasingly been drawn to ischemic damage occurring in the periventricular white matter (periventricular white matter injury [PWMI]) compared with the early days of neonatal imaging, when the focus was on intracranial hemorrhage (ICH). This is due to improvements in neonatal brain imaging, from only having access to cranial ultrasound (cUS) and computed tomography (CT) in the early 1980s to increased use of magnetic resonance imaging (MRI) at present. The majority of the neonatal MRI studies have focused on lesions in the white matter, especially the more subtle lesions, which now can be clearly visualized; this was not so easy, and certainly more subjective, when imaging was restricted to cUS. With better ultrasound equipment and more detailed examinations, using more acoustic windows than the anterior fontanel, for example, the mastoid window and the posterior fontanel, hemorrhagic lesions of the cerebellum have increasingly been recognized, especially in the very immature and extremely low-birth-weight infant. Germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) is still common, and especially the more severe hemorrhages can lead to adverse neurologic sequelae.

Neuropathology and Pathogenesis of GMH-IVH

The germinal matrix area is highly vascularized and is described as an *immature vascular rete* because the vessels within the germinal matrix are primitive and cannot be classified as arterioles, venules, or capillaries. It is a transient structure and is initially the site where neuroblast and glioblast mitotic activity occurs, before cells migrate to other parts of the cerebrum [1]. Once cell division and migration are complete, the germinal matrix progressively decreases in size, with regression being almost complete by term. The germinal matrix area is most abundant over the head and body of the caudate nucleus but is also seen in the roof of the temporal horn until approximately 33–34 weeks of gestation. MRI has recently confirmed the abundance of the germinal matrix. More than a third of cases from a large autopsy series from New Jersey with a germinal matrix hemorrhage had involvement of the temporal or occipital germinal matrix, and with the use of a new MRI sequence, susceptibility-weighted imaging (SWI), significantly more hemorrhages are identified in the germinal matrix [2,3]. With the use of SWI different anatomic variants can be identified and these variations are associated with GMH-IVH [3a]. The arterial supply of the germinal matrix is from the recurrent artery of Heubner (a branch of the anterior cerebral artery), as well as terminal branches of the lateral striate arteries. Venous drainage of the deep white matter occurs through a fan-shaped leash of short and long medullary veins through which blood flows into the germinal matrix and subsequently into the terminal

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vein that lies below the germinal matrix. This has led to the understanding of a unilateral parenchymal hemorrhage, which is now considered to be due to venous infarction or to a reperfusion injury following an ischemic insult [4,5].

It is most often considered that hemorrhage arises from the thin-walled veins [6], although Pape and Wigglesworth suggested from their injection studies that capillary bleeding was more common than terminal vein rupture [7]. Ment et al. have suggested that the germinal matrix vessels change significantly over the first days of life to greater continuity of the basement membrane [8]. This rapid maturation, presumably as a result of early birth, may be one of the reasons why GMH-IVH usually occurs during the first few days of life.

Incidence of GMH-IVH

The incidence of GMH-IVH is directly related to the maturity of the infant. Initial studies in the late 1970s and early 1980s showed an incidence as high as 40–50% in infants weighing less than 1500 g, but these numbers came down to 20% in the 1990s according to some studies – though not according to others. In a population-based study in France, a decline from 24.9% in 2005 to 12.4% in 2010 was reported, but the decrease was only significant for grade I hemorrhage [9]. In a study by Horbar, only the change in severe GMH-IVH grade III and IV was reported for preterm infants with birth weights of 500–1500 g [10]. The decrease in severe IVH was of borderline statistical significance ($p = 0.04$) and stabilized around 6%. The average incidence of a unilateral parenchymal hemorrhage varies from 3% to 11%, with the lowest incidence coming from a French population-based study [11]. No decrease in this type of lesion was seen by Hamrick et al., in contrast to the decrease they reported in cystic white matter disease [12].

Risk Factors for GMH-IVH

In the *prenatal* period, histologic signs of amniotic infection have been noted to increase the risk of GMH-IVH [13]. A correlation was shown between raised blood cytokine concentrations and altered hemodynamic function [14].

There is no evidence that cesarean section protects the premature infant against GMH-IVH. In a recent hospital-based study in preterm infants with birth weights of 1250 g or less, no beneficial effect was shown of an elective cesarean section on either reduced mortality or neurodisability at 2 years of age [15]. Breech delivery is in some studies associated with a higher risk of large GMH-IVH, but this effect was lost in a multivariate analysis [16]. In another study, a positive effect was shown for the most immature infants, with a gestation fewer than 27 weeks [8]. A reduced mortality but not a reduced risk of a GMH-IVH was recently reported in a Swedish population-based study for preterm infants with a gestation of 25–36 weeks [17]. Being born between midnight and 7:00 a.m. is also associated with an increased risk for developing a severe GMH-IVH [17a].

The importance of delayed cord clamping was suggested by Mercer et al., showing a reduction in GMH-IVH in 5 (14%) in the delayed clamping group versus 13 (36%) in the non-delayed group ($p = 0.03$) [18]. The impact of delayed cord clamping on IVH was evaluated adjusting for gestational age and cesarean section. The final model indicated that the IVH rate was more than three times higher in the immediate cord clamping group (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.1–11.1). In a Cochrane review by Rabe et al. there were no significant differences for infant deaths, but a significant difference in the incidence of all grades of IVH, but not grade III or IV, was reported by 10 of the 15 published studies enrolling 539 infants (relative risk [RR] 0.59, 95% CI 0.41–0.85) [19]. It was suggested that this could be due to a higher flow in the superior vena cava following delayed cord clamping.

It has also been suggested that infants born outside a perinatal center and transported in have a higher incidence of GMH-IVH [8,19,20]. Data from the NEOPAIN Trial did show that outborn babies were more likely to have severe IVH ($p = 0.0005$), and this increased risk persisted after controlling for severity of illness. However, when adjustments were made for the use of antenatal steroids, the effect of birth center was no longer significant [21]. It was recently suggested that it might not be the transport itself but rather the association with underlying clinical variables [22].

Cardiovascular and respiratory problems have always been considered to play a major role in the development of a GMH-IVH in the immediate *neonatal* period. Fluctuations in the intravascular pressure or blood flow may lead to rupture of the "immature vascular rete" in the germinal matrix, and hemorrhage is known to occur during reperfusion following a period of hypotension [23,24]. Early

assessment of the flow in the superior vena cava, within the first few hours after birth, showed that a low flow preceded a GMH-IVH [25]. Although the possible lack of cerebral autoregulation, rendering the cerebral circulation *pressure passive*, is still considered important, it is not present in all preterm infants [26,27]. Continuous monitoring with near-infrared spectroscopy (NIRS) may be a useful tool in the identification of infants at risk [26,27]. In a study using continuous NIRS and mean arterial blood pressure (MABP) measurements, MABP-rScO_2 correlation suggested more blood pressure-passive brain perfusion in infants with an IVH [28]. In another study, a lower systemic perfusion and cerebral blood flow (CBF) followed by an increase in these variables was found to precede the development of GMH-IVH [29]. When measuring perfusion waveforms in the internal vein with cUS, high-grade fluctuations in the perfusion waveform were seen significantly more commonly in the IVH group (n = 8) than the non-IVH group (n = 72) (87% versus 25%, $p < 0.001$) [30].

Respiratory risk factors can occur with complications during mechanical ventilation, such as vasodilation secondary to hypercapnia, for instance, following a pneumothorax [31]. Improvements in ventilatory techniques and increased use of nonventilatory support such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP) are likely to further reduce the incidence of GMH-IVH.

Several studies have shown that hypernatremia (>150 mmol/L) is an independent risk factor in the development of an IVH. High sodium levels are especially common in extremely preterm infants, a group known to be especially at risk to develop GMH-IVH [32,33].

Genetic Factors

Several studies have also studied the role of thrombophilic disorders, including factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate (MTHFR) mutation [34,35]. An association with polymorphism in the factor V Leiden gene was found in preterm infants with an atypical time of onset, either antenatal or beyond 96 hours after birth [36]. Interleukin-6 CC genotype increased the risk of the development of severe hemorrhagic lesions (OR 3.5, 95% CI 1.0–12.2, p = 0.038) and impairment of cognitive outcome. This observation could not be confirmed, however, in a considerably larger sample size [37,38]. Low cord blood CCL18 is an independent risk factor of IVH [39].

Antenatal porencephaly can be associated with a mutation in the collagen 4A1 and collagen4A2 gene (*COL4A1* and *COL4A2*) encoding procollagen type 4a1 or 4a2, a basement membrane protein [40,41]. The diagnosis can be made before birth and should be considered in the presence of a parenchymal hemorrhage, especially when associated with a cerebellar hemorrhage.

A *reduced risk* of GMH-IVH was found in several studies with maternal preeclampsia, which appears to be due to enhanced in utero maturation of the fetus, associated with a reduced risk of postnatal development of respiratory distress [42,43].

Diagnosis of GMH-IVH

Even though MRI is increasingly, being used GMH-IVH is still more likely to be diagnosed during routine bedside ultrasonography. Performing cUS as part of the admission procedure and several times during the first week will allow the most accurate timing and identification of antenatal onset of the lesion. Almost all hemorrhages will have developed by the end of the first week after birth and many within the first hours after birth. Only about 10% of GMH-IVH occurs beyond the end of the first week, in contrast to white matter injury, where late onset is not uncommon [44]. Progression from a small GMH-IVH to a parenchymal hemorrhage can occur, and this is most likely related to impaired venous drainage of the medullary veins in the white matter with obstruction at the site of the germinal matrix [45]. Sequential imaging over the first few days has helped in the past to identify the most common risk factors.

Clinical diagnosis does not play a major role because most GMH-IVHs will be silent. Three clinical syndromes have been described in the past [46], the first being associated with a *catastrophic* deterioration, with a sudden deterioration of the clinical state of the infant, such as a sudden fall in blood pressure and/or metabolic acidosis. It is, however, more common to find a sudden fall in hemoglobin without a clear change in the condition of the child. The second clinical syndrome is the *saltatory* one, with a more gradual onset, presenting with a change in general movements. Most commonly the *silent*, asymptomatic syndrome is seen, and this can even occur in infants who show a parenchymal hemorrhage on a routine repeat ultrasound examination.

The classification system suggested by Volpe is suitable to describe early and late ultrasound

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Table 24.1 Ultrasound Description of GMH-IVH

Description	Generic term
Grade I: Germinal matrix hemorrhage	GMH-IVH
Grade II: Intraventricular hemorrhage without ventricular dilatation	GMH-IVH
Grade III: Intraventricular hemorrhage with acute ventricular dilatation (clot fills > 50% of the ventricle)	GMH-IVH and ventriculomegaly
Intraparenchymal lesion – describe size, location	IPL

Source: Adapted from Volpe [46].

appearances (Table 24.1) [46]. The use of grade IV is avoided, and a separate description of the size, site, and appearance of a parenchymal lesion is preferred. Making a distinction between a small hemorrhage restricted to the germinal matrix and a GMH with some blood ruptured through the ependyma into the ventricular lumen is not always possible. Use of the posterior fontanel as an alternative acoustic window has been advocated by Correa et al., who showed improvement in the diagnosis of a small IVH [47]. GMHs at sites other than the head of the caudate nucleus, such as the roof of the temporal horn, often remain undiagnosed unless an MRI is also performed [48].

A small GMH-IVH may be missed with cUS, especially when the site of the GMH is not in the caudate nucleus. MRI, and especially the SWI sequence, often shows more GMHs than seen with cUS or even conventional T1- and T2-weighted imaging [49]. A large IVH can be confidently diagnosed with cUS, although associated white matter damage may be more reliably diagnosed with early MRI (Figure 24.1). Distinction of a large, bulky choroid plexus, which is common in very immature infants, from a large IVH is not always easy, and sequential examinations and an examination through the posterior fontanel may aid in making this distinction. Blood can acutely dilate the ventricle or can lead to posthemorrhagic ventricular dilation (PHVD) a few weeks later, and the larger the amount of blood, the more likely this will subsequently occur. Blood will rapidly spread through the foramen of Monro into the third ventricle, the aqueduct of Sylvius, the fourth ventricle, and the foramina of Magendie and Luschka to eventually spread into the posterior fossa. Clot formation can occur at any level and can lead to outflow obstruction, but it is seen most commonly at the level of the aqueduct or more diffusely in the posterior fossa. Depending on the degree of blood and the site of obstruction, PHVD can be rapidly progressive and noncommunicating, usually due to obstruction at the level of the aqueduct of Sylvius, or be more gradual in onset, communicating, and considered to be due to obliterative arachnoiditis.

A unilateral parenchymal hemorrhage accounts for 3–15% of all GMH-IVH [11]. It is usually unilateral, triangular in shape, with the apex at the outer border of the lateral ventricle, and associated with a moderate to large ipsilateral GMH-IVH. It has been thought in the past that parenchymal hemorrhage was due to direct extension of hemorrhage into the periventricular white matter, but this is no longer considered to be the most likely explanation for this type of parenchymal lesion. Most clinicians would now agree that this type of lesion is caused by the presence of GMH-IVH, which can lead to impaired venous drainage and subsequent venous infarction of the medullary veins of the white matter. This sequence of events can sometimes be followed by sequential ultrasound examinations, changing from a normal image to a stage of simple GMH-IVH and involvement of the parenchyma on the following day (Figure 24.2). While this type of lesion used to be globular and usually would communicate with the lateral ventricle, with subsequent evolution into a porencephalic cyst, more recently the pattern has been shown to be more variable, with a more discrete parenchymal lesion that does not necessarily communicate with the lateral ventricle and can evolve into a few small cysts in the white matter that may resolve with eventual ex-vacuo dilation on the affected side. These white matter cysts can be mistaken for unilateral cystic periventricular leukomalacia, but seeing the evolution of this unilateral lesion with sequential ultrasound examinations would not favor a diagnosis of leukomalacia, which is almost invariably bilateral and not often associated with a large IVH (Figure 24.3). MRI performed later in infancy or early childhood will also help to make a distinction between the two conditions, showing more focal injury in those with a parenchymal

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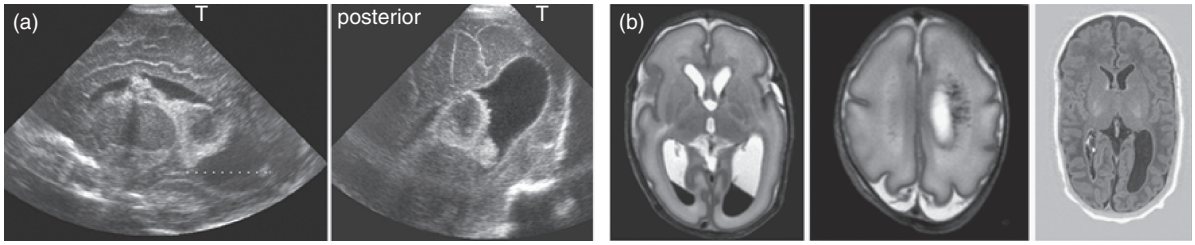


Figure 24.1 (a) Cranial ultrasound of a preterm infant born at 29 weeks' gestational age. Parasagittal views taken through the anterior (left) and posterior (right) fontanel showing a large intraventricular clot and a severely dilated occipital horn. (b) MRI of the same child, T2-weighted spin-echo sequence, taken at 2 weeks of age, shows associated punctate lesions in the white matter. The inversion recovery sequence taken at term-equivalent age still shows a dilated occipital horn and poor myelination of the posterior limb of the internal capsule, especially on the left.

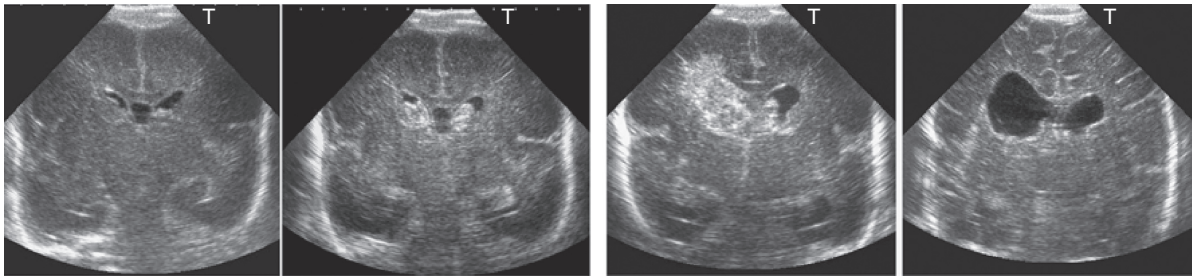


Figure 24.2 Cranial ultrasound of a preterm infant born at 27 weeks' gestational age. Coronal views taken on days 1, 3 and 5, and at 6 weeks showing a normal scan on day 1, a bilateral IVH on day 3, a parenchymal hemorrhage and a large IVH on the right on day 5, and evolution into a single porencephalic cyst 6 weeks later.

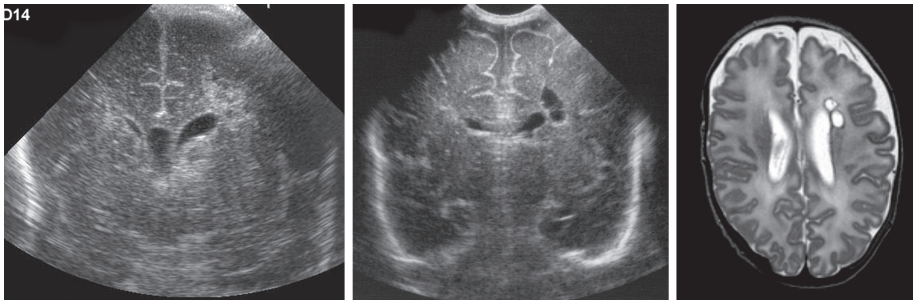


Figure 24.3 Cranial ultrasound of a preterm infant born at 29 weeks' gestational age. Coronal view, resolving left-sided hemorrhage on day 14 (left). Ultrasound taken at term-equivalent age (middle) showed cystic evolution, confirmed with MRI (T2 spin-echo sequence) (right). Also note the enlarged subarachnoid space. Outcome at 24 months was within the normal range (BSID-II; MDI 91; PDI 100).

hemorrhage. Detailed studies by Dudink et al. have made it possible to identify the veins that were involved in the parenchymal injury [50]. A proposal was made by Bassan et al. to grade the severity of this parenchymal lesion [51], taking the extent of the lesion, the presence of a contralateral parenchymal lesion, and also the presence of a midline shift due to this lesion into account. The grading system also helped in the prediction of neurodevelopmental outcome at 2 years of age [52].

Intracerebellar Hemorrhage

Intracerebellar hemorrhage is increasingly recognized together with a GMH-IVH. This type of lesion is especially common in those with a birth weight of

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less than 750 g and a gestational age below 27 weeks [53,54]. Twenty-five of the 35 infants examined by Limperopoulos et al. had a unilateral hemispheric hemorrhage [53]. Of the 35 infants, 27 also had supratentorial lesions. Apnea, bradycardia, and a falling hematocrit may be associated with this type of lesion. Ultrasonography can be diagnostic when the lesion is large (>4mm) and when care is taken to use the mastoid window as the acoustic window [54]. MRI will give better definition of the extent of the lesion. The lesion may be unilateral or bilateral, large or punctate, and may also affect the vermis [53,55]. The incidence varies between 3% and 9%, when using cUS including the mastoid fontanel [53] but was reported as high as 15% in a more recent cohort [54]. When using MRI, the incidence increases to almost 20%, mainly due to recognition of punctate lesions, which are a much more common finding in the extremely preterm infant but are less likely to be associated with severe adverse neurologic sequelae [56]. Steggerda et al [57] diagnosed these small cerebellar hemorrhagic lesions on routine term-equivalent-age (TEA) MRI in 16/108 very preterm infants (<32 weeks' gestation) and identified high-frequency oscillation (HFO) and severe IVH as independent predictors of small cerebellar hemorrhagic injury. There was no association between small cerebellar hemorrhages and neurodevelopmental outcome at 2 years of age. For the preterm infants with more severe isolated cerebellar hemorrhagic injury, neurologic abnormalities were found in 66% of the infants seen at a mean age of 32 months compared with 5% of the control preterm infants [58]. Infants with isolated cerebellar hemorrhagic injury versus controls had severe motor disabilities (48% versus 0%), deficits in expressive language (42% versus 0%), delayed receptive language (37% versus 0%), and cognitive deficits (40% versus 0%). Preterm infants with cerebellar hemorrhagic injury and supratentorial parenchymal injury were not at overall greater risk for neurodevelopmental disabilities, although neuromotor impairment was more severe. Cerebellar atrophy without apparent cerebellar hemorrhage has also been reported as a common sequel of severe immaturity. Srinivasan et al. showed reduced cerebellar volume only in preterm infants at term-equivalent age in association with supratentorial pathology such as hemorrhagic parenchymal infarction, intraventricular hemorrhage with dilation, and periventricular leukomalacia (PVL) [59]. Quantitative MRI using tractography showed reduced fractional anisotropy (FA) values in the superior cerebellar peduncle in extremely preterm infants with a low-grade GMH-IVH compared with controls [60]. The authors suggest that this is due to hemosiderin disposition in the proximity to the superior cerebellar peduncle, the most vulnerable white matter tract in the cerebellum. In another study, low-grade IVH led to disturbed cerebellar development, with cerebellar volume reduction shown by volumetric analysis [56].

Management of GMH-IVH

Once the diagnosis of a GMH-IVH is made, immediate clinical management will not be different from that of other at-risk preterm infants. Optimalization of any coagulopathy, minimal handling, prevention of fluctuations in blood pressure or CO_2 levels, and prevention of breathing against the ventilator may be used in an effort to prevent extension of the initial hemorrhage [61]. Continuous amplitude-integrated encephalographic (aEEG) registration may detect subclinical seizures, which may require treatment [62].

Repeat cUS scans are indicated for timely diagnosis of the development of PHVD, which is usually seen within 10–14 days following the occurrence of the hemorrhage. PHVD can progress either slowly or rapidly. In the majority of cases (65%), slowly progressive PHVD is followed by spontaneous arrest. In the remaining 30–35% of infants with PHVD, ventricular size increases rapidly over the course of days to weeks [63].

Increase in ventricular size, as assessed with serial US examinations, will precede any clinical symptoms, such as a rapid increase in head circumference (>2 cm/week), diastasis of the sutures, a full fontanel, vomiting, irritability, bradycardias, and apneas, by several weeks due to the large extracerebral space and the high water content of the white matter. Sunsetting will only be seen at a late stage [64]. There is no agreement as to whether treating progressive PHVD before the occurrence of any clinical symptoms is beneficial to the child. Measurements are usually taken in the coronal view at the foramen of Monro using the "ventricular width" according to Levene and Starte [65]. The *ventricular index* is the distance between the midline and the lateral border of the ventricle. Most intervention studies have taken the 97th percentile + 4 mm as a starting point for

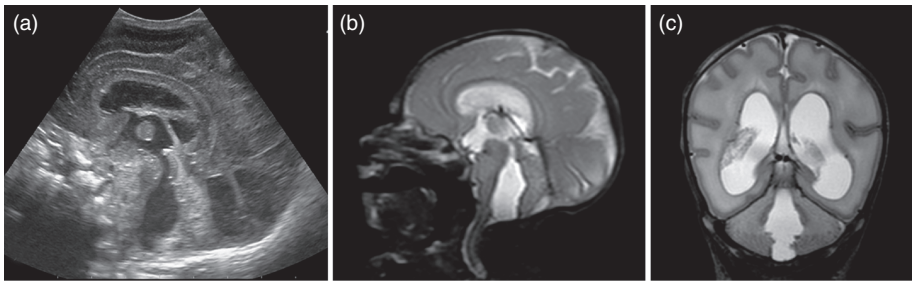


Figure 24.4 Cranial ultrasound of a preterm infant born at 30 weeks' gestational age. Midsagittal view shows (a) enlarged third and fourth ventricles at the end of the first week. The aqueduct appears to be patent. The MRI (T2-weighted sequence) in the sagittal (b) and coronal planes (c) performed on day 17 confirms the ultrasound findings.

randomization. Another useful measurement is the so-called anterior horn width, taken just anterior to the thalamic notch [66]. This anterior horn width measurement does not change much with increasing maturation and should be less than 3 mm, with measurements greater than 6 mm suggesting PHVD. Measuring the thalamo-occipital distance (TOD) in a sagittal plane can also be useful because there can be a discrepancy between dilation of the anterior and posterior horns. Although the best angle may be more variable in the sagittal plane, any measurement of the occipital horn of 25 mm or more also suggests severe PHVD. Because infants with a gestational age below 26 weeks included in the data set from Levene and Starte were not measured, new cross-sectional and longitudinal reference data for the VI, AHW, and TOD were recently published, with an age range between 24 and 42 weeks [65,67]. Obtaining a midsagittal view allows the assessment of the third and fourth ventricles. A discrepancy between a large third and a small fourth ventricle would suggest an obstruction at the level of the aqueduct and dilatation of an outflow obstruction due to obstruction of both the foramina of Luschka and Magendie (Figure 24.4). In both situations it is not recommended to perform a lumbar puncture. Assessing the shape of the lateral ventricles may be useful when making a distinction between pressure-driven PHVD and ex vacuo dilation following white matter injury, the latter being irregular in shape with predominant dilatation of the occipital horns. Measuring the CSF pressure may also aid in making a distinction, but reliable measurements can be hard to obtain [68].

Adverse short-term effects on the CNS have been shown using different techniques, including evoked potentials, aEEG, Doppler ultrasonography, and NIRS [69,70]. In one study of 17 preterm infants, a combination of flash visual evoked potentials (fVEPs) and aEEG was used [70]. Both methods showed normalization of fVEP latency and aEEG background pattern mostly within a week of successful therapeutic intervention (mean 8.5 days). Both changes in fVEP latencies and aEEG background patterns were detected before clinical signs of elevated intracranial pressure occurred. In only 10 patients (58.8%) did ventricular width exceed the 97th percentile + 4 mm. CSF measurements of cytokines, non-protein-bound iron, hypoxanthine, and sFas were all noted to be raised in infants with PHVD and especially so in those with associated periventricular leukomalacia [71–74]. In spite of all these data, there is no direct evidence that early drainage of CSF alters the natural and long-term outcomes of children with PHVD [74a]. In the two largest randomized, controlled trials (RCTs) so far, randomization was done once the 97th percentile + 4 mm line was crossed, and 60% of the infants in both arms subsequently required shunt placement [75]. The RCT for DRIFT (drainage intervention fibrinolytic therapy) also used this measurement as an entry point for the study [76]. The initial data were promising, with shunt requirement in 22%, but in the RCT a high risk (33%) of rebleeding was noted in the DRIFT group without an apparent positive effect on the need for a ventriculoperitoneal shunt [76]. In two retrospective observational studies, a significant reduction in the need for shunt placement was noted when intervention was started before this line was crossed and when the threshold for inserting a subcutaneous reservoir was low [77]. In another retrospective study performed in 32 preterm infants, early external ventricular drainage was found to be beneficial in infants with a grade III IVH ($n = 15$, $p < 0.05$), but it had no beneficial effects in infants with prior parenchymal injury ($n = 17$, $p = \text{NS}$) [78]. Whether earlier and more active intervention is effective is now being studied in a prospective RCT. Due to a decline in the number of infants who suffer a large IVH, the study has only recently completed recruitment, and results are still not reported.

Outcome following GMH-IVH

There is no agreement in the literature about the effect on outcome of low-grade GMH-IVH. Initially studies of infants with mild grades of GMH-IVH (hemorrhage restricted to the germinal matrix or small amount of ventricular blood) suggested that these infants were performing as well in cognitive and motor developmental outcomes as preterm infants with no GMH-IVH. Since then, neonatal three-dimensional (3D) volumetric imaging studies, however, have shown reduced gray matter volumes at term-equivalent age associated with a reduced MDI on the BSID-II, but this was only seen in the most immature infants, with gestation below 30 weeks [79,80]. A large study including 336 infants with a grade I–II GMH-IVH showed increased rates of neurosensory impairment (22% versus 12.1%), developmental delay (7.8% versus 3.4%), cerebral palsy (10.4% versus 6.5%), and deafness (6.0% versus 2.3%) compared with the no IVH group (n = 1043). After exclusion of 40 infants with late ultrasound findings (i.e., periventricular leukomalacia, porencephaly, ventricular enlargement), isolated grade I–II IVH (n = 296) had increased rates of moderate to severe neurosensory impairment (18.6% versus 12.1%). Isolated grade I–II IVH was also independently associated with a higher risk of neurosensory impairment (adjusted OR 1.73, 95% CI 1.22–2.46) [81]. Another large study looked at the 18- to 22-month outcome in 1472 infants born at fewer than 27 weeks' gestation and did not find a difference between those with a low-grade GMH-IVH and those without a hemorrhage [82]. A population-based study included all preterm infants with a gestation below 30 weeks born between 1993 and 2010. The authors did not find an increased risk of increased disability for infants with grade I–III but only for those with a grade IV hemorrhage. The risk of cerebral palsy (CP) was significantly increased, however, for those with a grade II hemorrhage (13%) compared with those without an IVH (7%) or a grade I hemorrhage. The risk of moderate to severe CP was only significantly increased in those with a grade IV hemorrhage (12%) compared with those without an IVH (2%) [83]. In all these studies the diagnosis of a GMH-IVH was based on cUS, and we can therefore not be certain whether associated mild white matter abnormalities were present and could have played a role. In a recent study by Ruebsaet et al. 136 preterm infants with low grade IVH were matched with 255 controls. There were no differences in outcome between cases and controls. MRI was performed as well in 42% of the infants studied and could explain CP in 2 out of 5 infants and epilepsy in 1 of 2 infants [83a].

The term *ventriculomegaly* (VM) has been used for infants with ventricular enlargement following a GMH-IVH and also for those without apparent preceding hemorrhage, in whom it is more likely to be due to white matter loss [84]. It is therefore preferable to use VM for those without an apparent preceding large GMH-IVH and to use the term *posthemorrhagic ventricular dilation* (PHVD) when ventricular enlargement follows a large hemorrhage. Having access to sequential ultrasound examinations and looking at the shape of the ventricles will enable us in most cases to make this important distinction. In a study of 93 preterm infants, sequential cUS and TEA MRI early and term cUS findings, as well as cerebellar apparent diffusion coefficient (ADC) values on term DWI, were independently associated with motor outcome at 2 years' of corrected age ($p < 0.05$). Ex-vacuo VM on term cUS was also related to a worse cognitive outcome ($p < 0.01$) [85].

Several studies have now also reported an adverse effect of a low-grade IVH on the cerebellum. Using tractography-reduced fractional anisotropy (FA), values in the superior cerebellar peduncle in extremely preterm infants with a low-grade GMH-IVH were noted and compared with controls [60]. These studies suggest that this is due to hemosiderin disposition in proximity to the superior cerebellar peduncle, the most vulnerable white matter tract in the cerebellum. In another study, low-grade IVH led to disturbed cerebellar development, with cerebellar volume reduction shown by volumetric analysis [56].

The risk of a poor outcome has been reported to increase significantly with the presence of PHVD following a large GMH-IVH (40–60%) and even further in those who require shunt insertion (75–88%) [86,87]. In the cohort from Sweden, associated problems (e.g., cerebral visual impairment, epilepsy, and especially cognitive problems) were very common [87]. In a retrospective hospital-based population study, outcome was considerably better than reported previously, with CP occurring in only 7.4% of the infants with a large IVH (grade III according to Papile) compared with 37 (48.7%) of the 76 infants with a parenchymal hemorrhage ($p < 0.001$). The mean developmental quotient (DQ) in the grade III group was 99, and in the grade IV group it was 95 at 24 months' corrected age [77]. Whether this better outcome was related to earlier treatment of PHVD or due to a cohort with more localized lesions and of higher gestational age needs to be determined, and a prospective study is now under way. MRI

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(at ~8.5 years) in children with arrested or shunted hydrocephalus has revealed persistence of enlarged lateral ventricles, enlarged occipital horns, hypoplastic corpus callosum, and atrophy or dysplasia of the cerebral cortex. When preterm infants with no hydrocephalus are compared with those with arrested hydrocephalus, shunted hydrocephalus, and a term comparison group, the children with shunted hydrocephalus have the lowest verbal and perceptual IQ scores. Visual-spatial-motor scores are lower in the shunted compared with the arrested hydrocephalus group and even lower in the arrested compared with the no-hydrocephalus group. Tests of academic skills (i.e., arithmetic, science, and writing) also demonstrate poorer performance in children with shunted hydrocephalus compared with those with arrested hydrocephalus.

While infants without apparent parenchymal involvement are more likely to develop diplegia, those with a PVHI are more at risk of developing a hemiplegia. Outcome with PVHI varies and depends on the extent and site of the lesion [45,52]. A recent scoring system reported by Bassan et al. showed an association between a higher score (based on the presence of a more extensive lesion, a midline shift, or bilateral parenchymal involvement) and mortality and outcome at 2 years of age [52]. Long-term outcome into adolescence showed that most of the 14 cases with hemorrhage, PVHI, and porencephaly were ambulatory, required learning assistance in school, and had social challenges [88].

Early prediction of development of a hemiplegia is now possible using MRI at 40–42 weeks. Myelination of the posterior limb of the internal capsule (PLIC) should be present at TEA. In infants who go on to develop a hemiplegia, asymmetry and even lack of myelination of the PLIC were noted in those who subsequently developed a hemiplegia [89]. Using diffusion tensor imaging, visualization of the tracts is already possible at an earlier stage, allowing prediction on an early MRI, performed when the infant is stable enough to be taken to the MR unit [90]. The same observation was made when looking at thalamocortical connectivity in preterm children studied in childhood [91].

Prevention of GMH-IVH in Preterm Infants

The incidence of GMH-IVH has decreased over time in most studies. Both pre- and postnatal pharmacologic prophylaxis has been used to reduce the incidence of GMH-IVH. Many different drugs have been used, such as phenobarbital, tranexamic acid, pancuronium, etamsylate, vitamin E, indomethacin, and magnesium sulfate. Only a few of these will be discussed here in more detail.

Antenatal Prevention

Antenatal Steroids. Administration of antenatal corticosteroids has been shown to be the most important protective factor against the development of GMH-IVH. A systematic review of 21 RCTs involving over 4000 babies has shown that corticosteroid administration is associated with a significant reduction in the risk of GMH-IVH (OR 0.54, 95% CI 0.43–0.69) and with a strong trend toward improving long-term neurologic outcome in survivors (OR 0.64, 95% CI 0.14–2.98) [92]. Dexamethasone was noted to have some benefits compared with betamethasone, such as less IVH and a shorter length of stay in the NICU [93]. Another study, however, recommended bethamethasone instead of dexamethasone because the latter was associated with an increased incidence of cystic PVL [94]. The effect of steroid administration could be due to a reduction in risk and severity of respiratory distress syndrome, postnatal stabilization of blood pressure, or maybe even a direct cerebral protective effect. Repeated courses of antenatal corticosteroids are not recommended because a negative effect on brain growth has been shown [95]. In a RCT, no significant difference was noted between infants who had been exposed to repeat as compared with a single course of antenatal corticosteroids in neurocognitive measures (Bayley score at 2 years of age). However, there was a not statistically significant higher rate of CP among children who had been exposed to repeat doses of corticosteroids [96].

Magnesium Sulfate. Maternal administration of magnesium sulfate ($MgSO_4$) before anticipated early preterm birth has been shown to reduce the risk of gross motor dysfunction and CP in surviving infants in several clinical trials and in meta-analyses. However, there was no reduction in the incidence of either a small or a large GMH-IVH in two large randomized multicenter studies [97–99]. In a small randomized study, cerebral oxygen consumption and continuous fractional oxygen extraction (cFTOE) were found to be lower in infants exposed to antenatal $MgSO_4$ ($p = 0.012$) compared with unexposed infants within 24 hours of delivery. This difference was no longer seen by 48 hours of age. Fewer infants in the

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$MgSO_4$ group developed any IVH by 72 hours of age ($p = 0.03$) [100]. Antenatal administration of $MgSO_4$ in children at risk for early preterm delivery exposed to chorioamnionitis was not associated with a reduced rate of severe IVH or an improved neurodevelopmental outcome [101].

Vitamin K. Vitamin K was used antenatally to prevent neonatal GMH-IVH because vitamin K–dependent factors are deficient in preterm infants. The initial reports were promising, but a systematic review compared seven randomized studies involving 607 women to evaluate the role of vitamin K given to women in labor or very likely to deliver a premature infant in the prevention of GMH-IVH and was not able to show a beneficial effect [102].

Postnatal Prevention

Phenobarbital. The rationale for phenobarbital use was sedation of the preterm infant to prevent the fluctuations in blood pressure that occur with clinical care of high-risk infants. Phenobarbital was the first drug used postnatally in the prevention of GMH-IVH. A meta-analysis of 12 trials involving 982 infants was unable to show a reduction in the incidence of GMH-IVH (typical (RR 0.91, 95% CI 0.77–1.08), severe IVH (typical RR 0.77, 95% CI 0.58–1.04), PHVD (typical RR 0.89, 95% CI 0.38–2.08), severe neurodevelopmental impairment (typical RR 1.44; 95% CI 0.41–5.04), or death before hospital discharge (typical RR 0.88; 95% CI 0.64–1.21). There was a consistent trend in the trials toward increased use of mechanical ventilation in the phenobarbital-treated group, which was supported by the meta-analysis (typical RR 1.18; 95% CI 1.06–1.32; typical risk difference 0.129; 95% CI 0.04–0.21) [103].

Indomethacin. A meta-analysis on the postnatal use of indomethacin in the prevention of GMH-IVH and subsequent brain injury [104] showed a significant reduction in the incidence of severe IVH (typical RR 0.66, 95% CI 0.53–0.82). Meta-analyses found no evidence of an effect on mortality (typical RR 0.96, 95% CI 0.81–1.12) or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months of age (typical RR 1.02, 95% CI 0.90–1.15) [105]. A post hoc analysis of the original indomethacin trial suggested that boys exposed to indomethacin had significantly better outcome in verbal test scores than girls, suggesting a gender-specific effect [106].

Ibuprofen. Ibuprofen is used as an alternative to indomethacin in the medical management of patent ductus arteriosus, and it acts in a similar manner by prostaglandin synthase inhibition. Several RCTs have evaluated whether ibuprofen, when given shortly after birth to a group of premature infants (<28 weeks' gestation), reduces the incidence of GMH-IVH [107]. Ibuprofen prophylaxis did decrease the occurrence of patent ductus arteriosus but did not reduce the frequency of IVH. A subsequent Cochrane review of four trials and 672 infants was unable to show a reduction in severe IVH [108].

General Measures. Paying closer attention to blood pressure, gentle handling, head positioning, synchronous ventilation, and less severe respiratory distress syndrome due to antenatal corticosteroid and postnatal surfactant therapy was associated with a reduction in GMH-IVH [61]. Data from the Canadian network also showed that the incidence and severity of GMH-IVH are affected by NICU characteristics. A high patient volume and a high neonatologist/staff ratio were associated with a lower rate of severe IVH [109].

Intracranial Hemorrhage in Term Infants

Intraventricular Hemorrhage

Intraventricular hemorrhage (IVH) is an uncommon problem in full-term as compared with preterm neonates. Origins of the IVH can be the germinal matrix, choroid plexus, or parenchyma. In term infants, only remnants of the germinal matrix remain. The incidence of germinal matrix hemorrhage is therefore low, and infants are often asymptomatic. The mechanism of IVH in term infants has been attributed to trauma at birth (precipitous delivery) or hypoxia, but no etiology is detected in many cases. Thalamic hemorrhage in term infants has been shown to be associated with cerebrosinovenous thrombosis [110]. The pathogenesis of thalamic hemorrhage is a hemorrhagic venous infarction of the large venous channels that are in close proximity to the ventricular walls. In the majority of infants, none of the previously associated risk factors for thalamic hemorrhage, such as coagulation disorders or hypoxic–ischemic birth injury, was noted.

Predisposing factors noted by Roland et al. included sepsis, cyanotic heart disease, and polycythemia [111]. Symptomatology (irritability, seizures, apnea, bulging fontanel) occurred later than that seen in infants with IVH from choroid plexus or germinal matrix hemorrhage.

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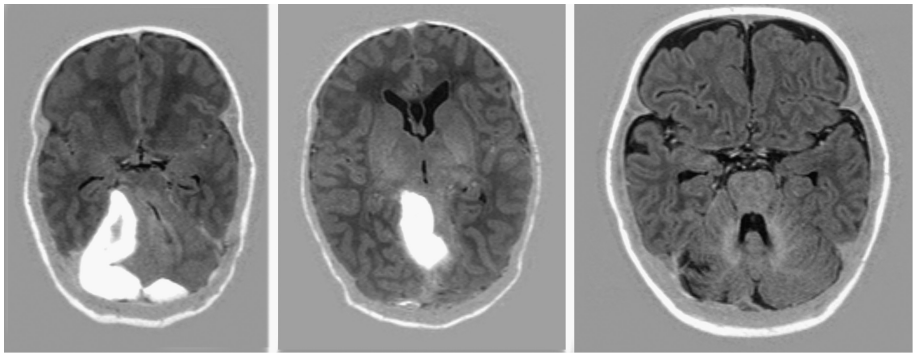


Figure 24.5 Term infant admitted because of PHVD. MRI on day 26 shows a large infratentorial subdural hemorrhage with a shift and possibly involvement of the right cerebellar hemisphere. A repeat scan at 3 months (right) shows loss of volume and loss of tissue of the right cerebellar hemisphere.

Management of IVH in term infants is supportive. Prognosis depends on the location and extent of the underlying insult. As a rule, among infants for whom no etiology of the IVH is detected, outcome appears to be good. In infants with IVH secondary to a GMH-IVH, prognosis is also good. Neurodevelopmental sequelae are seen in infants with IVH with parenchymal involvement [112]. When bilateral thalamic hemorrhage is associated with birth asphyxia, mortality is high, and sequelae in survivors are high. Thalamic hemorrhage with IVH seen in infants with an uneventful birth history is associated with a greater risk for CP than IVH from other sites.

Subdural Hemorrhage

Subdural and subarachnoid hemorrhages are probably underdiagnosed because they are often asymptomatic and difficult to recognize using cUS. Subdural hemorrhage usually occurs secondary to birth trauma. The more severe hemorrhages are relatively uncommon today because of improvements in obstetric care, but when MRI is performed routinely, smaller subdural hemorrhages are commonly seen [113,114]. Vaginal breech deliveries, for instance, are no longer commonly performed after recent multicenter randomized studies [115]. Occipital diastasis can occur during a vaginal breech delivery with excessive extension of the neck of the infant. The pathogenesis is secondary to mechanical injury to the cranium associated with instrumental delivery with forceps or ventouse extraction of the head, abnormal presentation (face or brow), precipitous delivery, and a large infant resulting in a difficult delivery [116]. There are shearing forces on the tentorium and the deep venous system. Children are usually born at term and present with a full fontanel, lethargy, apneas, and/or seizures. Hydrocephalus can develop due to outflow obstruction and may require temporary external drainage, sometimes followed by permanent drainage, due to difficulties of CSF reabsorption at the level of the arachnoid granulations. Secondary cerebral infarction has also been reported and has been related to prolonged arterial compression [117]. Most subdural hemorrhages are infratentorial (Figure 24.5), but a supratentorial location can also be noted and is then sometimes associated with a lobar hemorrhage, which can be large and associated with a shift of the midline, requiring neurosurgical intervention. Percutaneous needle aspiration of the subdural hematoma may be successful and is recommended as the treatment of choice [118]. Short-term outcome in children with an isolated infratentorial subdural hemorrhage, but also in those with a lobar hemorrhage, has often been reported to be more favorable than expected, but the groups are usually small [119].

Subgaleal Hemorrhage

Subgaleal hemorrhage is a rare and potentially fatal condition of the neonate often associated with instrumental delivery. It is caused by rupture of the emissary veins, which are connections between the dural sinuses and the scalp veins. Blood accumulates between the epicranial aponeurosis of the scalp and the periosteum. Most cases of subgaleal hemorrhage reported have been associated with use of the vacuum extractor. The incidence of subgaleal hemorrhage is estimated to be 4–6/10,000 spontaneous vaginal deliveries and 46–59/10,000 vacuum-assisted deliveries [120,121]. The children will present with diffuse swelling of the head and evidence of hypovolemic shock.

In a study by Kilani and Wetmore, associated intracranial hemorrhage was present in half the 34 infants studied, and 4 (11.8%) infants died [120].

In another study of 42 infants, 31% had a poor outcome (5 died, 4 had epilepsy, 3 had severe auditory dysfunction, 2 had CP, and 1 had renal vein thrombosis) [121]. The group with the poor outcome included significantly more patients who had been transferred from other hospitals ($p < 0.001$). Those with a poor outcome had significantly more hypotension ($p < 0.001$) and seizures ($p < 0.05$). Prompt and aggressive administration of blood products and treatment of associated coagulopathy are recommended to improve outcome.

Intracranial Hemorrhage Associated with Other Specific Conditions in Term Infants

Neonatal Alloimmune Thrombocytopenia

In neonatal alloimmune thrombocytopenia (NAITP), fetal and neonatal thrombocytopenia results from the formation of a maternal antiplatelet antibody to a paternally derived platelet antigen, usually platelet surface antigen (PlA1), expressed on the surface of the fetal platelets. NAITP occurs in 1/2000 to 1/5000 fetuses, and up to 30% of infants with this condition have ICH secondary to thrombocytopenia. ICH occurs in as many as 10–30% of the infants with alloimmune thrombocytopenia, 25–50% of which occur in utero [122]. NAITP has an estimated mortality rate of 15%, with ICH accounting for most deaths. Fetal and neonatal platelet counts of less than 20×10^9 are common even before 24 weeks′ gestation [123]. Management in the antenatal period includes administration of intravenous gammaglobulin to the mother with or without corticosteroids prior to delivery. Transfusion of matched, compatible platelets to the fetus may safeguard against ICH during the birthing process. Abdominal delivery is suggested if cordocentesis reveals fetal thrombocytopenia. After birth, transfusion with antigen-negative platelets (maternal platelets) is recommended. Hemispheric porencephalic cyst, following a hemorrhage that is most commonly located within a temporal lobe, is usually present at birth, but extra-axial hemorrhages, IVH, acute parenchymal hemorrhage, and neuronal migrational disorder have also been reported [122].

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is the treatment of choice in infants with persistent pulmonary hypertension and cardiorespiratory failure unresponsive to inhaled nitric oxide. In term infants, ICH following ECMO occurs in 10–13% [124]. The lesions are hemorrhagic, with ischemia (60%) or hemorrhage alone (40%). The pathogenesis of ICH following ECMO is multifactorial, and it has been attributed to reperfusion injury, hemodynamic and cerebrovascular instability, systemic heparinization, and increased central venous pressure. Initially, gestational age (GA) of less than 34 weeks, acidosis, sepsis, coagulopathy, and treatment with epinephrine were found to be major independent factors associated with ICH in neonates treated with ECMO. More recent data have shown that postconceptional age (PCA) shows a strong univariate correlation with decreasing ICH: 26% of patients of 32 weeks' or less PCA developed ICH, compared with 6% of patients of 38 weeks' PCA ($p = 0.004$) [124]. In ECMO-treated infants, the combination of a normal bedside US and an EEG without marked abnormalities is highly predictive of normal post-ECMO CT and MRI neuroimaging studies [125]. Among 183 ECMO survivors, 85 infants had neuroimaging abnormalities. Survivors with nonhemorrhagic abnormalities had a higher risk of delayed development than did those with isolated hemorrhagic abnormalities (39% versus 21%) [126,127]. Attempts at decreasing the risk of ICH with ECMO include venovenous (VV) ECMO, in which the integrity of blood flow to the brain is maintained and cannulation and sacrifice of only the internal jugular vein occur. Furthermore, there was a significant relation between the development of intracranial hemorrhage and more than eight infusions or more than 300 mL of volume infusion in the first 8 hours and more than 10 infusions in the first 24 hours of treatment [128].

References

1. Del Bigio MR. Cell proliferation in human ganglionic eminence and suppression after prematurity-associated haemorrhage. *Brain* 2011; **134**(Pt 5): 1344–61.
2. Paneth N, Rudelli R, Kazam E, et al. *Brain Damage in the Preterm Infant* (Clinics in Developmental Medicine 131). London: MacKeith Press, 1994.
3. Parodi A, Rossi A, Severino M et al. Accuracy of ultrasound in assessing cerebellar haemorrhages in very low birthweight babies. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**(4): F289–92.

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3a. Tortora D, Severino M, Malova M et al. Differences in subependymal vein anatomy may predispose preterm infants to GMH-IVH Arch Dis Child Fetal Neonatal Ed. 2017 Jun 6. pii: fetalneonatal-2017-312710. doi: 10.1136/archdischild-2017-312710. [Epub ahead of print]

4. Takashima S, Takashi M, Ando Y. Pathogenesis of periventricular white matter haemorrhage in preterm infants. *Brain Dev* 1986; **8**: 25–30.

5. Gould SJ, Howard S, Hope PL, et al. Periventricular intraparenchymal cerebral haemorrhage in preterm infants: the role of venous infarction. *J Pathol* 1987; **151**: 197–202.

6. Ghazi-Birry HS, Brown WR, Moody DM, et al. Human germinal matrix: venous origin of hemorrhage and vascular characteristics. *AJNR Am J Neuroradiol* 1997; **18**: 219–29.

7. Pape KE, Wigglesworth JS. *Haemorrhage, Ischaemia and Perinatal Brain* (Clinics in Developmental Medicine 69/70). London: SIMP/Heinemann, 1979: 133–48.

8. Ment LR, Stewart WB, Ardito TA, et al. Germinal matrix microvascular maturation correlates inversely with the risk period for neonatal intraventricular hemorrhage. *Brain Res Dev Brain Res* 1995; **84**: 142–9.

9. Pinto Cardoso G, Abily-Donval L, Chadie A, et al. Le réseau de périnatalité de Haute-Normandie [Epidemiological study of very preterm infants at Rouen University Hospital: changes in mortality, morbidity, and care over 11 years]. *Arch Pediatr* 2013; **20**(2): 156–63

10. Horbar JD, Carpenter JH, Badger GJ, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics* 2012; **129**: 1019–26

11. Larroque B, Marret S, Ancel PY, et al. White matter damage and intraventricular hemorrhage in very preterm infants: the EPIPAGE study. *J Pediatr* 2003; **143**: 477–83.

12. Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr* 2004; **145**: 593–9.

13. Thorp JA, Jones PG, Clark RH, et al. Perinatal factors associated with severe intracranial hemorrhage. *Am J Obstet Gynecol* 2001; **185**: 859–62.

14. Yanowitz TD, Jordan JA, Gilmour CH, et al. Hemodynamic disturbances in premature infants born after chorioamnionitis: association with cord blood cytokine concentrations. *Pediatr Res* 2002; **51**: 310–6.

15. Haque KN, Hayes AM, Ahmed Z, et al. Caesarean or vaginal delivery for preterm very-low-birth weight (≤1,250 g) infant: experience from a district general hospital in UK. *Arch Gynecol Obstet* 2008; **277**: 207–12.

16. Riskin A, Riskin-Mashiah S, Bader D et al. Delivery mode and severe intraventricular hemorrhage in single, very low birth weight, vertex infants. *Obstet Gynecol* 2008; **112**: 21–8.

17. Herbst A, Källén K. Influence of mode of delivery on neonatal mortality and morbidity in spontaneous preterm breech delivery. *Eur J Obstet Gynecol Reprod Biol* 2007; **133**: 25–9.

17a. Jensen EA, Lorch SA. Association between Off-Peak Hour Birth and Neonatal Morbidity and Mortality among Very Low Birth Weight Infants. J Pediatr. 2017 Jul; **186**: 41–48.e4

18. Mercer JS, Vohr BR, McGrath MM, et al. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. *Pediatrics* 2006; **117**: 1235–42.

19. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012; **15**(8): CD003248.

20. Heuchan AM, Evans N, Henderson Smart DJ. Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand Neonatal Network, 1995–97. *Arch Dis Child Fetal Neonatal Ed* 2002; **86**: F86–90.

21. Palmer KG, Kronsberg SS, Barton BA, et al. Effect of inborn versus outborn delivery on clinical outcomes in ventilated preterm neonates: secondary results from the NEOPAIN trial. *J Perinatol* 2005; **25**: 270–5.

22. Mohamed MA, Aly H. Transport of premature infants is associated with increased risk for intraventricular haemorrhage. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**: F403–7.

23. Limperopoulos C, Gauvreau KK, O'Leary H, et al. Cerebral hemodynamic changes during intensive care of preterm infants. *Pediatrics* 2008; **122**(5): e1006–13.

24. Vela-Huerta MM, Amador-Licona M, Medina-Ovando N, Aldana-Valenzuela C. Factors associated with early severe intraventricular haemorrhage in very low birth weight infants. *Neuropediatrics* 2009; **40**(5): 224–7.

25. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics* 2003; **112**: 33–9.

26. Tsuji M, Saul P, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000; **106**: 625–32.

27. Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007; **61**: 467–73.

28. Alderliesten T, Lemmers PM, Smarius JJ, et al. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr* 2013; **162**(4): 698–704.

29. Noori S, McCoy M, Anderson MP, et al. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. *J Pediatr* 2014; **164**(2): 264–70.
30. Ikeda T, Amizuka T, Ito Y, et al. Changes in the perfusion waveform of the internal cerebral vein and intraventricular hemorrhage in the acute management of extremely low-birth-weight infants. *Eur J Pediatr* 2015; **174**(3): 331–8
31. Fabres J, Carlo WA, Phillips V, et al. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. *Pediatrics* 2007; **119**: 299–305.
32. Dalton J, Dechert RE, Sarkar S. Assessment of association between rapid fluctuations in serum sodium and intraventricular hemorrhage in hypernatremic preterm infants. *Am J Perinatol* 2015; **32**(8): 795–802.
33. Barnette AR, Myers BJ, Berg CS, Inder TE. Sodium intake and intraventricular hemorrhage in the preterm infant. *Ann Neurol* 2010; **67**(6): 817–23
34. Ryckman KK, Dagle JM, Kelsey K, et al. Replication of genetic associations in the inflammation, complement, and coagulation pathways with intraventricular hemorrhage in LBW preterm neonates. *Pediatr Res* 2011; **70**: 90–5.
35. Ment LR, Adén U, Lin A et al. Gene Targets for IVH Study Group. Gene-environment interactions in severe intraventricular hemorrhage of preterm neonates. *Pediatr Res* 2014; **75**(1–2): 241–50.
36. Harteman JC, Groenendaal F, van Haastert IC, et al. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. *Dev Med Child Neurol* 2012; **54**(2): 140–7
37. Harding DR, Dhamrait S, Whitelaw A, et al. Does interleukin-6 genotype influence cerebral injury or developmental progress after preterm birth? *Pediatrics* 2004; **114**(4): 941–7
38. Göpel W, Härtel C, Ahrens P, et al. Interleukin-6–174-genotype, sepsis and cerebral injury in very low birth weight infants. *Genes Immun* 2006; **7**: 65–8.
39. Kallankari H, Kaukola T, Ojaniemi M, et al. Chemokine CCL18 predicts intraventricular hemorrhage in very preterm infants. *Ann Med* 2010; **42**: 416–25.
40. de Vries LS, Koopman C, Groenendaal F, et al. *COL4A1* mutation in two preterm siblings with antenatal onset of parenchymal haemorrhage. *Ann Neurol* 2009; **65**: 12–8.
41. Meuwissen ME, Halley DJ, Smit LS, et al. The expanding phenotype of *COL4A1* and *COL4A2* mutations: clinical data on 13 newly identified families and a review of the literature. *Genet Med* 2015; **7**(11): 843–53.
42. Shankaran S, Bauer CR, Bain R, et al. Prenatal and perinatal risk and protective factors for neonatal intracranial hemorrhage. *Arch Pediatr Adolesc Med* 1996; **150**: 491–7.
43. Gagliardi L, Rusconi F, Da Frè M, et al. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study. *Pediatr Res* 2013; **73**: 794–801.
44. Andre P, Thebaud B, Delavaucoupet J, et al. Late-onset cystic periventricular leukomalacia in premature infants: a threat until term. *Am J Perinatol* 2001; **18**: 79–86.
45. de Vries LS, Rademaker KJ, Roelantsvan-Rijn AM, et al. Unilateral haemorrhagic parenchymal infarction in the preterm infant. *Eur J Pediatr Neurol* 2001; **5**: 139–49.
46. Volpe JJ. *Neonatal Neurology*, 4th edn. Philadelphia: Saunders, 2001.
47. Correa F, Enríquez G, Rosselló J, et al. Posterior fontanelle sonography: an acoustic window into the neonatal brain. *AJNR Am J Neuroradiol* 2004; **25**: 1274–82.
48. Maalouf EF, Duggan PJ, Counsell SJ, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics* 2001; **107**: 719–27.
49. Parodi A, Morana G, Severino MS, et al. Low-grade intraventricular hemorrhage: is ultrasound good enough? *J Matern Fetal Neonatal Med* 2015; Suppl 1:2261–4.
50. Dudink J, Lequin M, Weisglas-Kuperus N, et al. Venous subtypes of preterm periventricular haemorrhagic infarction. *Arch Dis Child Fetal Neonatal Ed* 2007; **93**: F201–6.
51. Bassan H, Benson CB, Limperopoulos C, et al. Ultrasonographic features and severity scoring of periventricular hemorrhagic infarction in relation to risk factors and outcome. *Pediatrics* 2006; **117**: 2111–18.
52. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics* 2007; **120**: 785–92.
53. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. *Pediatrics* 2005; **116**: 717–24.
54. Steggerda SJ, Leijser LM, Wiggers-de Bruïne FT, et al. Cerebellar injury in preterm infants: incidence and findings on US and MR images. *Radiology* 2009; **252**: 190–9.
55. Ecury-Goossen GM, Dudink J, Lequin M, et al. The clinical presentation of preterm cerebellar haemorrhage. *Eur J Pediatr* 2010; **169**(10): 1249–53.

56. Tam EW, Miller SP, Studholme C, et al. Differential effects of intraven- tricular hemorrhage and white matter injury on preterm cerebellar growth. *J Pediatr* 2011; **158**(3): 366–71.

57. Steggerda SJ, De Bruïne FT, van den Berg-Huysmans AA, et al. Small cerebellar hemorrhage in preterm infants: perinatal and postnatal factors and outcome. *Cerebellum* 2013; **12**(6): 794–801

58. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? *Pediatrics* 2007; **120**: 584–93.

59. Srinivasan L, Allsop J, Counsell SJ, et al. Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. *AJNR Am J Neuroradiol* 2006; **27**: 573–9.

60. Morita T, Morimoto M, Yamada K, et al. Low-grade intraventricular hemorrhage disrupts cerebellar white matter in preterm infants: evidence from diffusion tensor imaging. *Neuroradiology* 2015; **57**(5): 507–14

61. McLendon D, Check J, Carteaux P, et al. Implementation of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics* 2003; **111**: e497–503.

62. Olischar M, Klebermass K, Waldhoer T, et al. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr* 2007; **96**: 1743–50.

63. Murphy BP, Inder TE, Rooks V, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. *Arch Dis Child Fetal Neonatal Ed* 2002; **87**: F37–41.

64. Ingram MC, Huguenard AL, Miller BA, Chern JJ. Poor correlation between head circumference and cranial ultrasound findings in premature infants with intraventricular hemorrhage. *J Neurosurg Pediatr* 2014; **14**: 184–9.

65. Levene MI, Starte DR. A longitudinal study of posthaemorrhagic ventricular dilatation in the newborn. *Arch Dis Child* 1981; **56**: 905–10.

66. Davies MW, Swaminathan M, Chuang SI, et al. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. *Arch Dis Child Fetal Neonatol Ed* 2000; **82**:F219–23.

67. Brouwer MJ, de Vries LS, Groenendaal F, et al. New reference values for the neonatal cerebral ventricles. *Radiology* 2012; **262**(1): 224–33.

68. Kaiser A, Whitelaw A. Cerebrospinal fluid pressure during posthaemorrhagic ventricular dilatation in newborn. *Arch Dis Child* 1985; **60**: 920–4.

69. Soul JS, Eichenwald E, Walter G, et al. CSF removal in infantile posthemorrhagic hydrocephalus results in significant improvement in cerebral hemodynamics. *Pediatr Res* 2004; **55**: 872–6.

70. Klebermass-Schrehof K, Rona Z, Waldhör T, et al. Can neurophysiological assessment improve timing of intervention in posthaemorrhagic ventricular dilatation? *Arch Dis Child Fetal Neonatal Ed* 2013; **98**(4): F291–7.

71. Sävman K, Blennow M, Hagberg H, et al. Cytokine response in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. *Acta Paediatr* 2002; **91**: 1357–63.

72. Felderhoff-Mueser U, Buhrer C, Groneck P, et al. Soluble Fas (CD95/Apo-1), soluble Fas ligand and activated caspase 3 in the cerebrospinal fluid of infants with posthemorrhagic and nonhemorrhagic hydrocephalus. *Pediatr Res* 2003; **54**: 59–64.

73. Heep A, Stoffel-Wagner B, Bartmann P, et al. Vascular endothelial growth factor and transforming growth factor-β1 are highly expressed in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus. *Pediatr Res* 2004; **56**: 768–74.

74. Schmitz T, Heep A, Groenendaal F, et al. Interleukin-1β, interleukin-18, and interferon-γ expression in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus–markers of white matter damage? *Pediatr Res* 2007; **61**: 722–6.

74a. Whitelaw A, Lee-Kelland R. Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev. 2017 Apr 6; 4: CD000216.

75. Ventriculomegaly Trial Group. Randomized trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. *Arch Dis Child Fetal Neonatal Ed* 1994; **70**: F129–36.

76. Whitelaw A, Evans D, Carter M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brainwashing versus tapping fluid. *Pediatrics* 2007; **119**: e1071–8.

77. Brouwer AJ, Groenendaal F, van Haastert IC, et al. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. *J Pediatr* 2008; **152**: 648–54.

78. Bassan H, Eshel R, Golan I, et al. External Ventricular Drainage Study Investigators. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. *Eur J Paediatr Neurol* 2012; **16**(6): 662–70.

79. Vasileiadis GT, Gelman N, Han VK, et al. Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age. *Pediatrics* 2004; **114**: e367–72.

80. Patra K, Wilson-Costello D, Taylor HG, et al. Grades I–II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. *J Pediatr* 2006; **149**: 169–73.

81. Bolisetty S, Dhawan A, Abdel-Latif M, et al. New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. *Pediatrics* 2014; **133**(1): 55–62.

82. Payne AH, Hintz SR, Hibbs AM, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. *JAMA Pediatr* 2013; **167**(5): 451–9.

83. Radic JAE, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. *J Neurosurg Pediatr* 2015; **15**: 580–8.

83a. Reubsaet P, Brouwer AJ, van Haastert IC, et al The Impact of Low-Grade Germinal Matrix-Intraventricular Hemorrhage on Neurodevelopmental Outcome of Very Preterm Infants. *Neonatology* 2017 Jul 14; **112**(3): 203–210

84. Kuban K, Sanocka U, Leviton A, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. *J Pediatr* 1999; **134**: 539–46.

85. Brouwer MJ, van Kooij BJ, van Haastert IC, et al. Sequential cranial ultrasound and cerebellar diffusion weighted imaging contribute to the early prognosis of neurodevelopmental outcome in preterm infants. *PLoS One*. 2014; **9**(10): e109556

86. Fernell E, Hagberg G, Hagberg B. Infantile hydrocephalus in preterm, low-birth-weight infants: a nationwide Swedish cohort study 1979–1988. *Acta Paediatr* 1993; **82**: 45–8.

87. Persson EK, Hagberg G, Uvebrant P. Disabilities in children with hydrocephalus: a population-based study of children aged between four and twelve years. *Neuropediatrics* 2006; **37**: 330–6.

88. Sherlock RL, Synnes AR, Grunau RE, et al. Long-term outcome after neonatal intraparenchymal echodensities with porencephaly. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F127–31.

89. De Vries LS, Groenendaal F, Eken P, et al. Asymmetrical myelination of the posterior limb of the internal capsule: an early predictor of hemiplegia. *Neuropediatrics* 1999; **30**: 314–19.

90. Roze E, Benders MJ, Kersbergen KJ, et al. Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction. *Pediatr Res* 2015; **78**(3): 298–303.

91. Counsell SJ, Dyet LE, Larkman DJ, et al. Thalamo-cortical connectivity in children born preterm mapped using probabilistic magnetic resonance tractography. *Neuroimage* 2007; **34**: 896–904.

92. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006; **3**: CD004454.

93. Brownfoot FC, Gagliardi DI, Bain E, et al. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2013; **8**: CD006764.

94. Baud O, Foix-L'Helias L, Kaminski M, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Engl J Med* 1999; **341**: 1190–6.

95. Modi N, Lewis H, Al-Naqeeb N, et al. The effects of repeated antenatal glucocorticoid therapy on the brain. *Pediatr Res* 2001; **50**: 581–5.

96. Wapner RJ, Sorokin Y, Mele L, et al. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357**(12): 1190–8.

97. Crowther CA, Hiller JE, Doyle LW, et al. Effect of magnesium sulfate given for neuroprotection before preterm birth. *JAMA* 2003; **290**: 2669–76.

98. Rouse DJ, Hirtz DG, Thom E, et al. A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.

99. Doyle LW, Crowther CA, Middleton P, Marret S. Antenatal magnesium sulfate and neurologic outcome in preterm infants: a systematic review. *Obstet Gynecol* 2009; **113**: 1327–33.

100. Stark MJ, Hodyl NA, Andersen CC. Effects of antenatal magnesium sulphate treatment for neonatal neuro-protection on cerebral oxygen kinetics. *Pediatr Res* 2015; **78**(3): 310–4.

101. Kamyar M, Manuck TA, Stoddard GJ, et al. Magnesium sulfate, chorioamnionitis, and neurodevelopment after preterm birth. *BJOG* 2016; **123**(7): 1161–6.

102. Crowther CA, Crosby DD, Henderson-Smart DJ. Vitamin K prior to preterm birth for preventing

neonatal periventricular haemorrhage. *Cochrane Database Syst Rev* 2010; **20**(1): CD000229.

103. Smit E, Odd D, Whitelaw A. Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants. *Cochrane Database Syst Rev* 2013; **13**(8): CD001691.

104. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev* 2010; **7**(7): CD000174.

105. Schmidt B, Davis P, Moddeman D, et al. Trial of indomethacin prophylaxis in preterm investigators: long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Eng J Med* 2001; **344**: 1966–72.

106. Ment LR, Peterson BS, Meltzer JA, et al. A functional magnetic resonance imaging study of the long-term influences of early indomethacin exposure on language processing in the brains of prematurely born children. *Pediatrics* 2006; **118**: 961–70.

107. Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364**(9449): 1945–9.

108. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2006; **1**: CD004213.

109. Synnes AR, Macnab YC, Qiu Z, et al. Neonatal intensive care unit characteristics affect the incidence of severe intraventricular hemorrhage. *Med Care* 2006; **44**: 754–9.

110. Wu YW, Hamrick SEG, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. *Ann Neurol* 2003; **54**: 123–6.

111. Roland EH, Flodmark O, Hill A. Thalamic hemorrhagic with intraventricular hemorrhage in the full term newborn. *Pediatrics* 1990; **85**: 737–42.

112. Jocelyn LJ, Casiro OG. Neurodevelopmental outcome of term infants with intraventricular hemorrhage. *Am J Dis Child* 1992; **146**: 194–7.

113. Whitby EH, Griffiths PD, Rutter S, et al. Frequency and natural history of subdural haemorrhages in babies and relation to obstetric factors. *Lancet* 2004; **363**: 846–51.

114. Looney CB, Smith JK, Merck LH, et al. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. *Radiology* 2007; **242**: 535–41.

115. Hofmeyr GJ, Hannah ME. Planned caesarean section for term breech delivery. *Cochrane Database Syst Rev* 2003; **3**: CD000166.

116. Chamnanvanakij S, Rollins N, Perlman JM. Subdural hematoma in term infants. *Pediatr Neurol* 2002; **26**: 301–14.

117. Govaert P, Vanhaesebrouck P, de Praeter C. Traumatic neonatal intracranial bleeding and stroke. *Arch Dis Child* 1992; **67**: 840–5.

118. Brouwer AJ, Groenendaal F, Koopman C, et al. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. *Neuroradiology* 2010; **52**(6): 567–76

119. Vinchon M, Pierrat V, Tchofo PJ, et al. Traumatic intracranial hemorrhage in newborns. *Childs Nerv Syst* 2005; **21**: 1042–8.

120. Kilani RA, Wetmore J. Neonatal subgaleal hematoma: presentation and outcome. Radiological findings and factors associated with mortality. *Am J Perinatol* 2006; **23**: 41–8.

121. Chang HY, Peng CC, Kao HA, et al. Neonatal subgaleal hemorrhage: clinical presentation, treatment, and predictors of poor prognosis. *Pediatr Int* 2007; **49**: 903–7.

122. Dale ST, Coleman LT. Neonatal alloimmune thrombocytopenia: antenatal and postnatal imaging findings in the pediatric brain. *AJNR Am J Neuroradiol* 2002; **23**: 1457–65.

123. Berkowitz RL, Bussel JB, McFarland JG. Alloimmune thrombocytopenia: state of the art 2006. *Am J Obstet Gynecol* 2006; **195**(4): 907–13.

124. Hardart GE, Hardart MKM, Arnold JH. Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptional age. *J Pediatr* 2004; **145**: 184–9.

125. Gannon CM, Kornhauser MS, Gross GW, et al. When combined, early bedside head ultrasound and electroencephalography predict abnormal computerized tomography or magnetic resonance brain images obtained after extracorporeal membrane oxygenation treatment. *J Perinatol* 2001; **21**: 451–5.

126. Bulas DI, Glass P, O'Donnell RM, et al. Neonates treated with ECMO: predictive value of early CT and US neuroimaging findings on short-term neurodevelopmental outcome. *Radiology* 1995; **195**: 407–12.

127. Bulas D, Glass P. Neonatal ECMO: neuroimaging and neurodevelopmental outcome. *Semin Perinatol* 2005; **29**(1): 58–65.

128. de Mol AC, Gerrits LC, van Heijst AF, et al. Intravascular volume administration: a contributing risk factor for intracranial hemorrhage during extracorporeal membrane oxygenation? *Pediatrics* 2008; **121**(6): e1599–603.

Chapter 25

Neonatal Stroke

Dawn Gano and Donna M. Ferriero

Introduction

Neonatal stroke is increasingly recognized as an important cause of neurologic morbidity including cerebral palsy (CP), epilepsy, and behavioral disorders, as well as impaired visual function and language development [1–8]. The estimated incidence of neonatal stroke is approximately 1/2,000 live births [9].

Neonatal stroke can be classified by blood supply (venous versus arterial), age at stroke (fetal versus neonatal), age at diagnosis (neonatal symptomatic versus presumed perinatal/neonatal asymptomatic), or type of stroke (ischemic versus hemorrhagic). Investigators have used a variety of terms, including *neonatal stroke, perinatal stroke, arterial ischemic stroke*, and *perinatal arterial stroke* to describe the conditions. *Perinatal arterial ischemic stroke* (PAIS), now the term of choice, is defined as "a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral sinovenous thrombosis (CSVT) or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies" [10]. PAIS is further divided into three categories based on the timing of diagnosis: (1) *fetal ischemic stroke*, diagnosed prior to birth using fetal imaging or following stillbirth on the basis of neuropathologic examination, (2) *neonatal ischemic stroke*, diagnosed after birth and up to an including the twenty-eighth postnatal day (including preterm infants), and (3) *presumed perinatal ischemic stroke* (PPIS), diagnosed in children after 28 days of life in whom the ischemic event is presumed to have occurred between the twentieth week of fetal life and the twenty-eighth postnatal day [10]. This terminology does not take into account venous thrombosis without ischemic infarction or purely hemorrhagic conditions. Hemorrhagic perinatal stroke is less well characterized, and there is no consensus on terminology or classification.

Epidemiology

Neonatal stroke accounts for approximately 25% of arterial and 50% of cerebral sinovenous thrombosis (CSVT) in the pediatric population [4]. The incidence of neonatal stroke is estimated to be between 1/1,600 and 1/5,000 live births [9,11–13]. Among children with motor impairment due to neonatal stroke, approximately two-thirds present after 3 months of age [14]. There are no apparent differences by infant sex or racial group, though data are somewhat inconsistent between study cohorts [9,12,13].

Clinical Manifestations

The clinical manifestations of neonatal stroke depend on the timing of presentation (i.e., fetal, neonatal, or during infancy and childhood) as well as the extent and location of brain involvement.

Fetal Ischemic Stroke

Fetal ischemic stroke is diagnosed prior to birth using ultrasound and/or magnetic resonance imaging (MRI) or following stillbirth on the basis of neuropathologic examination. Though typically asymptomatic to the mother and child before delivery, there is a high rate of pregnancy termination, preterm delivery, and neonatal complications including hypotonia and seizures [15].

Neonatal Ischemic Stroke

Neonatal ischemic stroke includes both arterial stroke and CSVT diagnosed after birth and before or on the twenty-eighth postnatal day. This category includes the special case of infants with ischemic stroke who were born prematurely.

Neonatal Arterial Stroke

Term newborn infants with arterial stroke present most commonly with persistent focal seizures in the first hours of life [16,17]. Infants may otherwise

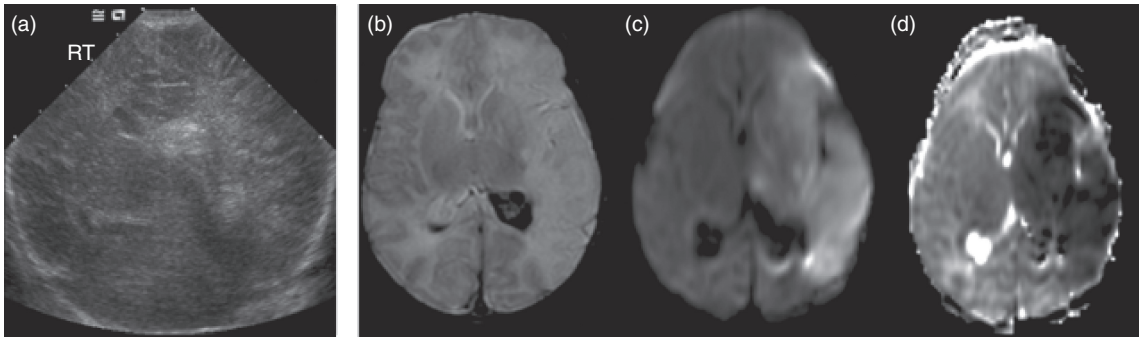


Figure 25.1 Neonatal ischemic arterial stroke in a 2-day term infant with seizures at 36 hours of life. (a) High-resolution ultrasound through the anterior fontanel showing echogenic left thalamus, basal ganglia, and hemispheric white matter with mild mass effect effacing the left ventricle in keeping with left middle cerebral territory infarct. MRI showing (b) T2 prolongation and (c, d) reduced diffusion in the entire left middle cerebral area territory including cortex, basal ganglia, and caudate.

appear well or have subtle motor asymmetry, generalized hypotonia, or, especially in the setting of concurrent global hypoxic-ischemic brain injury, signs of encephalopathy, including depressed level of alertness, apnea, and altered feeding [3,18]. Motor asymmetry, if present, is typically subtle, though the infant's general movements are frequently abnormal [19].

Arterial infarcts are slightly more common in the left hemisphere than in the right hemisphere and occur more commonly in the anterior circulation (Figure 25.1) [20]. The stroke may involve small- or large-artery territory, and multiple infarcts are present in up to 20% of cases [4]. Recent data have demonstrated that noncortical strokes in regions supplied by perforator arteries have similar pathogenic mechanisms to large-artery-territory infarcts, such as hypoxia-ischemia, embolism, and infection [21]. Perforator artery strokes are frequently asymptomatic [21].

Neonatal Cerebral Sinovenous Thrombosis

Cerebral sinovenous thrombosis (CSVT) typically presents in the first weeks of life with nonspecific signs and symptoms including encephalopathy, apnea, and seizures. Infants with CSVT frequently have comorbid risk factors, including dehydration, cardiac defects, sepsis, or meningitis and an extracorporeal life-support requirement [22–25].

Computed tomography or magnetic resonance or conventional angiographic venography may show that one or more venous structures are involved, most often the sagittal, transverse, and straight sinuses [22,25]. Common sequelae include venous infarction with parenchymal and intraventricular hemorrhage [22,26,27].

Neonatal Ischemic Stroke in the Preterm Infant

Increased use of imaging in premature infants has led to greater recognition of arterial stroke prior to term-equivalent postmenstrual age. The clinical presentation in premature infants is very different from that in term infants, with less than a third presenting with seizures or apnea. Premature infants with stroke are most often identified during routine cranial ultrasound monitoring, with the diagnosis later confirmed using MRI [28]. As with term infants, arterial stroke in premature newborns is more often unilateral, in the middle cerebral artery territory distribution, and left sided. Lenticulostriate distribution is common, especially in infants born at 28–32 weeks' gestation [29]. Twin-to-twin transfusion syndrome, fetal heart rate abnormalities, and hypoglycemia appear to be risk factors for preterm arterial stroke [29].

Presumed Perinatal Ischemic Stroke

Presumed perinatal ischemic stroke (PPIS) is diagnosed in a child more than 28 days old with a normal neonatal period who presents with nonacute neurologic signs or symptoms referable to focal, remote (gliosis, encephalomalacia, and/or atrophy and absent restricted diffusion) infarct(s) on neuroimaging [10,30]. Presenting signs and symptoms include asymmetric motor development (typically pathologic early hand preference or hemiplegia), nonmotor delay, or seizures, leading to a diagnosis of PPIS at a median age of 1 year [31,32]. PPIS may be due to either arterial or venous infarction but excludes global

injuries such as periventricular leukomalacia and basal ganglia or watershed injury due to hypoxic-ischemic injury [30–32]. Children diagnosed with arterial PPIS are more likely to have acute perinatal risk factors, such as fetal distress, emergency cesarean section, or a requirement for neonatal resuscitation [31].

Hemorrhagic Stroke

Perinatal hemorrhagic stroke has received little attention. The estimated incidence of perinatal hemorrhagic stroke in a population-based study (6.2/100,000) is similar to the incidence of subarachnoid hemorrhage in adults [33]. In this same study, neonates with hemorrhagic stroke presented with encephalopathy or seizures, and strokes were typically unilateral and in the frontal or parietal lobes. Fetal distress and post-term delivery at more than 41 weeks' gestation were both independently associated with neonatal hemorrhagic stroke. Type IV collagen α1 (*COL4A1*) mutation is a risk factor for intracerebral hemorrhage and results in porencephaly due to in utero hemorrhagic stroke [34–37]. Recently, a widened phenotypic spectrum of *COL4A1* mutation–related disorders have been described [37]. In addition to porencephaly and transmantle lesions, which result in hydranencephaly or schizencephaly, mutations in *COL4A1* and *COL4A2* are also associated with systemic features including lesions of the kidneys, eyes, heart, and skeletal muscle. Mutations in *COL4A1* and *COL4A2* are autosomal dominant and often occur de novo [37].

Risk Factors

The etiology and pathogenesis of perinatal stroke are not well understood. Multiple potential risk factors have been recognized through case series and reports, as well as population-based epidemiologic studies. Frequently, multiple concurrent risk factors are present, and in one study, the presence of multiple risk factors before delivery significantly increased the risk of perinatal stroke [12]. It is important to note that the majority of infants with one or more risk factors for stroke are entirely normal and that, conversely, in many cases no risk factor for the stroke is identified. Further understanding of the genetic factors that predispose newborns to stroke may help to explain the cause in a proportion of newborns with no discernible etiology.

Maternal Factors

Maternal acquired and inherited thrombophilias are important risk factors for perinatal stroke. Pregnancy itself is a physiologic prothrombotic and pro-inflammatory state for the mother and her child [38]. Antiphospholipid antibodies (lupus anticoagulant and cardiolipin antibody) present in women with systemic lupus erythematosus or other autoimmune disorders increase the risk for fetal loss and for ischemic perinatal stroke [39–41]. Inherited thrombophilias may be present in either the mother or her child with perinatal stroke and are further discussed under infant factors [42].

Hypertensive disorders of pregnancy, specifically eclampsia and preeclampsia, are associated with a higher risk of neonatal stroke [12,43]. The pathophysiology may be related to a high frequency of factor V Leiden mutation in women with preeclampsia and with hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP) syndrome [43].

Further maternal risk factors for perinatal stroke include a history of infertility and primiparity [12]. Obesity, older maternal age, family history of thromboemboblic events, surgery, dehydration, shock, and prolonged bed rest are all risk factors for maternal thrombosis [44]. Maternal cocaine use is a rare but important cause of ischemic perinatal stroke [45,46].

Antepartum and Intrapartum Factors

Independent risk factors that may occur during pregnancy and delivery include oligohydramnios, cord abnormality, chorioamnionitis, and prolonged rupture of the membranes [12].

Infant Factors

A number of systemic illnesses or conditions may increase the risk of stroke in newborn infants. Meningitis/encephalitis, polycythemia, congenital heart disease, and extracorporeal membrane oxygenation have all been reported in infants with stroke [47–50]. Several prothrombotic disorders have been reported in infants with stroke, including protein S, protein C, and antithrombin III deficiencies; elevated lipoprotein(a), antiphospholipid antibodies, factor V G1691A, prothrombin G20210A, and *MTHFR* mutations; and elevated homocysteine [41,51–56]. However,

many of these prothrombotic disorders are seen with high frequency in the general population, and conversely, some infants with stroke have no detectable abnormality [57]. Therefore, the exact role of thrombophilia in the pathophysiology of perinatal stroke remains uncertain. Mutations in the genes *COL4A1* and *COL4A2* are associated with a wide spectrum of cerebrovascular lesions in newborns, in particular, hemorrhagic stroke and porencephaly (see "Hemorrhagic Stroke") [37].

Evaluation

History and Physical Examination

The history and physical examination are important in the initial evaluation of an infant with suspected stroke (Table 25.1). Detailed family history, as well as evaluation of maternal medical conditions and events during pregnancy and delivery, may reveal one or more risk factors for perinatal stroke. Although the initial examination may be normal, newborns with arterial ischemic stroke are often systemically sick, presenting with seizures, encephalopathy, and nonfocal neurologic signs [20].

Neuroimaging

Magnetic resonance imaging (MRI) is the study of choice for the diagnosis and evaluation of perinatal stroke. Cranial ultrasound with transcranial Doppler may detect obliteration of normal gyral patterns, echogenicity in an arterial territory distribution, mass effect, or a decrease in cerebral artery flow velocities in the affected hemisphere [58,59]. However, cranial ultrasound is less sensitive than other imaging modalities and should be supplemented with computed tomography (CT) or, preferably, MRI, when available [60,61]. CT has the advantage of being readily available and can often be performed without sedation. However, it provides less detailed anatomy than MRI and exposes the infant to ionizing radiation.

Restricted water motion on diffusion-weighted imaging (DWI) sequences is apparent shortly after the injury but becomes falsely negative (pseudonormalizes) by approximately 7 days [62]. Conventional T1- and T2-weighted MRI sequences may be normal in the first 48 hours, making 2–5 days of life an ideal time to image the infant with suspected stroke [63]. In cases of suspected CSVT, vascular imaging (magnetic resonance venography [MRV]) with or without gadolinium contrast is essential to accurately diagnose and follow venous thrombosis [25,64].

In cases of presumed perinatal ischemic stroke, conventional T1- and T2-weighted images may reveal signs of remote infarct, including cystic encephalomalacia, gliosis, focal ventricular dilation, and Wallerian degeneration of the descending corticospinal tracts (Figures 25.2 and 25.3) [30,31,65–67].

Electroencephalography

Recurrent focal seizure is the most common initial presentation of neonatal stroke [17]. An electroencephalogram (EEG) is essential to evaluate for subclinical seizures (especially after administration of antiseizure medication, which may lead to electroclinical dissociation) and to identify background abnormalities, which indicate poor neuromotor prognosis [3,68]. EEG abnormalities, including focal attenuation, epileptiform discharges, and/or focal seizures, are typically transient and present only during the first days to weeks after the injury [69].

Laboratory Studies

Initial laboratory evaluation should include studies that are routinely performed in an infant with seizures or encephalopathy, such as complete blood count with differential electrolytes (including calcium and magnesium), glucose levels, prothrombin time with international normalized ratio, partial thromboplastin time, and cultures for infection. Once ischemic stroke is confirmed by imaging, the infant and mother can be investigated for thrombophilia, both in the acute period and again at 3 months, though the results are unlikely to change management [70]. A transthoracic echocardiogram should be performed in infants with abnormal cardiac examination or suspected embolic infarct to exclude underlying cardiac disease. Pathologic examination of the placenta may identify lesions to support a pathogenic mechanism, such as a thromboinflammatory process, stressful intrauterine environment, or catastrophic event [71].

Management

During the acute phase of neonatal stroke, excellent supportive care is important to minimize secondary brain injury. While there are no data from human neonatal trials, animal and adult studies support active maintenance of physiologic homeostasis,

Table 25.1 Evaluation and Investigation of Perinatal Stroke

Investigation	Comment
History	
Family	Careful history may reveal one or more risk factors for perinatal stroke
Maternal	Lupus and autoimmune disease, history of infertility, cocaine use
Antepartum/intrapartum	Hypertensive disorders of pregnancy, oligohydramnios, cord abnormality, chorioamnionitis
Delivery	Prolonged rupture of the membranes, fetal distress, emergency cesarean section, requirement for neonatal resuscitation
Infant	Meningitis/encephalitis, polycythemia, congenital heart disease, extracorporeal membrane oxygenation
Imaging	
Magnetic resonance imaging (MRI)	MRI with diffusion-weighted imaging is the imaging study of choice
Computed tomography	
Cranial ultrasound	
Laboratory evaluation	
Complete blood count with differential	
Serum electrolytes and glucose	
Prothrombin time with international normalized ratio (PT/INR)	
Partial thromboplastin time (PTT)	
Thrombophilia evaluation	Thrombophilia evaluation can be performed in the mother and child in the acute and convalescent periods
Protein S/C activity	
Antithrombin III activity	
Activated protein C resistance	
Lipoprotein(a)	
Homocysteine	
Factor V Leiden	
Prothrombin 20210A	
Antiphospholipid antibody testing	
Other	
Electroencephalogram	Further evaluation can be tailored to the nature and timing of the insult
Echocardiogram	
Placental pathology	

including temperature and blood glucose levels [72,73]. Expert opinion supports aggressive treatment of clinical and electrographic seizures that are frequent and/or prolonged [74].

The value of antithrombotic therapy in neonates with ischemic stroke is uncertain, and guidelines or recommendations are based on clinical experience in older populations, observational or case studies, and clinical consensus. Guidelines by the American College of Chest Physicians recommend 3 months of anticoagulation with unfractionated or low-molecular-weight heparin for infants with cardioembolic arterial stroke or CSVT and without large-territory involvement or hemorrhage [75]. Antithrombotic

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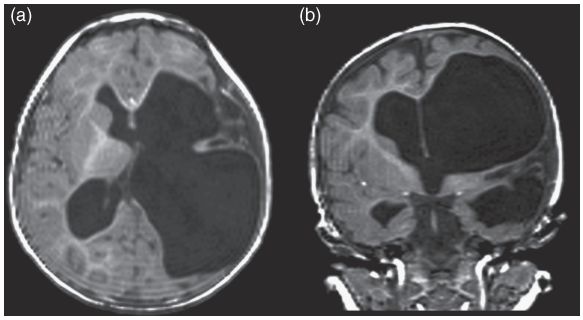


Figure 25.2 Chronic T1 appearance of the infarct seen in Figure 25.1. (a) Axial and (b) coronal images show a large porencephalic cyst that encompasses the left middle cerebral artery territory and causes mass effect with midline shift and expansion of the left hemicalvarium.

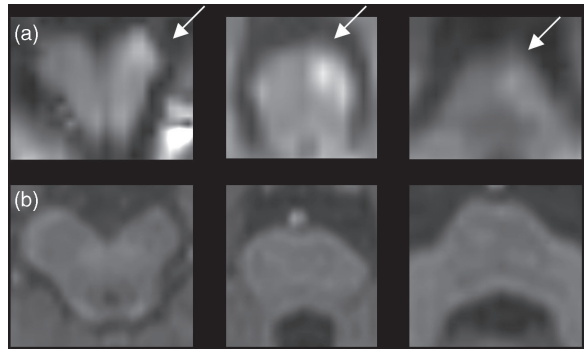


Figure 25.3 (a) Acute appearance of diffusion-weighted imaging and (b) chronic T1 changes in midbrain and pons of the patient seen in Figures 25.1 and 25.2. Note that the areas of reduced diffusion (arrows) show later Wallerian degeneration on the T1 images.

therapy is not suggested for noncardioembolic neonatal arterial stroke. For infants with CSVT who are not treated with antithrombotic therapy, imaging should be repeated at 1 week to look for propagation of the thrombosis. Infants with CSVT who are treated with antithrombotic therapy should be imaged again at 3 months to ensure complete recanalization of the venous sinuses [75]. In the Canadian Registry of Perinatal Stroke, 25–30% of neonates with arterial stroke or CSVT were treated with antithrombotic therapy [4,25]. There were no cases of death or neurologic complication due to hemorrhage, but the impact of treatment on outcome is unknown.

Long-term management of cerebral palsy (CP) due to perinatal stroke diagnosed in the neonatal period or retrospectively involves traditional rehabilitation with passive stretching, splinting, and casting, as well as medical or surgical treatment for spasticity, including baclofen, tendon release surgery, or botulinum toxin A [76]. Constraint-induced movement therapy (CIMT), which involves restraint of the nonaffected limb and frequent repetition of manual therapeutic tasks with the affected limb, is a promising treatment approach for children with hemiplegic CP. Emerging evidence from studies using functional MRI suggests that CIMT is associated with changes in cortical activation [77,78]; however, a Cochrane review concluded that there is only limited evidence of the clinical effect and suggested further trials to evaluate the efficacy of CIMT for hemiplegic children [79]. Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation and neuromodulation technique that is currently under investigation in children with perinatal stroke [80]. Preliminary data indicate safety and tolerability of contralesional inhibitory TMS with CIMT and intensive rehabilitation.

Children with neonatal stroke should also be monitored through school age to look for subtle signs of cognitive impairment, and they should be referred for psychoeducational testing as needed.

Outcome

Neurodevelopmental outcome following perinatal stroke is extremely variable between studies due to a variety of factors, including heterogeneity of the injury, variable duration of follow-up, and differences in outcome measures. Most studies suggest high risk for neurodevelopmental disability (including CP, epilepsy, and behavioral disorders, as well as impaired visual function and language development) [1–8,81,82]. In one population-based study, 68% of children who presented in the neonatal period and 94% of children with delayed presentation were diagnosed with one or more disability [8].

Despite high rates of neurologic disabilities, many studies show that children who survive perinatal stroke have good functional outcomes. This result may be due in part to the high plasticity in the developing brain. Studies using functional MRI (fMRI) have shown bilateral or right-sided activation of language-area homologues in children with a history of left-hemisphere perinatal stroke [83,84]. A recent study of resting-state functional connectivity in children with neonatal stroke supports the hypothesis of plasticity by demonstrating that connectivity values in areas of injury were better correlated with simulated values of a healthy brain than those of an injured brain [85].

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Neuromotor Outcome

Perinatal stroke is a common cause of hemiplegic CP. Functional motor impairment is present in up to 30–40% of children examined after 12 months of age, and 30% have some asymmetry of tone without definite hemiplegia [1,3,8]. The risk of motor impairment is approximately twice as high in children who present after the neonatal period, which may reflect ascertainment bias because many of these children are diagnosed following evaluation of pathologic early handedness or evolving CP [8,30]. In spite of the high frequency of motor abnormalities, the great majority of children with neonatal ischemic stroke achieve independent walking, especially in cases of unilateral infarct [86].

Predicting neuromotor outcome based on early clinical, EEG, and imaging features is important for providing prognostic information to families and facilitating rehabilitation. Furthermore, accurate early tools for predicting outcome ultimately may aid in selecting patients for therapeutic interventions. Stroke size and location are helpful in predicting neuromotor outcome. Infants with a large stroke size have a higher risk of hemiplegia, especially when there is injury to the motor cortex, basal ganglia, *and* posterior limb of the internal capsule [1,3,8]. Children with injury to only cortex, basal ganglia, or posterior limb of the internal capsule have a good chance of normal neuromotor outcome [1,3]. Neuromotor outcome is also highly correlated with the length and volume of diffusion change along the descending corticospinal tracts [65,87]. Early abnormal EEG background may also be helpful in predicting hemiparesis outcome, with 93% sensitivity and 100% specificity in one study [1].

Neonatal Seizures and Epilepsy

The incidence of epilepsy after perinatal stroke is variable and probably depends not only on the nature of the lesion but also on the timing and duration of follow-up. Published rates of epilepsy after age 6 months range widely from 0% to 67% [6,8,69,88,89]. In one study of 64 children with neonatal stroke and at least 6 months' follow-up, 67% developed seizures after age 6 months (median age 16 months), but most were seizure free with or without medication, and only 11% of children had one or more seizures per month [89].

Neurobehavioral Outcome

Cognitive outcome in children with perinatal arterial stroke or sinovenous thrombosis is variable but often impaired. Some studies report "language delay" in up to 25–30% of children [8,30]. In a study of preschool children, average scores on the Mental Developmental Index of the Bayley Scales of Infant Development (whose normative mean is 100 and standard deviation 15) at age 24 months were in the low 90s (range 50s–120s) [5]. In school-age children, language development and IQ were lower in infants with unilateral hemispheric neonatal stroke than in age-matched peers [90]. Interestingly, the side of the lesion (right versus left hemisphere) did not appear to be an important factor in language development, whereas presence of seizures beyond the neonatal period was associated with worse outcome.

In one population-based study, behavioral abnormalities were diagnosed by a physician in 11% of children who presented with stroke in the neonatal period and 35% of children with delayed presentation [8]. Another study, which used the Achenbach Child Behavior Checklist, found no evidence of clinically significant behavioral or emotional problems in children and adolescents with neonatal stroke, even when the frontal lobe was involved [91]. However, children with more extensive and bilateral injury may be at higher risk for behavioral and emotional dysfunction.

Visual Function

Impairment of acuity, visual fields, or stereopsis was present in approximately 30% of school-age children with a history of perinatal stroke [2]. In this study, there was no relationship between lesions of the optic radiations or visual cortex and visual impairment, but larger middle cerebral artery lesions were more often associated with visual findings. Children presenting with congenital hemiplegia had a higher incidence of visual field defects [92,93].

Stroke Recurrence

The rate of stroke recurrence following perinatal stroke is much lower than for childhood or adult stroke, which suggests that long-term prophylaxis is probably unwarranted in most cases. There were no recurrences in a population-based study that identified 40 children with perinatal stroke [8]. Most of the symptomatic recurrences (including extracerebral

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venous thrombosis) seen in a prospective cohort of 215 children occurred in the context of congenital or acquired systemic illness [56].

Modeling Stroke

Although mechanisms of ischemic injury in the developing nervous system have been studied in sheep and rodent models for over 20 years, it is only recently that animal models recapitulating stroke have been established [94–96]. It is clear from these newer models that mechanisms of neonatal stroke differ both from adult stroke and from global hypoxia-ischemia. For example, the blood-brain barrier breaks down early after injury in the mature brain, but in the transient ischemia-reperfusion model in the newborn rat, the blood-brain barrier remains intact for over 48 hours [97]. This finding will influence the development of therapies because the ability to cross the blood-brain barrier will greatly affect efficacy of a drug. In addition, although necrosis is a prominent feature of adult stroke, especially in the core of the lesion, in the newborn animal the core undergoes apoptotic cell death [98]. Again, these findings will influence the development of therapies because cell injury may be reversible in larger areas of the newborn brain, and the cell death cascade is very different in apoptotic cell death (see Chapter 3 for mechanisms of ischemic injury). Recent data from animal models have also demonstrated that erythropoietin is a promising therapy to promote repair of injury following neonatal stroke [99,100].

References

1. Mercuri E, Barnett A, Rutherford M, et al. Neonatal cerebral infarction and neuromotor outcome at school age. *Pediatrics* 2004; **113**: 95–100.
2. Mercuri E, Anker S, Guzzetta A, et al. Neonatal cerebral infarction and visual function at school age. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**:F487–91.
3. Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics* 1999; **103**:39–46.
4. deVeber GA, MacGregor D, Curtis R, et al. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2000; **15**: 316–24.
5. McLinden A, Baird AD, Westmacott R, et al. Early cognitive outcome after neonatal stroke. *J Child Neurol* 2007; **22**: 1111–16.
6. Sran SK, Baumann RJ. Outcome of neonatal strokes. *Am J Dis Child* 1988; **142**: 1086–8.
7. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr* 2000; **137**: 351–5.
8. Lee J, Croen LA, Lindan C, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol* 2005; **58**: 303–8.
9. Schulzke S, Weber P, Luetschg J, Fahnenstich H. Incidence and diagnosis of unilateral arterial cerebral infarction in newborn infants. *J Perinat Med* 2005; **33**: 170–5.
10. Raju TN, Nelson KB, Ferriero D, et al. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics* 2007; **120**: 609–16.
11. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke* 2007; **38**: 2234–40.
12. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA* 2005; **293**: 723–9.
13. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke* 2007; **38**: 2234–40.
14. Wu YW, March WM, Croen LA, et al. Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics* 2004; **114**: 612–19.
15. Ozduman K, Pober BR, Barnes P, et al. Fetal stroke. *Pediatr Neurol* 2004; **30**: 151–62.
16. Levy SR, Abroms IF, Marshall PC, et al. Seizures and cerebral infarction in the full-term newborn. *Ann Neurol* 1985; **17**: 366–70.
17. Clancy R, Malin S, Laraque D, et al. Focal motor seizures heralding stroke in full-term neonates. *Am J Dis Child* 1985; **139**: 601–6.
18. Ramaswamy V, Miller SP, Barkovich AJ, et al. Perinatal stroke in term infants with neonatal encephalopathy. *Neurology* 2004; **62**: 2088–91.
19. Guzzetta A, Mercuri E, Rapisardi G, et al. General movements detect early signs of hemiplegia in term infants with neonatal cerebral infarction. *Neuropediatrics* 2003; **34**: 61–6.
20. Kirton A, Armstrong-Wells J, Chang T, et al. Symptomatic neonatal arterial ischemic stroke: The international pediatric stroke study. *Pediatrics* 2011; **128**:e1402–10.

21. Ecury-Goossen GM, Raets MM, Lequin M, et al. Risk factors, clinical presentation, and neuroimaging findings of neonatal perforator stroke. *Stroke* 2013; **44**: 2115–20.
22. Fitzgerald KC, Williams LS, Garg BP, et al. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol* 2006; **63**: 405–9.
23. Wu YW, Miller SP, Chin K, et al. Multiple risk factors in neonatal sinovenous thrombosis. *Neurology* 2002; **59**: 438–40.
24. Fitzgerald KC, Golomb MR. Neonatal arterial ischemic stroke and sinovenous thrombosis associated with meningitis. *J Child Neurol* 2007; **22**: 818–22.
25. deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001; **345**: 417–23.
26. Roland EH, Flodmark O, Hill A. Thalamic hemorrhage with intraventricular hemorrhage in the full-term newborn. *Pediatrics* 1990; **85**: 737–42.
27. Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. *Ann Neurol* 2003; **54**: 123–6.
28. Benders MJ, Groenendaal F, Uiterwaal CS, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke* 2007; **38**: 1759–65.
29. de Vries LS, Groenendaal F, Eken P, et al. Infarcts in the vascular distribution of the middle cerebral artery in preterm and fullterm infants. *Neuropediatrics* 1997; **28**:88–96.
30. Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol* 2001; **50**: 163–8.
31. Kirton A, Shroff M, Pontigon AM, et al. Risk factors and presentations of periventricular venous infarction vs. arterial presumed perinatal ischemic stroke. *Arch Neurol* 2010; **67**: 842–8.
32. Takanashi J, Tada H, Barkovich AJ, et al. Magnetic resonance imaging confirms periventricular venous infarction in a term-born child with congenital hemiplegia. *Dev Med Child Neurol* 2005; **47**: 706–8.
33. Armstrong-Wells J, Johnston CS, Wu YW, et al. Prevalence and predictors of perinatal hemorrhagic stroke: results from the Kaiser pediatric stroke study. *Pediatrics* 2009; **123**: 823–8.
34. Gould DB, Phalan FC, Breedveld GJ, et al. Mutations in *Col4a1* cause perinatal cerebral hemorrhage and porencephaly. *Science* 2005; **308**: 1167–71.
35. Breedveld G, de Coo IF, Lequin MH, et al. Novel mutations in three families confirm a major role of *COL4A1* in hereditary porencephaly. *J Med Genet* 2006; **43**: 490–5.
36. de Vries LS, Koopman C, Groenendaal F, et al. *COL4A1* mutation in two preterm siblings with antenatal onset of parenchymal hemorrhage. *Ann Neurol* 2009; **65**: 12–8.
37. Meuwissen MEC Halley DJJ, Smit LS, et al. The expanding phenotype of *COL4A1* and *COL4A2* mutations: clinical data on 13 newly identified families and a review of the literature. *Genet Med* 2015; **17**(11): 843–53.
38. Arkel YS, Ku DH. Thrombophilia and pregnancy: review of the literature and some original data. *Clin Appl Thromb Hemost* 2001; **7**: 259–68.
39. Silver RK, MacGregor SN, Pasternak JF, et al. Fetal stroke associated with elevated maternal anticardiolipin antibodies. *Obstet Gynecol* 1992; **80**: 497–9.
40. Akanli LF, Trasi SS, Thuraisamy K, et al. Neonatal middle cerebral artery infarction: association with elevated maternal anticardiolipin antibodies. *Am J Perinatol* 1998; **15**:399–402.
41. Gunther G, Junker R, Strater R, et al. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. *Stroke* 2000; **31**: 2437–41.
42. Ballem P. Acquired thrombophilia in pregnancy. *Semin Thromb Hemost* 1998; **24**: 41–7.
43. Rigo J, Nagy B, Fintor L, et al. Maternal and neonatal outcome of preeclamptic pregnancies: the potential roles of factor V Leiden mutation and 5,10 methylenetetrahydrofolate reductase. *Hypertens Pregnancy* 2000; **19**: 163–72.
44. Hague WM, Dekker GA. Risk factors for thrombosis in pregnancy. *Best Pract Res Clin Haematol* 2003; **16**: 197–210.
45. Chasnoff IJ, Bussey ME, Savich R, et al. Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; **108**: 456–9.
46. Heier LA, Carpanzano CR, Mast J, et al. Maternal cocaine abuse: the spectrum of radiologic abnormalities in the neonatal CNS. *AJNR Am J Neuroradiol* 1991; **12**: 951–6.
47. Ment LR, Ehrenkranz RA, Duncan CC. Bacterial meningitis as an etiology of perinatal cerebral infarction. *Pediatr Neurol* 1986; **2**: 276–9.
48. Amit M, Camfield PR. Neonatal polycythemia causing multiple cerebral infarcts. *Arch Neurol* 1980; **37**: 109–10.
49. Jarjour IT, Ahdab-Barmada M. Cerebrovascular lesions in infants and children dying after extracorporeal membrane oxygenation. *Pediatr Neurol* 1994; **10**:13–19.
50. Pellicer A, Cabanas F, Garcia-Alix A, et al. Stroke in neonates with cardiac right-to-left shunt. *Brain Dev* 1992; **14**: 381–5.

51. Brenner B, Fishman A, Goldsher D, et al. Cerebral thrombosis in a newborn with a congenital deficiency of antithrombin III. *Am J Hematol* 1988; **27**: 209–11.
52. Hogeveen M, Blom HJ, Van Amerongen M, et al. Hyperhomocysteinemia as risk factor for ischemic and hemorrhagic stroke in newborn infants. *J Pediatr* 2002; **141**: 429–31.
53. Garoufi AJ, Prassouli AA, Attilakos AV, et al. Homozygous *MTHFR C677T* gene mutation and recurrent stroke in an infant. *Pediatr Neurol* 2006; **35**:49–51.
54. Curry CJ, Bhullar S, Holmes J, et al. Risk factors for perinatal arterial stroke: a study of 60 mother-child pairs. *Pediatr Neurol* 2007; **37**:99–107.
55. Lynch JK, Han CJ, Nee LE, et al. Prothrombotic factors in children with stroke or porencephaly. *Pediatrics* 2005; **116**: 447–53.
56. Kurnik K, Kosch A, Strater R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. *Stroke* 2003; **34**: 2887–92.
57. Miller SP, Wu YW, Lee J, et al. Candidate gene polymorphisms do not differ between newborns with stroke and normal controls. *Stroke* 2006; **37**: 2678–83.
58. Hernanz-Schulman M, Cohen W, Genieser NB. Sonography of cerebral infarction in infancy. *AJR Am J Roentgenol* 1988; **150**:897–902.
59. Messer J, Haddad J, Casanova R. Transcranial Doppler evaluation of cerebral infarction in the neonate. *Neuropediatrics* 1991; **22**: 147–51.
60. Golomb MR, Dick PT, MacGregor DL, et al. Cranial ultrasonography has a low sensitivity for detecting arterial ischemic stroke in term neonates. *J Child Neurol* 2003; **18**:98–103.
61. Cowan F, Mercuri E, Groenendaal F, et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? *Arch Dis Child Fetal Neonatal Ed* 2005; **90**:F252–6.
62. Mader I, Schoning M, Klose U, et al. Neonatal cerebral infarction diagnosed by diffusion-weighted MRI: pseudonormalization occurs early. *Stroke* 2002; **33**: 1142–5.
63. Kuker W, Mohrle S, Mader I, et al. MRI for the management of neonatal cerebral infarctions: importance of timing. *Childs Nerv Syst* 2004; **20**: 742–8.
64. Shroff M, deVeber G. Sinovenous thrombosis in children. *Neuroimag Clin North Am* 2003; **13**: 115–38.
65. De Vries LS, Van der Grond J, Van Haastert IC, et al. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics* 2005; **36**:12–20.
66. Groenendaal F, Benders MJ, de Vries LS. Pre-Wallerian degeneration in the neonatal brain following perinatal cerebral hypoxia-ischemia demonstrated with MRI. *Semin Perinatol* 2006; **30**: 146–50.
67. Kirton A, Deveber G, Pontigon AM, et al. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol* 2008; **63**: 436–43.
68. Weiner SP, Painter MJ, Geva D, et al. Neonatal seizures: electroclinical dissociation. *Pediatr Neurol* 1991; **7**: 363–8.
69. Koelfen W, Freund M, Varnholt V. Neonatal stroke involving the middle cerebral artery in term infants: clinical presentation, EEG and imaging studies, and outcome. *Dev Med Child Neurol* 1995; **37**: 204–12.
70. Chalmers EA. Perinatal stroke: risk factors and management. *Br J Haematol* 2005; **130**: 333–43.
71. Elbers J, Viero S, MacGregor D, et al. Placental pathology in neonatal stroke. *Pediatrics* 2011; **127**: e722–9.
72. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003; **34**: 2208–14.
73. Vannucci RC, Mujsce DJ. Effect of glucose on perinatal hypoxic-ischemic brain damage. *Biol Neonate* 1992; **62**: 215–24.
74. Clancy RR. Prolonged electroencephalogram monitoring for seizures and their treatment. *Clin Perinatol* 2006; **33**: 649–65, vi.
75. Monagle P, Chan A, Massicotte P, et al. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126**: 645S–87S.
76. Jones MW, Morgan E, Shelton JE. Primary care of the child with cerebral palsy: a review of systems (part II). *J Pediatr Health Care* 2007; **21**: 226–37.
77. Juenger H, Linder-Lucht M, Walther M, *et al.* Cortical neuromodulation by constraint-induced movement therapy in congenital hemiparesis: an FMRI study. *Neuropediatrics* 2007; **38**: 130–6.
78. Sutcliffe TL, Gaetz WC, Logan WJ, et al. Cortical reorganization after modified constraint-induced movement therapy in pediatric hemiplegic cerebral palsy. *J Child Neurol* 2007; **22**: 1281–7.
79. Hoare BJ, Wasiak J, Imms C, et al. Constraint-induced movement therapy in the treatment of the upper limb in children with hemiplegic cerebral palsy. *Cochrane Database Syst Rev* 2007; **2**:CD004149.
80. Rajapakse T, Kirton A. Non-invasive brain stimulation in children: applications and future directions. *Transl Neurosci* 2013; **4**: 217–33.

81. Trauner DA, Chase C, Walker P, et al. Neurologic profiles of infants and children after perinatal stroke. *Pediatr Neurol* 1993; **9**: 383–6.

82. Wulfeck BB, Trauner DA, Tallal PA. Neurologic, cognitive, and linguistic features of infants after early stroke. *Pediatr Neurol* 1991; **7**: 266–9.

83. Tillema JM, Byars AW, Jacola LM, et al. Cortical reorganization of language functioning following perinatal left MCA stroke. *Brain Lang* 2008; **105**:99–111.

84. Jacola LM, Schapiro MB, Schmithorst VJ, et al. Functional magnetic resonance imaging reveals atypical language organization in children following perinatal left middle cerebral artery stroke. *Neuropediatrics* 2006; **37**:46–52.

85. Adhikari MH, Beharelle AR, Griffa A, et al. Computational modeling of resting-state activity demonstrates markers of normalcy in children with prenatal or perinatal stroke. *J Neurosci* 2015; **35**: 8914–24.

86. Golomb MR, deVeber GA, MacGregor DL, et al. Independent walking after neonatal arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2003; **18**: 530–6

87. Kirton A, Shroff M, Visvanathan T, et al. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke* 2007; **38**: 974–80.

88. Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**:F88–93.

89. Golomb MR, Garg BP, Carvalho KS, et al. Perinatal stroke and the risk of developing childhood epilepsy. *J Pediatr* 2007; **151**:409–13.e2.

90. Hetherington R, Tuff L, Anderson P, et al. Short-term intellectual outcome after arterial ischemic stroke and sinovenous thrombosis in childhood and infancy. *J Child Neurol* 2005; **20**: 553–9.

91. Trauner DA, Nass R, Ballantyne A. Behavioural profiles of children and adolescents after pre- or perinatal unilateral brain damage. *Brain* 2001; **124**:995–1002.

92. Mercuri E, Spano M, Bruccini G, et al. Visual outcome in children with congenital hemiplegia: correlation with MRI findings. *Neuropediatrics* 1996; **27**: 184–8.

93. Guzzetta A, Fazzi B, Mercuri E, et al. Visual function in children with hemiplegia in the first years of life. *Dev Med Child Neurol* 2001; **43**: 321–9.

94. Wen TC, Rogido M, Gressens P, et al. A reproducible experimental model of focal cerebral ischemia in the neonatal rat. *Brain Res Brain Res Protoc* 2004; **13**:76–83.

95. Derugin N, Ferriero DM, Vexler ZS. Neonatal reversible focal cerebral ischemia: a new model. *Neurosci Res* 1998; **32**: 349–53.

96. Renolleau S, Aggoun-Zouaoui D, Ben-Ari Y, et al. A model of transient unilateral focal ischemia with reperfusion in the P7 neonatal rat: morphological changes indicative of apoptosis. *Stroke* 1998; **29**: 1454–61.

97. Wendland M, Manabat C, Fox CK, et al. The blood–brain barrier is more preserved in neonatal versus adult rats following transient focal cerebral ischemia. *J Cereb Blood Flow Metab* 2003; **23**:169.

98. Manabat C, Han BH, Wendland M, et al. Reperfusion differentially induces caspase-3 activation in ischemic core and penumbra after stroke in immature brain. *Stroke* **200**(34): 207–13.

99. Gonzalez FF, Larpthaveesarp A, McQuillen P, et al. Erythropoietin increases neurogenesis and oligodendrogliosis of subventricular zone precursor cells after neonatal stroke. *Stroke* 2013; **44**: 753–8.

100. Gonzalez FF, Abel R, Almli CR, et al. Erythropoietin sustains cognitive function and brain volume after neonatal stroke. *Dev Neurosci* 2009; **31**: 403–11.

Chapter

26

Neurodevelopmental Consequences of Neonatal Hypoglycemia

Molly O. Regelmann and Mark A. Sperling

Scope of the Problem

Neurodevelopmental deficits of varying degrees are the hallmark complications of hypoglycemia in the newborn. This is due to the fact that glucose is the major and preferred substrate for brain metabolism and that cerebral extraction from plasma and subsequent use depend on plasma concentration independent of any effects of insulin. The extent of the deficits depends on several factors, including the mechanism(s) responsible, degree and duration of hypoglycemia, coexisting conditions such as ischemia-hypoxia or sepsis, and the age of onset. Hypoglycemia due to excessive insulin secretion and action, the severity of hypoglycemia as judged by unresponsiveness to medical therapies, and onset in the first week of life are generally associated with the worst prognosis unless recognized and treated appropriately. Insulin restricts glucose production from either glycogenolysis or gluconeogenesis while promoting glucose use in peripheral tissues. In addition, insulin restricts lipolysis and ketone production, thereby limiting all forms of fuel availability for the brain in cases of severe hyperinsulinism. The term *hyperinsulinism* is now used to signify excessive insulin action because peripheral insulin levels are determined in part by the degree of hepatic extraction, a genetically regulated process that may vary among individuals and for which no data are available in human newborns [1]. Hence peripheral levels of insulin do not reflect the concentrations and effect of insulin in the liver, the first organ to receive insulin after its release from the pancreas into the portal vein. Moreover, insulin action is governed in part by the interaction of insulin with its cognate receptor, and the insulin receptor number and affinity are markedly higher in newborns than in adults [2,3]. Thus the newborn is highly sensitive to the actions of insulin, so even a small increase in secretion results in increased action. Hyperinsulinism imparts a metabolic profile of near-complete deprivation of nutrients that can be used by the brain; no other form of hypoglycemia limits all potential metabolites for brain metabolism. As shown in Figure 26.1, defects in glycogen storage and gluconeogenesis may provide lactate and ketones that can be used as fuel for brain metabolism and thereby limit the neurodevelopmental deficits in such conditions. Cases of neonatal hypoglycemia due to deficient cortisol and/or growth hormone secretion may have structural anatomic defects of the central nervous system (CNS) regulating pituitary development and function so that it may be the anatomic defect rather than hypoglycemia per se that determine neurodevelopmental competence.

Much of our understanding of pathophysiologic changes to the brain during episodes of neuroglycopenia come from studies in animals. Comparisons of studies in humans are frequently plagued by a lack of consistent definition for hypoglycemia, other potential complicating medical conditions (e.g., prematurity and hypoxia), and a lack of control patients. The best defined and studied pediatric diagnosis is congenital hyperinsulinism. Even within the population of patients with congenital hyperinsulinism, the underlying severity of disease, timing of presentation, and treatments vary greatly and seem to influence neurocognitive development. Reports of developmental delays associated with congenital hyperinsulinism vary from roughly a quarter to half of all patients, and rates of epilepsy are reported to be 13–25% [4–9]. Three large retrospective surveys involving a total of 272 subjects confirm the poor neurologic outcomes of persistent hyperinsulinism and hypoglycemia in newborns. Those presenting in the newborn period were more likely to fail medical treatment and develop severe psychomotor retardation; among all three series, 20–45% developed severe or intermediate psychomotor/mental retardation and up to 25% developed epilepsy [5–7]. Developmental outcomes do not seem to vary depending on whether the congenital hyperinsulinism is transient or persistent. In a cohort of 67

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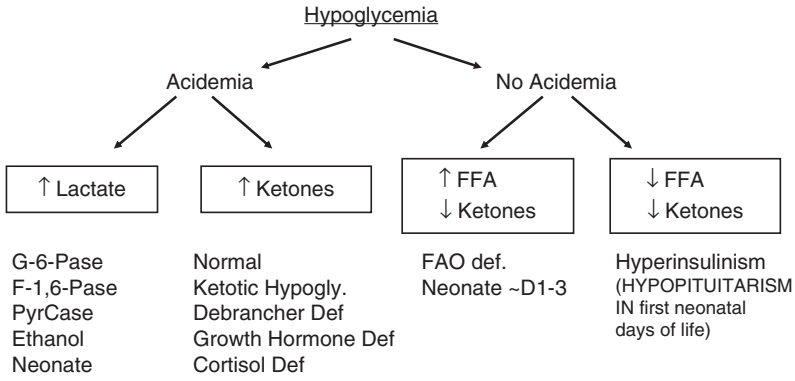


Figure 26.1 Metabolic profiles of common forms of hypoglycemia. Note that hyperinsulinism is associated with suppression of all metabolic fuels, a pattern also only occasionally seen with growth hormone and/or cortisol deficiency in the newborn. Distinct patterns characterize defects in glycogen storage–gluconeogenic disorders and fatty acid oxidation defects.

PyrCase = Pyruvate Carboxylase
Note that in the first days of life, it may be difficult to distinguish fatty acid oxidation defects (FAO) from normal transitional adaptations in the newborn, and Hyperinsulinism from Hypopituitarism.

children presenting with congenital hyperinsulinism, half the patients were defined to have *transitory congenital hyperinsulinism* because they were no longer hypoglycemic after discontinuation of medical therapy. Abnormal neurodevelopmental outcomes in the domains of speech/language, motor, and vision occurred in almost 40% of the cohort, with similar rates in the transient group compared with the permanent group (30% versus 47%, p = NS). The proportion presenting with severe cognitive impairment also did not significantly vary based on the transient versus persistent nature of the hyperinsulinism [8]. Similarly, almost half the children were reported to be affected with neurodevelopmental deficits in a series of patients from the United States [9]. Early presentation before 7 days of life and severity, as judged by use of maximal doses of medication (diazoxide), were most closely related to abnormal neurodevelopment. The type of genetic defect and histopathology of the pancreas after removal were not significantly associated with neurodevelopment outcomes [8,9].

A form of transient hyperinsulinism, often severe, occurs after intrauterine stress, including asphyxia-hypoxia, and may be associated with neurodevelopmental deficits [10]; the contribution of the hypoxia as opposed to the hypoglycemia may be reflected, in part, by the patterns of injury found on imaging studies, as discussed below.

Almost 20% of preterm newborns (gestation 32 weeks) are prone to hypoglycemia with an inability to maintain the glucose concentrations above 47 mg/dL if they fast for only 6 hours (miss one scheduled feeding) even at the time of discharge (at 37–38 weeks); in almost a third of these infants, glucose falls and remains below 40 mg/dL after 6 hours of fasting [11]. If hypoglycemia to these levels occurs on 5 or more separate days, the adjusted mental and motor developmental scores at 18 months (*corrected age*) were reported to be significantly reduced by 14 and 13 points, respectively, and the incidence of neurodevelopmental impairment (cerebral palsy or developmental delay) was increased 3.5-fold [12]. Recovery to some extent was reported in this same cohort when retested at 7–8 years of age [13]. Thus it is not clear that these consequences in preterm infants at 18 months were solely the result of hypoglycemia, and indeed, an attempt to replicate the result in a newer study found no correlation between hypoglycemia and neurodevelopmental outcomes [14]. Studies continue to identify hypoglycemia not caused by hyperinsulinism as a risk factor for neonatal brain injury and adverse neurodevelopmental outcomes [15–19]. A systematic review of published results concerning neurodevelopment after neonatal hypoglycemia concluded that valid scientific evidence was lacking in this field and proposed a well-designed prospective study to resolve the issue [20].

Children with hypoglycemia due to causes other than hyperinsulinism tend to have more favorable neurocognitive outcomes with respect to the effects of hypoglycemia; however, children with fatty acid oxidation defects or multiple pituitary hormone deficiencies may have additional neurodevelopmental concerns, unrelated to the hypoglycemia. Fortunately, children with fatty acid oxidation defects are now typically identified on newborn screening, prior to the onset of hypoglycemia, although hypoglycemia may still occur.

A retrospective case series of 85 children identified with fatty acid oxidation defect prior to the development of overt symptoms showed that a majority (54%) had a developmental concern, with speech delays being the most common (31%), followed by motor delays (29%). Six percent of children with fatty acid oxidation defects detected prior to the onset of symptoms had developmental or intelligence quotients below 85 [21]. In children with multiple pituitary hormone deficiencies, the neurodevelopmental outcomes are critically dependent not only on prevention of hypoglycemia but also on adequate thyroid hormone replacement, if central hypothyroidism is present. Children with multiple pituitary hormone deficiencies may also have brain and optic nerve abnormalities, which may further impair neurocognitive development. Large developmental studies of children with multiple pituitary hormone deficiencies are limited. In children with septo-optic dysplasia, a condition associated with a high risk for multiple pituitary hormone deficiencies, the extent to which hypoglycemia and/or brain malformations affect neurocognitive development is difficult to assess. In a reported series of 17 children with septo-optic dysplasia, 5 of the children had hypoglycemia in the neonatal period (2 presented with seizures). Nine of the 17 children were noted to have pituitary dysfunction, 15 were noted to have hypotonia, and gross and/or fine motor delays were noted in 13. Developmental/cognitive assessment was normal for only 6 of the 17, and 4 were noted to have a development quotients of less than 40 [22].

Thus the etiologies of hypoglycemia consistently resulting in neurodevelopmental deficits are predominantly hyperinsulinism, deficiencies in cortisol and/or growth hormone secretion due to abnormal pituitary development or function, and defects in adrenal formation or function. Severe defects in fatty acid oxidation also may cause hypoglycemia-related neurodevelopmental deficits. Onset in the first week of life and severity of hypoglycemia appear to be the major determining factors for neurodevelopmental deficits. These considerations prompted a panel of experts to recommend vigilance in those who manifest hypoglycemia in the first days of life. Out of an abundance of caution, the panel recommended that by day 3 of life a glucose level of 60 mg/dL or less should be viewed with suspicion and treated, as neuroglycopenic symptoms develop at glucose levels less than 55 mg/dL [23,24].

Physiology of Brain Energy Metabolism

Glucose is the major substrate used for brain metabolism. Glucose turnover of 4–8 mg/kg per minute is three- to four-fold higher in infants than the average of approximately 2–2.5 mg/kg per minute in adults, and brain utilization accounts for almost 90% in infants, whose brain size in proportion to total body weight is larger than in adults [25]. Because glucose uptake by brain is proportional to arterial glucose concentration, any reduction in arterial glucose concentration results in reduced uptake and metabolism, which can be partly compensated by circulatory autoregulation. During prolonged fasting, when concentrations of β-hydroxybutyrate reach levels of 2.5 mM, these ketone bodies may be used for brain metabolism [23]. However, these concentrations are not achieved in the first weeks of life; the gradient of ketones from maternal to fetal circulation ceases at parturition, and ketones are low in the first days of life in part due to delay in activation of the enzymatic machinery and in part due to insulin sensitivity of the newborn [2,26,27]. Lactate also may be used as an alternate fuel, but again, critical concentrations may not be reached [28]. All newborns have a period of transition after birth when maternal fuel is interrupted, and thus they may have glucose concentrations that decline to levels of approximately 50 mg/dL, with recovery to levels greater than 60 mg/dL by day 3 of life [23,29,30]. Hyperinsulinism, the most common cause of persistent hypoglycemia in a newborn, limits release of fatty acids and ketone body formation and lowers glucose; lactate is not available absent anaerobic glycolysis. Thus hyperinsulinism is the form of hypoglycemia most urgently in need of recognition and treatment [23,31].

The precise concentration of blood glucose and duration of hypoglycemia required to cause neurologic damage remain undefined and seem to vary among individuals. It would appear that blood glucose concentrations of approximately 50 mg/dL and higher are not associated with severe neurodevelopmental defects [32]. It is known that electroencephalographic (EEG) changes are noted at blood glucose concentrations as high as 3.5 mM (63 mg/dL). However, the EEG becomes flat at glucose concentrations of 1 mM or less (≤18 mg/dL) for approximately 20–30 minutes [33]. At this stage, energy failure is

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associated with release of large amounts of aspartic acid, which interacts with excitatory receptors on neuronal dendrites. The subsequent release of calcium leads to the rupture of cell membranes, release of various neurotransmitters, and neuronal necrosis. Activation of enzymes such as phospholipase and changes in the cellular redox state also occur and likely contribute to neuronal damage. Hypoglycemia also is reported to activate A1 adenosine receptors, permitting influx of calcium and activating caspase-3, a pro-apoptotic enzyme; in a mouse model, the neuronal damage was ameliorated by blockade of adenosine A1 receptors [34,35].

The mechanisms for the parietal-occipital lobes' increased sensitivity to hypoglycemic injury are not fully understood but may be related to variations in blood flow. A newborn dog hypoglycemia model demonstrated a decreased cerebral blood flow to the occipital white matter, which may, in turn, lead to hypoperfusion and/or a loss of autoregulation [36,37]. Hypoglycemia also leads to tissue alkalosis due to a combination of lack of lactate and elevations in ammonia that result from an increase in protein catabolism. The low levels of lactate and inability to lower pH prevent infarction and may, along with a lack of ischemia, be an explanation for the parietal-occipital pattern of damage noted in a hypoglycemic state [33].

The areas involved are predominantly the parietal-occipital regions with changes in both gray and white matter, hippocampus, and thalamic nuclei; the cerebellum and brainstem are spared in hypoglycemic brain damage, attributed to a greater efficiency of the cerebellar glucose transporter [38]. From the areas involved, neurodevelopmental deficits in memory, motor function, vision, and hearing are predictable complications. In addition, these changes imply identifiable patterns of change in imaging modalities and the possibility to distinguish hypoglycemic from hypoxic-ischemic encephalopathies. Clinically, repeated episodes of hypoglycemia of 1–1.5 mm (≤18–27mg/dL) or less or these levels for more than 20 minutes are those in which severe neurodevelopmental deficits may be anticipated.

Diagnostic Approach

Recognition of hypoglycemia in a neonate requires a high index of suspicion followed by prompt evaluation and treatment, which are critical for the prevention of long-term sequelae. A complete medical history, including the infant's gestational age and size at birth, maternal history of diabetes and degree of control of blood glucoses during the pregnancy, ease of delivery including need for resuscitation, family history of siblings or parents with hypoglycemia, and timing of hypoglycemia in relationship to feedings or cessation of intravenous dextrose administration, should be obtained. A thorough physical examination, including assessment of growth parameters and notation of dysmorphology, can assist in determining the underlying cause of the hypoglycemia.

Infants at highest risk for hypoglycemia include those born preterm and those small for gestational age because they lack the tissue reserves to maintain glucose production or immaturity of the enzymatic processes required. Large-for-gestational-age infants born to mothers without diabetes and those born to diabetic mothers likely have hyperinsulinism that is responsible for their macrosomia [39–41]. These neonates, as well as those who experience perinatal stress, those who have a family history of a genetic form of hypoglycemia, and those with congenital anomalies or syndromes concerning for an increased risk for hypoglycemia, should have blood glucose monitoring prior to feeds before discharge from the nursery [24]. Among the entities to be considered are defects in cortisol synthesis, which may result in ambiguous genitalia, micropenis or midline facial defects that suggest hypopituitarism, and macroglossia with hemihypertrophy and umbilical hernia, which suggest Beckwith-Wiedemann syndrome (Table 26.1).

In the neonatal period, manifestations of hypoglycemia tend to be nonspecific and related to the neuroglycopenia (Table 26.2). Any infant considered at high risk for hypoglycemia or exhibiting signs of hypoglycemia should have bedside point-of-care blood glucose monitoring [24,39]. Diagnostic evaluation is indicated for any infant with persistent preprandial blood glucose values of 50 mg/dL or less prior to 48 hours or 60 mg/dL or less after 48 hours of life or for neonates requiring intravenous dextrose to prevent hypoglycemia. Because transitional (adaptive) hypoglycemia is common in the neonatal period, it is recommended to delay diagnostic testing until the neonate is 2–3 days or more old [24].

Before initiating treatment, it is strongly recommended to draw a "critical sample" of blood at the time of hypoglycemia. In this critical sample, insulin, C-peptide, β-hydroxybutyrate, free fatty acids,

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Table 26.1 Diagnostic Clues for Hypoglycemia

Cause of hypoglycemia	Diagnostic clues
Hyperinsulinism	Born large for gestational age Requirement for glucose infusion rate >10 mg/kg/min
Hypopituitarism (ACTH and/or growth hormone deficiencies)	Midface hypoplasia Cleft lip/palate Micropenis Cryptorchidism Prolonged jaundice
Adrenal insufficiency	Ambiguous genitalia Hyperpigmentation Hyponatremia/ Hyperkalemia
Gluconeogenic defect	Hepatomegaly
Beckwith-Wiedemann syndrome	Macroglossia Earlobe fissures Hemihypertrophy Umbilical hernia/ Omphalocele

Table 26.3 "Critical Sample"

Blood
Essential:
1. Plasma glucose, Insulin, C-peptide
2. β-Hydroxybutyrate
3. Bicarbonate
4. Cortisol, Growth hormone
5. Reserve additional serum for free fatty acids
Desirable:
6. Ammonia (to exclude hyperinsulinism/ hyperammonemia)
7. IGFBP-1 (see text for details)
Urine
1. Ketones
2. Organic acids

cortisol, and growth hormone levels should be measured. These analytes may change rapidly following treatment of hypoglycemia, making the critical sample blood draw at the time of hypoglycemia essential for establishing the diagnosis. Table 26.3 summarizes the recommended specimens to obtain at the time of hypoglycemia. Figure 26.1 outlines an algorithm for establishing the diagnosis.

Table 26.2 Signs of Hypoglycemia in the Neonate

Lethargy/somnolence
Irritability/fussiness
Feeding difficulty
Jitteriness/myoclonic jerks
Hypotonia/wilting spells
Temperature instability (subnormal temperature)
High-pitched cry
Sweating
Apnea
Seizures
Coma

Hypoglycemia determined at the bedside by a glucose meter should be confirmed by a laboratory plasma glucose level; any plasma glucose concentration of 50 mg/dL or less is considered sufficient for diagnostic testing. Measuring serum bicarbonate, β-hydroxybutyrate, lactate, and plasma free fatty acids at the time of hypoglycemia can narrow the potential etiologies for the cause of hypoglycemia. Reserving serum at the time of the critical sample is ideal so that additional targeted testing may be performed. While the algorithm in Figure 26.1 outlines the preferred blood tests, many hospital laboratories are not able to rapidly report β-hydroxybutyrate and free fatty acids. Judgment should be used to prioritize laboratory tests based on baseline clinical assessments (common diagnostic clues are found in Table 26.1). Caution must be used when interpreting any one test, particularly an undetectable serum insulin level at the time of hypoglycemia. In a retrospective study of children with confirmed hyperinsulinism, using a control population with ketotic hypoglycemia, the sensitivity of a measureable serum insulin level was reported to be 82.2%, whereas a detectable C-peptide level had a sensitivity of 88.5%; the specificity for both measures together was reported to be 100%. A suppressed concentration of insulin-like growth factor binding protein 1 (IGFBP-1) (≤110 ng/mL) was also reported to have a sensitivity of 85% and a specificity of 97%. At the time of hypoglycemia, the most sensitive and specific marker for hyperinsulinism was a β-hydroxybutyrate level of less than 1.8 mM, as measured by a bedside meter (100% sensitive and specific) [42].

One retrospective study of infants and children found that at the time of hypoglycemia, the critical sample showed that 70% of the 68 children tested had

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Table 26.4 Diagnostic Criteria for Hyperinsulinism

At the time plasma glucose is less than 50 mg/dL:

- Measurable C-peptide (>0.5 ng/mL) or insulin (>2 mIU/mL)
- Low β-hydroxybutyrate (<1.8 mmol/mL)
- Low free fatty acids (<1.5 mmol/L)
- >30 mg/dL change in plasma glucose 20 minutes following glucagon administration (1 mg)

growth hormone levels below the 7.5 ng/mL threshold, but only one child was confirmed to have growth hormone deficiency. In the same cohort of patients, cortisol levels were drawn in 76 of the children at the time the critical sample was obtained, and of those, 61% had a value of less than 18 μg/dL, but only one child was found to have adrenal insufficiency [43]. When primary adrenal insufficiency is suspected, cosyntropin (ACTH) stimulation testing should be considered. Growth hormone (GH) deficiency may be considered to be present in a newborn if a random value is 10 ng/mL or less because in the first month of life GH values are generally in the range of 20–40 ng/mL and do not change significantly in response to provocative agents, including growth hormone–releasing hormone [44–46]. At later ages, GH deficiency may be evaluated via various provocative agents [47]. Hyperinsulinism is the most likely diagnosis if the fasting glucagon stimulation test is positive and β-hydroxybutyrate and free fatty acids are suppressed (Table 26.4).

The glucagon stimulation test is performed by administering 1 mg of glucagon (via intravenous, intramuscular, or subcutaneous injection) when the plasma glucose concentration is less than 50 mg/dL. The plasma glucose is measured again at 20 minutes. In the setting of hyperinsulinism, the plasma glucose rises more than 30 mg/dL after 20 minutes, reflecting the restraint on mobilizing glucose from glycogen by excessive insulin action, which can be overcome by the large dose of glucagon [48]. In patients with persistent hyperinsulinism, genetic testing may confirm the clinical diagnosis [49].

Imaging

The initial findings of magnetic resonance imaging (MRI) in neonatal hypoglycemia were reported in a small retrospective series of five patients in 1998 [50]. The authors reported diffuse cortical and subcortical white matter damage, with the parietal and occipital lobes most severely affected. Also noted was globus pallidus injury in one patient who had the most severe cortical injury (Figure 26.2).

This was considered a specific pattern that differed from hypoxic-ischemic injury. A larger series of 23 cases was reported in 2005; 82% had involvement of the occipital lobes, and half of these patients had visual impairments. The median glucose concentrations was 7 mg/dL (range 2–26 mg/dL), and the age at which hypoglycemia was first detected was 48 hours (range 1–72 hours) [51]. In a follow-up study, these authors reported on 89 infants, of whom more than 95% had plasma glucose levels of less than 25 mg/dL, initially detected at more than 10 hours of age, and of these, approximately 20% had neurologic sequelae [52]. The most recent and largest series involved 179 term infants with neonatal encephalopathy due to hypoxia-ischemia or hypoglycemia, prospectively imaged on day 3 of life. Radiologic hypoglycemia, defined as selective edema of the posterior white matter, as well as posterior and anterior thalamic nuclei, was compared with available glucose levels; hypoxic-ischemic changes were rated as displaying watershed basal ganglia, total focal-multifocal lesions, or no injury. Based on these characteristics, 52 subjects had hypoxic-ischemic encephalopathy, 34 had hypoglycemia, and 85 had no injury seen on MRI; 60 had clinical hypoglycemia before imaging. Clinically symptomatic hypoglycemia was associated with an almost 18-fold greater odds of MRI identification; posterior white matter and pulvinar edema were most predictive of clinical hypoglycemia. Compared with the laboratory-confirmed hypoglycemia, MRI findings had a positive predictive value of 82% and a negative predictive value of 78%. The authors concluded that in term infants with evidence of neonatal encephalopathy, specific imaging features for both hypoxia-ischemia and hypoglycemia can be identified [53].

Burns et al. reported a more varied pattern of injury in full-term (37–42 weeks gestational age) neonates with hypoglycemia and without evidence of hypoxic-ischemic injury. In the cohort of 35 neonates, 29% had the typically described parietal and occipital pattern of involvement, 51% had cortical abnormalities, 30% had evidence of white matter hemorrhage, 40% had basal ganglia/thalamic lesions, 11% had an abnormal posterior limb of the interval capsule, and 9% had evidence of middle cerebral artery infarction. The severity of the hypoglycemia was not associated

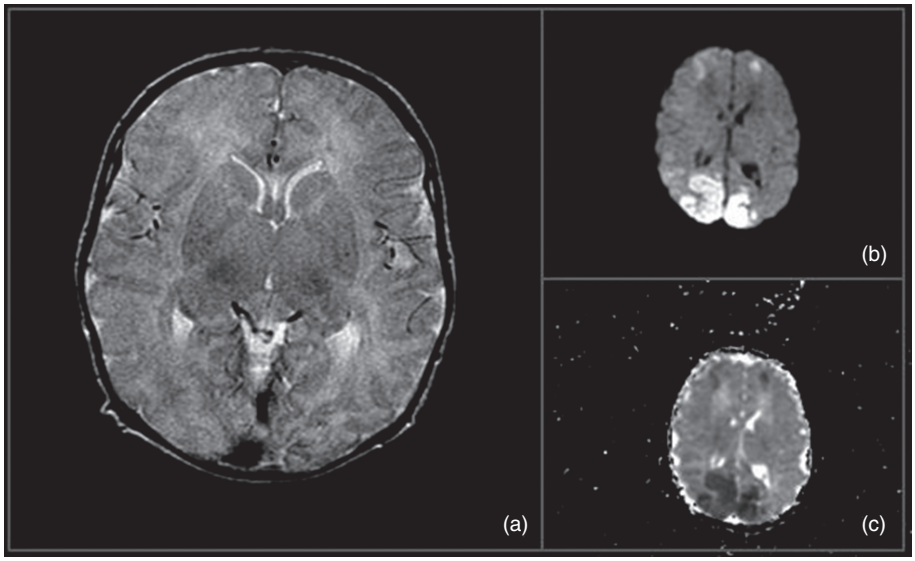


Figure 26.2 Characteristic MRI after neuroglycopenic injury. (a) Axial T2 images demonstrate subtle hyperintensity and effacement of the sulci in the posterior parietal lobes and occipital lobes bilaterally. Axial DWI (b) and ADC (c) images confirm extensive cytotoxic edema in the posterior parietal and occipital lobes bilaterally. Courtesy of Dr. Vera R Sperling MD, Department of Radiology, Childrens Hospital of Pittsburgh

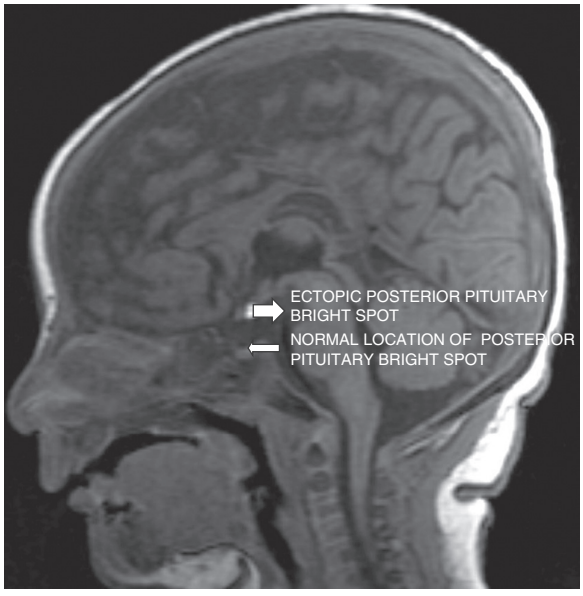


Figure 26.3 Ectopic posterior pituitary gland. Sagittal T1-weighted image of a 7-week-old boy demonstrating hyperintensity at the hypothalamic infundibulum without significant hyperintensity in the sella. Findings are compatible with an ectopic posterior pituitary gland. Complementary sequences did not reveal a hypothalamic-pituitary stalk.

(Image courtesy of Dr. Bradley Delman, Department of Neuroradiology, Icahn School of Medicine at Mount Sinai.)

with a particular brain injury pattern by MRI, and the authors concluded that the MRI findings prior to 6 weeks of life, rather than the degree and duration of hypoglycemia, were more predictive of neurodevelopmental outcomes at 18 months [54].

Infants suspected of ACTH and/or GH deficiency as the cause of hypoglycemia have been reported to have anatomic abnormalities, including ectopic posterior pituitary (Figure 26.3), pituitary hypoplasia, septo-optic dysplasia, and various midline defects such as absence of the corpus callosum [55–57].

Treatment

Once a neonate has been established to have a hypoglycemia disorder, the goal of treatment should be to maintain blood glucose values at 70 mg/dL or greater. For neonates without a suspected congenital hypoglycemia disorder, the suggested treatment goal is greater than 50 mg/dL in those younger than 48 hours and greater then 60 mg/dL in those older than 48 hours of age [24]. Treatment of the hypoglycemia depends on the underlying etiology. Infants with fatty acid oxidation defects require special formulas that restrict long-chain fatty acid intake and supplementation with medium-chain triglycerides [58]. Infants found to have adrenal insufficiency as the cause of the hypoglycemia should be treated with hydrocortisone rather than other glucocorticoids because hydrocortisone also has mineralocorticoid activity in high doses. Initial treatment may require an intravenous or intramuscular hydrocortisone bolus followed by an additional "stress dose" of hydrocortisone (stress-dose bolus of 50–75 mg/m^2, followed by 75 mg/m^2 either

as a continuous drip or divided every 4–6 hours). Once clinically improved, oral hydrocortisone, at a physiologic dose (9–12 mg/m^2 per day divided every 8 hours) is typically sufficient to avoid hypoglycemia. The hydrocortisone dose may be increased to 30–50 mg/m^2 per day divided every 6–8 hours during times of stress, such as fever or during surgical procedures [59]. Children with hypoglycemia associated with GH deficiency should be treated with daily subcutaneous recombinant human growth hormone (rhGH) starting at a dose of 22–35 μg/kg per day [60]. In cases of multiple pituitary hormone deficiencies, hydrocortisone replacement should be initiated prior to treatment with rhGH or levothyroxine for treatment of congenital hypothyroidism because there is the potential for inducing an adrenal crisis in the absence of glucocorticoid [59].

Congenital hyperinsulinism, whether transient or persistent, is by far the most challenging cause of neonatal hypoglycemia to treat. Children with hyperinsulinism are frequently unable to maintain blood glucoses above 70 mg/dL with standard oral formula or breast milk. "Thickening" the formula or expressed breast milk with polycose may be sufficient in mild, transient forms, but patients frequently require much higher glucose infusion rates. Continuous-feed infusion via gastric or nasogastric tube often fails, and frequently for neonates with the severe hyperinsulinism, the dextrose infusion rates exceed 10 and occasionally 20 mg/kg per minute, requiring central line placement. Diazoxide (5–15 mg/kg per day) is the first-line medication for the treatment of hyperinsulinism. Diazoxide inhibits insulin secretion by maintaining the potassium-ATP channel in an open state and is effective in some, but not all, forms of hyperinsulinism. Diazoxide is bound to plasma proteins, primarily albumin, and metabolized in the liver; dose adjustments may be necessary in infants with liver dysfunction and/or hypoalbuminemia/hypoproteinemia [61]. Side effects of diazoxide, particularly in doses at the higher end of the dosing range, include fluid retention, which may lead to hyponatremia, pulmonary edema, and congestive heart failure. Addition of chlorothiazide to the diazoxide treatment regimen has been suggested to avoid water and salt retention [61]. Diazoxide has also been reported to be associated with thrombocytopenia, neutropenia, anemia, hyperuricemia, and pancreatitis. Long-term use of diazoxide is associated with hypertrichosis. [62,63].

In those unresponsive to diazoxide, octreotide, which inhibits voltage-dependent calcium channels, can be used to stop the β-cells from secreting insulin. Octreotide is administered subcutaneously divided every 6–8 hours or as an intravenous drip at a dose range of 5–20 μg/kg per day [62]. Long-term monotherapy with octreotide is ineffective because tachyphylaxis frequently develops; however, the initial response can be excellent. Caution should also be used with octreotide because it has been reported to be associated with risk for necrotizing enterocolitis [64]. Long-term use of octreotide has been reported to be associated with higher rates of gallbladder pathology and liver enzyme abnormalities [65]. Continuous glucagon infusion may also be used to maintain blood glucoses at goal while infants are hospitalized and awaiting surgical interventions [62,63]. A recent report of four infants also suggested that sirolimus, a rapamycin (mTOR) inhibitor, may be an alternative treatment for those nonresponsive to diazoxide and octreotide [66]. The safety of sirolimus for the indication of hyperinsulinism has not been established.

With the exception of those thought to have hyperinsulinism related to perinatal stress or being born to mothers with uncontrolled diabetes, genetic testing for the causative genes associated with congenital hyperinsulinism, as well as an 18-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F L-DOPA) positron-emission tomography (PET) scan, should be considered as soon as possible. Medical and surgical therapy can be directed based on molecular diagnostics. ^{18}F L-Dopa PET scans are available in a very limited number of centers and can be used to distinguish diffuse and focal disease [67]. Surgical resection should be guided by preoperative ^{18}F L-DOPA imaging or, if available prior to the operation, genetic confirmation of diffuse disease. Surgical resection, which may be aided by intraoperative histopathology, should only be performed by experienced pediatric surgical teams [68–70]. Resection of focal lesions is curative, and following near-total pancreatectomies, hypoglycemia is more easily managed in those with severe diffuse disease. Surgery is not without potential complications. Surgical pancreatectomy places children at high risk for developing diabetes mellitus later in life. In a series of 121 patients with congenital hyperinsulinism who underwent pancreatectomy for either diffuse or focal disease, 44 of 121 developed diabetes mellitus, with the median age of diagnosis of 7.7 years (range 8

months–43 years). Almost all patients with diabetes mellitus (41/44) had 95% or more of their pancreas resected, and the majority of those developing diabetes (86%) required insulin treatment [9].

Prior to discharge from the hospitalized setting, an infant who has a persistent pathology leading to hypoglycemia should have a 6- to 8-hour fasting challenge to demonstrate the ability to maintain blood glucose concentrations greater than 60 mg/dL [24].

Unfortunately, even with the advent of newer diagnostic technologies, including the ^{18}F L-DOPA PET scan and genetic testing, there do not seem to be significant improvements in developmental outcomes, and those symptomatic in the first week of life are at particularly high risk [9]. The neurocognitive sequelae of neonatal hypoglycemia, particularly secondary to hyperinsulinism, emphasize the need for treatment even when the cause is thought to be transient in nature [23,24].

References

1. Tamaki M, Fujitani Y, Hara A, et al. The diabetes-susceptible gene *SLC30A8*/*ZnT8* regulates hepatic insulin clearance. *J Clin Invest* 2013; **123**(10): 4513–24.
2. Thorsson AV, Hintz RL. Insulin receptors in the newborn: increase in receptor affinity and number. *N Engl J Med* 1977; **297**(17): 908–12.
3. Chernausek SD, Beach DC, Banach W, Sperling MA. Characteristics of hepatic receptors for somatomedin-C/insulin-like growth factor I and insulin in the developing human. *J Clin Endocrinol Metab* 1987; **64**(4): 737–43.
4. Harken AH, Filler RM, AvRuskin TW, Crigler JF Jr. The role of "total" pancreatectomy in the treatment of unremitting hypoglycemia of infancy. *J Pediatr Surg* 1971; **6**(3): 284–9.
5. Menni F, de Lonlay P, Sevin C, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001; **107**(3): 476–9.
6. Meissner T, Wendel U, Burgard P, et al. Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur J Endocrinol* 2003; **149**(1):43–51.
7. Steinkrauss L, Lipman TH, Hendell CD, et al. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. *J Pediatr Nurs* 2005; **20**(2): 109–18.
8. Avatapalle HB, Banerjee I, Shah S, et al. Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. *Front Endocrinol (Lausanne)* 2013; **4**:60.
9. Lord K, Radcliffe J, Gallagher PR, et al. High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. *J Clin Endocrinol Metab* 2015; **100**(11): 4133–9.
10. Hoe FM, Thornton PS, Wanner LA, et al. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *J Pediatr* 2006; **148**(2): 207–12.
11. Hume R, McGeechan A, Burchell A. Failure to detect preterm infants at risk of hypoglycemia before discharge. *J Pediatr* 1999; **134**(4):499–502.
12. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. *BMJ* 1988; **297**(6659): 1304–8.
13. Cornblath M, Schwartz R. Outcome of neonatal hypoglycaemia: complete data are needed. *BMJ* 1999; **318**(7177): 194–5.
14. Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. *Pediatrics* 2012; **130**(6): e1497–503.
15. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, et al. Neonatal morbidities and developmental delay in moderately preterm-born children. *Pediatrics* 2012:**130**(2): e265–72.
16. McIntyre S, Taitz D, Keogh J, et al. A systemic review of risk factors for cerebral palsy in children born at term in developed countries. *Dev Med Child Neurol* 2013; **55**(6): 499–508.
17. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. *J Pediatr* 2012; **161**(1): 88–93.
18. Kaiser JR, Bai S, Gibson N, et al. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. *JAMA Pediatr* 2015; **169**(10): 913–21.
19. McKinlay CJ, Harding JE. Revisiting transitional hypoglycemia: only time will tell. *JAMA Pediatr* 2015; **169**(10): 892–4.
20. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systemic review and design of an optimal future study. *Pediatrics* 2006; **117**(6): 2231–43.
21. Waisbren SE, Landau Y, Wilson J, Vockley J. Neuropsychological outcomes in fatty acid oxidation disorders: 85 cases detected by newborn screening. *Dev Disabil Res Rev* 2013; **17**(3): 260–8.
22. Signorini SG, Decio A, Fedeli C, et al. Septo-optic dysplasia in childhood: the neurological, cognitive and neuro-ophthalmological perspective. *Dev Med Child Neurol* 2012; **54**(11): 1018–24.

23. Stanley CA, Rozance PJ, Thornton PS, et al. Re-evaluating "transitional neonatal hypoglycemia": mechanism and implications for management. *J Pediatr* 2015; **166**(6): 1520–5.
24. Thornton PS, Stanley CA, De León DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr* 2015; **167**(2): 238–45.
25. Bier DM, Leake RD, Haymond MW, et al. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 1977; **26**(11): 1016–23.
26. Kalhan SC, D'Angelo LJ, Savin SM, Adam PA. Glucose production in pregnant women at term gestation: sources of glucose for human fetus. *J Clin Invest* 1979; **63**(3): 388–94.
27. Bougneres PF, Lemmel C, Ferré P, Bier DM. Ketone body transport in the human neonate and infant. *J Clin Invest* 1986; **77**(1): 42–8.
28. Boardman JP, Hawdon JM. Hypoglycemia and hypoxic-ischaemic encephalopathy. *Dev Med Child Neurol* 2015; **57**(Suppl 3):29–33.
29. Sperling MA, DeLamater PV, Phelps D, et al. Spontaneous and amino acid-stimulated glucagon secretion in the immediate postnatal period: relation to glucose and insulin. *J Clin Invest* 1974; **53**(4): 1159–66.
30. Guemes M, Rahman SA, Hussain K. What is a normal blood glucose? *Arch Dis Child* 2016; **101**(6): 569–74.
31. Dekelbab BH, Sperling MA. Recent advances in hyperinsulinemic hypoglycemia of infancy. *Acta Paediatr* 2006; **95**(10): 1157–64.
32. McKinlay CJ, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. *N Engl J Med* 2015; **373**(16): 1507–18.
33. Auer RN. Hypoglycemic brain damage. *Metab Brain Dis* 2004; **19**(3–4): 169–75.
34. Turner CP, Blackburn MR, Rivkees SA. A1 adenosine receptors mediate hypoglycemia-induced neuronal injury. *J Mol Endocrinol* 2004; **32**(1): 129–44.
35. Kim M, Yu ZX, Fredholm BB, Rivkees SA. Susceptibility of the developing brain to acute hypoglycemia involving A1 adenosine receptor activation. *Am J Physiol Endocrinol Metab* 2005; **289**(4): E562–9.
36. Mujsce DJ, Christensen MA, Vannucci RC. Regional cerebral blood flow and glucose utilization during hypoglycemia in newborn dogs. *Am J Physiol* 1989; **256** (6 Pt 2): H1659–66.
37. Karaoğlu P, Polat AI, Yiş U, Hiz S. Parieto-occipital encephalomalacia in children: clinical and electrophysiological features of twenty-seven cases. *J Pediatr Neurosci* 2015; **10**(2): 103–7.
38. LaManna JC, Harik SI. Regional comparisons of brain glucose influx. *Brain Res* 1985; **326**(2): 299–305.
39. Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia. *Pediatr Clin North Am* 2004; **51**(3): 703–23.
40. Duvanel CB, Fawer CL, Cotting J, et al. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *J Pediatr* 1999; **134**(4): 492–8.
41. Rozance PJ. Update on neonatal hypoglycemia. *Curr Opin Endocrinol Diabetes Obes* 2014; **21**(1):45–50.
42. Ferrara C, Patel P, Becker S, et al. Biomarkers of insulin for the diagnosis of hyperinsulinemic hypoglycemia in infants. *J Pediatr* 2016; **168**: 212–9.
43. Kelly A, Tang R, Becker S, Stanley CA. Poor specificity of low growth hormone and cortisol levels during fasting hypoglycemia for the diagnoses of growth hormone deficiency and adrenal insufficiency. *Pediatrics* 2008; **122**(3): e522–8.
44. Cornblath M, Parker ML, Reisner SH, et al. Secretion and metabolism of growth hormone in premature and full-term infants. *J Clin Endocrinol Metab* 1965; **25**: 209–18.
45. Kaplan SL, Grumbach MM, Shepard TH. The ontogenesis of human fetal hormones. I. Growth hormone and insulin. *J Clin Invest* 1972; **51**(12): 3080–93.
46. Lanes R, Nieto C, Bruguera C, et al. Growth hormone release in response to growth hormone-releasing hormone in term and preterm neonates. *Biol Neonate* 1989; **56**(5): 252–6
47. Secco A, di lorgi N, Napoli F, et al. The glucagon test in the diagnosis of growth hormone deficiency in children with short stature younger than 6 years. *J Clin Endocrinol Metab* 2009; **94**(11): 4251–7.
48. Finegold DN, Stanely CA, Baker L. Glycemic response to glucagon during fasting hypoglycemia: an aid in the diagnosis of hyperinsulinism. *J Pediatr* 1980; **96**(2): 257–9.
49. Rahman SA, Nessa A, Hussain K. Molecular mechanisms of congenital hyperinsulinism. *J Mol Endocrinol* 2015; **54**(2): R119–29.
50. Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. *AJNR Am J Neuroradiol* 1998; **19**(3): 523–8.
51. Alkalay AL, Flores-Sarnat L, Sarnat HB, et al. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. *Clin Pediatr (Phila)* 2005; **44**(9): 783–90.
52. Alkalay AL, Flores-Sarnat L, Sarnat HB, et al. Plasma glucose concentrations in profound

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neonatal hypoglycemia. *Clin Pediatr (Phila)* 2006:**45** (6): 550–8.

53. Wong DS, Poskitt KJ, Chau V, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. *AJNR Am J Neuroradiol* 2013; **34**(7): 1456–61.
54. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics* 2008; **122**(1): 65–74.
55. Bozzola M, Adamsbaum C, Biscaldi I, et al. Role of magnetic resonance imaging in the diagnosis and prognosis of growth hormone deficiency. *Clin Endocrinol (Oxf)* 1996; **45**(1): 21–6.
56. Kornreich L, Horev G, Lazar L, et al. MR findings in growth hormone deficiency: correlation with severity of hypopituitarism. *AJNR Am J Neuroradiol* 1998; **19**(8): 1495–9.
57. Dutta P, Bhansali A, Singh P, et al. Congenital hypopituitarism: clinico-radiological correlation. *J Pediatr Endocrinol Metab* 2009; **22**(10): 921–8.
58. Saudubray JM, Martin D, de Lonlay P, et al. Recognition and management of fatty acid oxidation defects: a series of 107 patients. *J Inherit Metab Dis* 1999; **22**(4): 488–502.
59. Shulman DI, Palmert MR, Kemp SF, Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics* 2007; **119**(2): e484–94.
60. Grimberg A, DiVall SA, Polychronakos C, et al.; Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016; **86** (6): 361–97.
61. Tas E, Mahmood B, Garibaldi L, Sperling M. Liver injury may increase the risk of diazoxide toxicity: a case report. *Eur J Pediatr* 2015; **174**(3): 403–6.
62. Sperling MA, Menon R. Hypoglycemia in the Newborn. In Stevenson DK, Cohen RS, Sunshine P, eds., *Neonatology: Clinical Practice and Procedures*, 1st ed. New York: McGraw-Hill Education, 2015: 649–64.
63. Palladino AA, Bennett MJ, Stanley CA. Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. *Clin Chem* 2008; **54**(2): 256–63.
64. Laje P, Halaby L, Adzick NS, Stanley CA. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes* 2010; **11**(2): 142–7.
65. Demirbilek H, Shah P, Arya VB, et al. Long-term follow-up of children with congenital hyperinsulinism on octreotide therapy. *J Clin Endocrinol Metab* 2014; **99**(10): 3660–7.
66. Senniappan S, Alexandrescu S, Tatevian N, et al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. *N Engl J Med* 2014; **370**(12): 1131–7.
67. Gopal-Kothandapani JS, Hussain K. Congenital hyperinsulinism: role of fluorine-18 L-3,4 hydroxyphenylalanine positron emission tomography scanning. *World J Radiol* 2014; **6**(6): 252–60.
68. Suchi M, MacMullen CM, Thornton PS, et al. Molecular and immunohistochemical analyses of the focal form of congenital hyperinsulinism. *Mod Pathol* 2006; **19**(1): 122–9.
69. Adzick NS, Thornton PS, Stanley CA, et al. A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. *J Pediatr Surg* 2004; **39**(3): 270–5.
70. Laje P, Stanley CA, Palladino AA, et al. Pancreatic head resection and roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. *J Pediatr Surg* 2012:**47**(1): 130–5.

Chapter

27

Hyperbilirubinemia and Kernicterus

David K. Stevenson, Ronald J. Wong, and Phyllis A. Dennery

Introduction

The term *kernicterus* was originally used to describe the deposition of bilirubin in the basal ganglia. It was first described in 1903 by Schmorl [1]. More recently, the term has also been used in reference to the chronic and permanent clinical sequelae of bilirubin toxicity [2]. For the acute manifestations of bilirubin toxicity, the term *acute bilirubin encephalopathy* (ABE) has been adopted. Another acronym, BIND, for *bilirubin-induced neurologic dysfunction*, has been adopted recently to describe a spectrum of subtle neurologic damage [3,4] manifesting as disorders in vision [5], hearing [6], gait [7], and speech, cognition, and language [8]. Although technically the diagnosis of kernicterus can only be confirmed at autopsy, brain magnetic resonance imaging (MRI) studies may now aid in the confirmation of the diagnosis in a living child with severe hyperbilirubinemia. The MRI signature for kernicterus includes high signal intensity on T1-weighted images in the globus pallidus, internal capsule, thalamus, and hippocampi. The associated T2-weighted images have abnormal increased signals in the globus pallidus and thalamus in the same regions as the high signals on the T1-weighted images. Loss of demarcation between the globus pallidus, internal capsule, and anterior thalamus was the major finding [9,10] (Figures 27.1 and 27.2). The source of these abnormal signals has not been definitively identified, and therefore, the MRI findings should not be considered diagnostic in themselves[11] but only consistent with the diagnosis of kernicterus in the context of severe neonatal hyperbilirubinemia and the acute and chronic clinical features of BIND (Table 27.1) and associated organ system manifestations (Table 27.2).

Neonatal Hyperbilirubinemia and Neurotoxicity

Most often a benign condition, a majority of term neonates develop jaundice that is a consequence of relatively increased bilirubin production (two- to threefold higher in a neonate compared with an adult) and limited ability to conjugate bilirubin in the transitional period after birth. Compared with healthy term infants, polycythemic infants or those with hemolysis can produce significant amounts of bilirubin and become hyperbilirubinemic [12]. By convention, a serum or plasma bilirubin (TB) concentration higher than the 95th percentile (or "high-risk" zone) on the Bhutani hour-specific TB nomogram [13] is considered pathologic. Moreover, there is no known safe level of bilirubin that can be universally agreed on because the level at which neurotoxicity develops and the conditions under which toxicity manifests remain incompletely understood. Importantly, BIND or bilirubin toxicity, including ABE and kernicterus, does not occur in the absence of hyperbilirubinemia. Among the survivors, the acute and chronic features of ABE and kernicterus, respectively, are listed in Table 27.1. Importantly, each infant may not have all the features of BIND, and the permanent injuries may vary in severity and include subtle neurologic deficits, suggesting that there may be a spectrum of injuries caused specifically by bilirubin.

The topic of bilirubin neurotoxicity also was reviewed by Volpe in 2000 [14] and in a recent supplement on BIND edited by Bhutani and Wong [3]. That bilirubin is toxic is undisputed, and a variety of cellular toxic effects of bilirubin have been described in detail [15–21]. More recent evidence has emerged that there may be injury to the cerebellum [22] (and other circuitry pathways) that contributes to the subtle manifestations of BIND. From a clinical perspective, there are a variety of factors that influence empirically the neurotoxic effects of bilirubin. However, the exact mechanism (s) by which bilirubin injures the brain, and in particular, what contributes to injury in an individual infant, is poorly understood.

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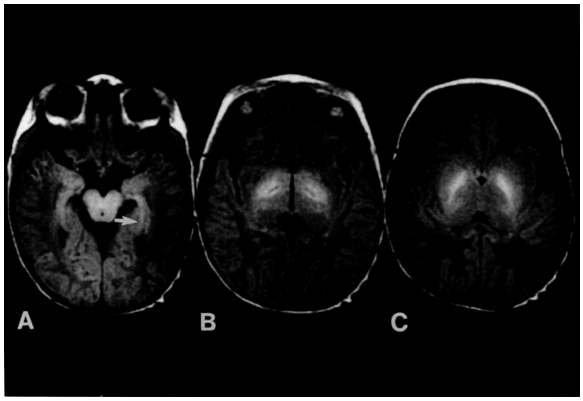


Figure 27.1 Series of three axial T1-weighted images showing the following anatomy: (a) the hippocampus and temporal lobe; (b) the basal ganglia and subthalamus; (c) the lenticular nuclei and thalamus. The major abnormality on these T1-weighted images was the abnormal high signal intensity seen in the hippocampus in the mediotemporal lobe (arrow, a). This was confirmed on sagittal images. This abnormally high signal intensity was also noted in the globus pallidus but not the putamen (b, c). The thalamus was less involved, but some increased signal intensity was present in the ventroposterolateral nucleus. The findings were bilateral and symmetric in these structures and typical of regions of the brain damaged in kernicterus. (*Source:* Reproduced with permission from *Pediatrics* 93:1003–6, 1994, by the AAP [10].)

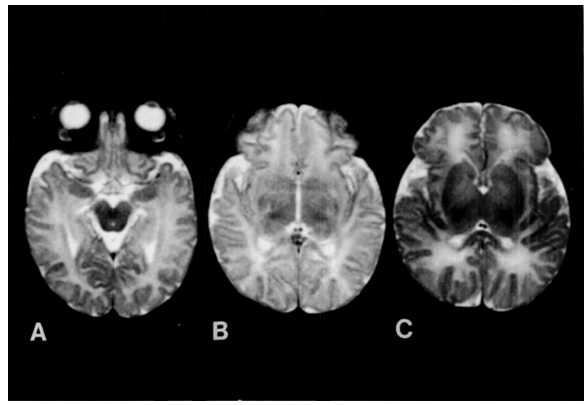


Figure 27.2 T2-weighted images at the same anatomic levels as the T1-weighted images shown in Figure 27.1. Findings on these images are more subtle than the T1-weighted abnormalities and are characterized by increased signal intensity in the same regions: the globus pallidus and anterior thalamus are best seen in image (c). The basal ganglia abnormality is seen primarily as a loss of demarcation between the globus pallidus, internal capsule, and thalamus. The increased signal in the hippocampi is also subtle and best seen in image (a) as an area of increased signal intensity paralleling the temporal horn medially. (*Source:* Reproduced with permission from *Pediatrics* 93:1003–6, 1994, by the AAP [10].)

Most of the experimental work on bilirubin toxicity has been performed using in vitro cell culture models. In such systems, the binding of bilirubin to albumin is key to the understanding of bilirubin toxicity [23–27]. However, its relevance to toxicity in intact animals or humans remains uncertain or is not known in most cases [28]. Nothing is known with certainty with respect to where bilirubin acts and how it acts. Overall, in vitro studies of bilirubin toxicity are inconclusive, and extrapolation to in vivo conditions is uncertain because of confounding uncontrolled factors. Additionally, data suggest a beneficial antioxidant role of bilirubin [29,30], although it is not clear whether this is of physiologic relevance in neonates. Conjugating capacity (hence the ability to excrete bilirubin) probably varies significantly in the general population and is further influenced by genetic conditions such as Gilbert syndrome, which is associated with a mildly decreased uridine diphosphate glucuronosyltransferase (UGT) activity attributed to an expansion of thymine-adenine (TA) repeats in the promoter region of the *UGT1A1* gene, the principal gene encoding UGT [31–33]. There may also be racial variations in the number of TA repeats, thus suggesting a causation for differences in bilirubin metabolism between certain ethnic groups [34]. A DNA sequence variant (Gly71Arg) has also been associated with decreased UGT activity and neonatal hyperbilirubinemia in Asians [35]. Even more interesting is the potential for gene interaction suggested in a number of reports on glucose-6-phosphate dehydrogenase (G6PD) deficiency and Gilbert syndrome [33,36,37]. Besides genetic differences in conjugating capacity, genetic differences in the capacity to produce bilirubin [38] attributed to polymorphisms (number of GT repeats) in the heme oxygenase (HO) 1 gene promoter [38–43] and genetic differences in the transporters (organic anion transporter protein 2) involved in bilirubin update from the circulation [44,45] also may contribute to individual differences in transitional hyperbilirubinemia and are under active investigation.

One of the major risk factors for severe neonatal hyperbilirubinemia and BIND is severe hemolysis [46]. Under such conditions (Rh disease), a TB level of 20 mg/dL (342 μmol/L) or greater has been empirically associated with a risk for neonatal brain injury or death. Thus *vigintiphobia* has a historical and not a scientific basis, but extrapolation to other hyperbilirubinemic

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Table 27.1 Clinical Features of Bilirubin Toxicity

Acute bilirubin encephalopathy (ABE)	
Early phase (reversible)	Lethargy Hypotonia Poor sucking
Intermediate phase (reversible)	Moderate stupor Irritability Hypertonia, manifested by backward arching of the neck (retrocollis) and trunk (opisthotonos) Fever High-pitched cry
Advanced phase (probably irreversible)	Pronounced retrocollis-opisthotonos Shrill cry No feeding Apnea Fever Deep stupor to coma Sometimes seizures and death
Chronic bilirubin encephalopathy or kernicterus	
(Irreversible)	Severe form of athetoid cerebral palsy Auditory dysfunction Dental enamel dysplasia Paralysis of upward gaze Sometimes intellectual and other handicaps

Table 27.2 Associated Manifestations of Bilirubin-Induced Neurologic Dysfunction (BIND)

Behavioral	Lethargy Sleepiness Difficulty to arouse "Affect"-less facies
Cardiopulmonary	Periodic breathing Apnea Hypertension Tachycardia
Metabolic	Hyponatremia, maybe associated with IADH Altered auditory brainstem responses
Musculoskeletal	Hypotonia and alternating hypertonia
Neurologic	Oculogyric movements Irritability Seizures Stupor

Source: Modified, with permission, from Bhutani and Wong, *J Clin Neonatol* 2013; 2:61–9.

conditions besides Rh disease is not clear [47,48]. One historical exception to the role of hemolysis in severe hyperbilirubinemia is the clinical experience reported by Silverman et al. in 1956 [49] with premature infants treated with sulfisoxazole. This tragedy suggested that great caution should be exercised in using any new drug in a neonate. In fact, all drugs considered for use in neonates should be tested for their capacities to displace bilirubin from albumin in order to avoid history repeating itself. Practically, the prediction of severe hyperbilirubinemia or, more accurately, the lack of it is possible by combining an hour-specific TB level with an estimate of the degree of bilirubin production with measurements of carboxyhemoglobin (COHbc) or end-tidal breath carbon monoxide (ETCOc), both corrected for ambient CO [50].

Prediction of Hyperbilirubinemia

With early discharge, it is often difficult to observe infants long enough to detect pathologic hyperbilirubinemia. Although not perfect, hour-specific TB levels can assist in the prediction of which infants might develop severe hyperbilirubinemia or be less likely to develop it according to predetermined thresholds [13]. An hour-specific TB measurement represents the interaction of an increased bilirubin load with the ability to excrete the load. Hemolysis can be diagnosed, with sensitivity, by estimating bilirubin production noninvasively. Measurements of ETCOc or COHbc are useful techniques that have been used experimentally to estimate hemolysis and the potential for hemolytic jaundice [51,52]. We have also recently shown that the calculation of an individual's bilirubin-binding capacity (BBC) can be used to assess an infant's risk of bilirubin neurotoxicity as a function of gestational age [26]. These detection tools may help in deciding which infants should be observed more frequently and treated because hyperbilirubinemia associated with hemolysis represents one of the most common serious conditions. The importance of identifying increased bilirubin production as a contributing cause of neonatal hyperbilirubinemia cannot be overemphasized.

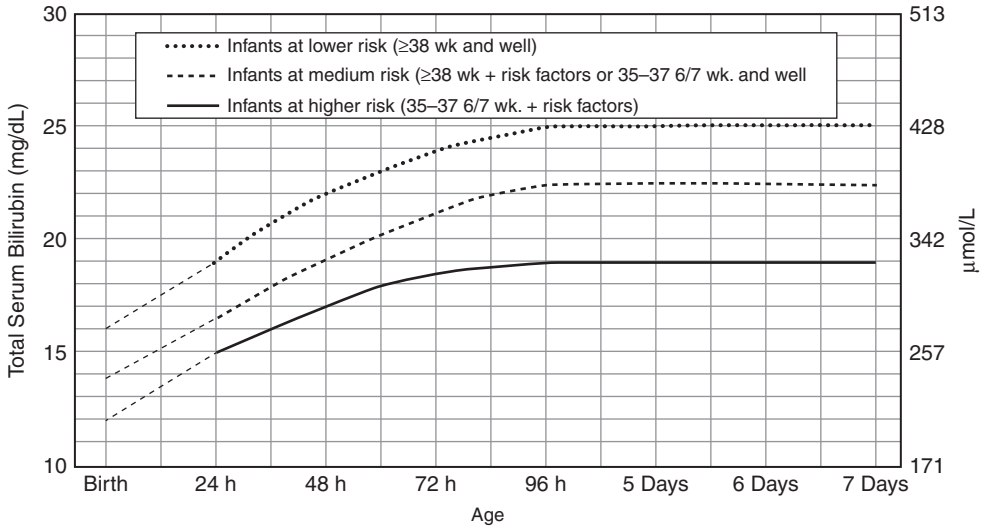
Empirically, the rate of rise of the TB level serves as a surrogate for this bilirubin load phenomenon. The risk of injury associated with hyperbilirubinemia depends on how much bilirubin enters tissues. This varies with the capacity to keep bilirubin in circulation (mainly determined by the albumin concentration or BBC) [23,26,27,53], the amount of bilirubin produced over time relative to what can be eliminated, and the metabolic state of the infant [45,54]. Thus, the TB level by itself may not always reflect the magnitude of risk, but the higher the TB level associated with increased production of the pigment, the higher the risk. An estimate of the magnitude of the bilirubin load using an index of bilirubin production, such as ETCOc or COHbc, combined with an hour-specific TB level provides even more information about the nature of the infant's transitional hyperbilirubinemia [50,52]. Such a diagnostic approach could allow clinicians to make better judgments about which infants could be discharged early, who should be followed more closely over the first week of life, and who might require therapy, including home phototherapy. With the burden still on physicians to exclude hemolytic disease for compliance with the 2004 American Academy of Pediatrics (AAP) clinical practice guideline for management of hyperbilirubinemia in the newborn infant ≥ 35 weeks' gestation [2], infants who are discharged before 48 h should probably have more than a direct Coombs test in order to determine if they have hemolysis. A positive direct Coombs test does not make this diagnosis. Only 50% of infants with a positive Coombs test are actually undergoing hemolysis, and up to 25% of those with an ABO blood type incompatibility with their mother and lacking a positive Coombs test will have evidence of hemolysis based on a more sensitive test, such as ETCOc [55,56].

Management of Neonatal Hyperbilirubinemia

The AAP has attempted to address the management of hyperbilirubinemia in healthy term newborns [2]. However, the latter practice parameter now does apply to term infants with a variety of complicating conditions and to near-term (35–37 weeks' gestation) or preterm infants. This guideline should not be characterized as a standard because it has important limitations. Nonetheless, it should be followed with the exclusion of infants less than 35 weeks' gestation. When newborn infants are discharged before the TB level is likely to have peaked, the medical responsibility for follow-up of the infant cannot be shifted to the parents without clear recommendations for follow-up by a physician or an appropriately trained individual [2].

The practice in many communities suggests that some lower-risk infants with TB levels above 20 mg/dL (depending on the postnatal age in hours) may be managed without exchange transfusion, but according to the new guideline, all should be treated with intensive phototherapy, and if the TB level is 25 mg/dL (428 μmol/L) or higher, it should be considered a medical emergency and the infant should be admitted to the hospital pediatrics service for intensive phototherapy while preparation for an exchange transfusion is undertaken (Figure 27.3) [2]. Immediate exchange transfusion is recommended if the infant shows signs of BIND or if the TB is 5 mg/dL (86 μmol/L) or greater above the hour-specific lines for the various risk categories. The many other nomograms for guiding the decision making of practitioners with respect to the treatment of hyperbilirubinemia also should not be considered irrefutable standards but rather recommendations for practice that need to be adapted and modified on an individual basis. Furthermore, there is no absolute standard level at which phototherapy should be applied, although the AAP recommendation is reasonable in this regard. In premature infants, some investigators have recommended the use of phototherapy at very low TB levels because kernicterus has been diagnosed in such infants at TB levels between 5 (86 μmol/L) and 8 mg/dL (137 μmol/L) [57]. Common sense usually weighs heavily in the decision to start phototherapy in an effort to avoid exchange transfusion – a procedure that carries a small but definite risk. Another factor that needs to be considered is the duration of exposure to high TB levels, and this may also influence the decision to intervene earlier or more aggressively in a context when a TB level remains high despite intensive phototherapy.

However, results from a recent randomized, controlled trial [58] comparing the use of aggressive (initiated at a 5 mg/dL [86 μmol/L]) versus conventional phototherapy (initiated at a 8 mg/dL [137 μmol/L]) suggests that although aggressive phototherapy decreased neurodevelopment impairment in extremely low-birth-weight (ELBW) infants (501–750 g), mortality was increased [59], further emphasizing the need for alternative treatment methods in this high-risk group. In our work, we



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines
- Risk factors – isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35–37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age

Figure 27.3 Guideline for exchange transfusion in infants at 35 or more weeks' gestation. Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TB rises to these levels despite intensive phototherapy. For readmitted infants, if the TB level is above the exchange level, repeat TSB measurement every 2–3 hours, and consider exchange if the TB remains above the levels indicated after intensive phototherapy for 6 hours. (*Source:* Reproduced with permission from *Pediatrics* 114:297–316, 2004, by the AAP [2].)

have found that the use of phototherapy devices incorporating narrow-wavelength-band blue light-emitting diodes (LEDs, 470–490 nm) is the light of choice for these smallest of infants because it has less photo-oxidative effects than fluorescent tubes [60]. In addition, we have published a semiempirical mathematical model that shows that an infant's hemoglobin level may also affect the efficacy of phototherapy [61]. Ongoing clinical studies are being performed in Denmark and Norway to validate our in vitro findings.

In the presence of hemolysis, a TB level of 20 mg/dL or greater has been associated with an increased risk of neonatal brain injury or death. Therefore, exchange transfusion should be seriously considered in the infant under such circumstances, particularly if the TB level does not decrease rapidly under intensive phototherapy. A jaundiced infant who is breastfeeding is a typical example. Such infants should not have markedly increased bilirubin production. However, despite the assumed benign nature of jaundice associated with breastfeeding, some practitioners would recommend exchange transfusion for any infant with a TB level greater than 25 mg/dL (428 µmol/L) who does not respond to intensive phototherapy. Moreover, exchange transfusion might be considered at a lower level if the infant were preterm or sick in any way, in particular, if the infant were asphyxiated or infected or had cardiorespiratory or metabolic instability. Infants with TB levels greater than 30 mg/dL (513 µmol/L) definitely should be exchanged if technically possible. Occasionally, an exchange might reasonably be avoided if the TB level dropped dramatically below 25 mg/dL (428 µmol/L) under intense phototherapy while preparing for the exchange. Exchange transfusion can be considered with lower TB levels in any infant who is sick, in particular, if the infant is asphyxiated or infected or

has cardiorespiratory or metabolic instability. The use of drugs capable of displacing bilirubin from albumin in general should be avoided in newborns. The use of intralipid as a continuous infusion at a rate to prevent central fatty acid deficiency is not dangerous because free fatty acid albumin ratios are not elevated into the range at which displacement of bilirubin from albumin would be expected. Breastfeeding of any infant with a propensity for increased bilirubin production (e.g., bruising, hematoma, prematurity) represents an increased risk for hyperbilirubinemia and warrants close follow-up of the infant throughout the first week and into the second week of life. Early discharge of an infant from the hospital requires that a practitioner follow the AAP practice guideline [2].

Reemergence of Kernicterus

In the 1980s and 1990s, kernicterus had become a rare occurrence. However, with discharge from the hospital occurring sooner after birth, the peak of neonatal hyperbilirubinemia more often occurs outside the hospital observed by parents and not by physicians or other trained personnel. Thus there has been a reemergence of reported kernicterus in the United States and elsewhere [62–66].

There are some particular clinical problems that get practitioners into trouble more often than others. Most of them can be related to the early discharge of infants from the hospital. One example is the breastfeeding infant with increased bilirubin production. The source of the increased bilirubin production may be unrecognized hemolytic disease or simply bruising or hematoma formation. The increased bilirubin production, combined with a lack of a decrease in the enterohepatic circulation, may contribute to a very rapid early rise in the TB level over the first several days of life that can be missed if the infant is discharged before the time of peak hyperbilirubinemia at approximately 3–4 days. The peak may also be later, as is often the case when increased bilirubin production is a major factor contributing to jaundice or a conjugating defect is present, such as in a certain proportion of Asians [67,68]. Even a large premature or near-term infant who is breastfeeding and does not have an obvious complication predisposing to increased bilirubin production may have more difficulty in lowering the TB level and should be followed closely throughout the first 2 weeks of life. Currently, practitioners rarely see term newborns in this period because they are normally discharged from the hospital. This is not a good practice. In hemolytic disease, late anemia is a complication that also should not be overlooked once hyperbilirubinemia has been successfully managed. Such anemia may be so severe as to require transfusion by the second to fourth week of life. An estimate of bilirubin production will help in the recognition of this problem in the absence of hyperbilirubinemia.

In summary, bilirubin toxicity or BIND, manifested as either ABE or kernicterus, is a real entity that has been reported more frequently in the last decade due to relaxed vigilance in the treatment of neonatal hyperbilirubinemia. It is most often preventable by the use of predictive tools and aggressive intervention when appropriate.

References

1. Schmorl G. Zur kenntis des icterus neonatorum. *Verh Dtsch Ges Pathol* 1903; **6**: 109.
2. American Academy of Pediatrics. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004; **114**: 297–16.
3. Bhutani VK, Wong R. Bilirubin-induced neurologic dysfunction (BIND). *Semin Fetal Neonatal Med* 2015; **20**:1.
4. Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. *Semin Perinatol* 2011; **35**: 101–13.
5. Good WV, Hou C. Visuocortical bilirubin-induced neurological dysfunction. *Semin Fetal Neonatal Med* 2015; **20**:37–41.
6. Olds C, Oghalai JS. Audiologic impairment associated with bilirubin-induced neurologic damage. *Semin Fetal Neonatal Med* 2015; **20**: 42–6.
7. Rose J, Vassar R. Movement disorders due to bilirubin toxicity. *Semin Fetal Neonatal Med* 2015; **20**: 20–5.
8. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. *Semin Fetal Neonatal Med* 2015; **20**: 52–7.
9. Govaert P, Lequin M, Swarte R, et al. Changes in globus pallidus with (pre)term kernicterus. *Pediatrics* 2003; **112**: 1256–63.
10. Penn AA, Enzmann DR, Hahn JS, Stevenson DK. Kernicterus in a full term infant. *Pediatrics* 1994; **93**: 1003–6.
11. Wisnowski JL, Panigrahy A, Painter MJ, Watchko JF. Magnetic resonance imaging of bilirubin encephalopathy: current limitations and future promise. *Semin Perinatol* 2014; **38**: 422–8.

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.028

12. Stevenson DK, Bartoletti AL, Ostrander CR, Johnson JD. Pulmonary excretion of carbon monoxide in the human newborn infant as an index of bilirubin production. III. Measurement of pulmonary excretion of carbon monoxide after the first postnatal week in premature infants. *Pediatrics* 1979; **64**:598–600.
13. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* 1999; **103**:6–14.
14. Volpe JJ. Bilirubin and brain injury. In Volpe JJ, ed., *Neurology of the Newborn*, 2nd edn. Philadelphia: Saunders, 2000:490–514.
15. Amato M. Mechanisms of bilirubin toxicity. *Eur J Pediatr* 1995; **154**:S54–9.
16. Amit Y, Chan G, Fedunec S, et al. Bilirubin toxicity in a neuroblastoma cell line N-115. I. Effects on Na^+K^+-ATPase, [^{3}H]-thymidine uptake, L-[35S]-methionine incorporation, and mitochondrial function. *Pediatr Res* 1989; **25**: 364–8.
17. Brito MA, Silva RF, Brites D. Bilirubin induces loss of membrane lipids and exposure of phosphatidylserine in human erythrocytes. *Cell Biol Toxicol* 2002; **18**: 181–92.
18. Hanko E, Hansen TW, Almaas R, et al. Bilirubin induces apoptosis and necrosis in human NT2-N neurons. *Pediatr Res* 2005; **57**: 179–84.
19. Wennberg RP. Cellular basis of bilirubin toxicity. *NY State J Med* 1991; **91**: 493–6.
20. Wennberg RP, Gospe SM, Jr., Rhine WD, et al. Brainstem bilirubin toxicity in the newborn primate may be promoted and reversed by modulating PCO_2. *Pediatr Res* 1993; **34**:6–9.
21. Brites D, Fernandes A. Bilirubin-induced neural impairment:a special focus on myelination, age-related windows of susceptibility and associated co-morbidities. *Semin Fetal Neonatal Med* 2015; **20**: 14–9.
22. Watchko JF, Painter MJ, Panigrahy A. Are the neuromotor disabilities of bilirubin-induced neurologic dysfunction disorders related to the cerebellum and its connections? *Semin Fetal Neonatal Med* 2015; **20**:47–51.
23. Ahlfors CE. Measurement of plasma unbound unconjugated bilirubin. *Anal Biochem* 2000; **279**: 130–5.
24. Ahlfors CE. Unbound bilirubin associated with kernicterus: a historical approach. *J Pediatr* 2000; **137**: 540–4.
25. Ahlfors CE, Wennberg RP. Bilirubin-albumin binding and neonatal jaundice. *Semin Perinatol* 2004; **28**: 334–9.
26. Lamola AA, Bhutani VK, Du L, *et al*. Neonatal bilirubin binding capacity discerns risk of neurological dysfunction. *Pediatr Res* 2015; **77**: 334–9.
27. Morioka I, Nakamura H, Koda T, et al. Serum unbound bilirubin as a predictor for clinical kernicterus in extremely low birth weight infants at a late age in the neonatal intensive care unit. *Brain Dev* 2015; **37**(8):753–7.
28. Levine RL, Fredericks WR, Rapoport SI. Clearance of bilirubin from rat brain after reversible osmotic opening of the blood-brain barrier. *Pediatr Res* 1985; **19**: 1040–3.
29. Dennery PA, McDonagh AF, Spitz DR, et al. Hyperbilirubinemia results in reduced oxidative injury in neonatal Gunn rats exposed to hyperoxia. *Free Radic Biol Med* 1995; **19**: 395–04.
30. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. *Science* 1987; **235**: 1043–6.
31. Berardi A, Lugli L, Ferrari F, et al. Kernicterus associated with hereditary spherocytosis and *UGT1A1* promoter polymorphism. *Biol Neonate* 2006; **90**: 243–6.
32. Kaplan M, Hammerman C, Rubaltelli FF, et al. Hemolysis and bilirubin conjugation in association with UDP-glucuronosyltransferase 1A1 promoter polymorphism. *Hepatology* 2002; **35**: 905–11.
33. Kaplan M, Renbaum P, Levy-Lahad E, et al. Gilbert syndrome and glucose-6-phosphate dehydrogenase deficiency: a dose-dependent genetic interaction crucial to neonatal hyperbilirubinemia. *Proc Natl Acad Sci USA* 1997; **94**: 12128–32.
34. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (*UGT1A1*) promoter:A balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci USA* 1998; **95**: 8170–4.
35. Akaba K, Kimura T, Sasaki A, et al. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int* 1998; **46**: 21–6.
36. Kaplan M, Hammerman C, Renbaum P, et al. Differing pathogenesis of perinatal bilirubinemia in glucose-6-phosphate dehydrogenase-deficient versus-normal neonates. *Pediatr Res* 2001; **50**: 532–7.
37. Kaplan M, Renbaum P, Vreman HJ, et al. (TA)n UGT 1A1 promoter polymorphism: a crucial factor in the pathophysiology of jaundice in G-6-PD deficient neonates. *Pediatr Res* 2007; **61**: 727–31.
38. Kaplan M, Renbaum P, Hammerman C, et al. Heme oxygenase-1 promoter polymorphisms and neonatal jaundice. *Neonatology* 2014; **106**: 323–9.

39. Denschlag D, Marculescu R, Unfried G, et al. The size of a microsatellite polymorphism of the haem oxygenase 1 gene is associated with idiopathic recurrent miscarriage. *Mol Hum Reprod* 2004; **10**: 211–4.
40. Exner M, Minar E, Wagner O, Schillinger M. The role of heme oxygenase-1 promoter polymorphisms in human disease. *Free Radic Biol Med* 2004; **37**: 1097–104.
41. Takeda M, Kikuchi M, Ubalee R, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to cerebral malaria in Myanmar. *Jpn J Infect Dis* 2005; **58**: 268–71.
42. Yamada N, Yamaya M, Okinaga S, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. *Am J Hum Genet* 2000; **66**: 187–95.
43. Katayama Y, Yokota T, Zhao H, et al. Association of HMOX1 gene promoter polymorphisms with hyperbilirubinemia in the early neonatal period. *Pediatr Int* 2015; **57**(4):645–9.
44. Huang MJ, Kua KE, Teng HC, et al. Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res* 2004; **56**: 682–9.
45. Watchko JF, Daood MJ, Hansen TW. Brain bilirubin content is increased in P-glycoprotein-deficient transgenic null mutant mice. *Pediatr Res* 1998; **44**: 763–6.
46. Mollison PL, Cutbush M. Haemaolytic disease of the newborn. In Gairdner D, ed., *Recent Advances in Pediatrics*. New York: Blakinston, 1954:110.
47. Watchko JF. Vigintiphobia revisited. *Pediatrics* 2005; **115**: 1747–53.
48. Watchko JF, Oski FA. Bilirubin 20 mg/dL = vigintiphobia. *Pediatrics* 1983; **71**: 660–3.
49. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics* 1956; **18**: 614–25.
50. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. *Pediatrics* 2001; **108**: 31–9.
51. Vreman HJ, Stevenson DK, Oh W, et al. Semiportable electrochemical instrument for determining carbon monoxide in breath. *Clin Chem* 1994; **40**: 1927–33.
52. Castillo Cuadrado ME, Bhutani VK, Aby JL, et al. Evaluation of a new end-tidal carbon monoxide monitor from the bench to the bedside. *Acta Paediatr* 2015; **104**:e279–82.
53. Brodersen R, Stern L. Deposition of bilirubin acid in the central nervous system: a hypothesis for the development of kernicterus. *Acta Paediatr Scand* 1990; **79**: 12–9.
54. Bratlid D, Cashore WJ, Oh W. Effect of acidosis on bilirubin deposition in rat brain. *Pediatrics* 1984; **73**: 431–4.
55. Herschel M, Karrison T, Wen M, et al. Evaluation of the direct antiglobulin (Coombs') test for identifying newborns at risk for hemolysis as determined by end-tidal carbon monoxide concentration (ETCOc); and comparison of the Coombs' test with ETCOc for detecting significant jaundice. *J Perinatol* 2002; **22**: 341–7.
56. Tidmarsh GF, Wong RJ, Stevenson DK. End-tidal carbon monoxide and hemolysis. *J Perinatol* 2014; **34**: 577–81.
57. Gartner LM, Snyder RN, Chabon RS, Bernstein J. Kernicterus: high incidence in premature infants with low serum bilirubin concentrations. *Pediatrics* 1970; **45**: 906–17.
58. Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med* 2008; **359**: 1885–96.
59. Tyson JE, Pedroza C, Langer J, et al. Does aggressive phototherapy increase mortality while decreasing profound impairment among the smallest and sickest newborns? *J Perinatol* 2012; **32**: 677–84.
60. Vreman HJ, Knauer Y, Wong RJ, et al. Dermal carbon monoxide excretion in neonatal rats during light exposure. *Pediatr Res* 2009; **66**: 66–9.
61. Lamola AA, Bhutani VK, Wong RJ, et al. The effect of hematocrit on the efficacy of phototherapy for neonatal jaundice. *Pediatr Res* 2013; **74**:54–60.
62. Ebbesen F. Recurrence of kernicterus in term and near-term infants in Denmark. *Acta Paediatr* 2000; **89**: 1213–7.
63. Ebbesen F, Andersson C, Verder H, et al. Extreme hyperbilirubinaemia in term and near-term infants in Denmark. *Acta Paediatr* 2005; **94**:59–64.
64. Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. *Pediatrics* 1995; **96**: 730–3.
65. Newman TB, Maisels MJ. Less aggressive treatment of neonatal jaundice and reports of kernicterus: lessons about practice guidelines. *Pediatrics* 2000; **105**: 242–5.
66. Perlman JM, Rogers BB, Burns D. Kernicteric findings at autopsy in two sick near term infants. *Pediatrics* 1997; **99**: 612–5.
67. Fischer AF, Nakamura H, Uetani Y, et al. Comparison of bilirubin production in Japanese and Caucasian infants. *J Pediatr Gastroenterol Nutr* 1988; **7**: 27–9.
68. Stevenson DK, Vreman HJ, Oh W, et al. Bilirubin production in healthy term infants as measured by carbon monoxide in breath. *Clin Chem* 1994; **40**: 1934–9.

Chapter 28

Polycythemia and Fetal-Maternal Bleeding

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Introduction

Since the third edition of this book, this chapter has been expanded to cover both polycythemia and fetomaternal hemorrhage, a topic that is not extensively or comprehensively discussed in most commonly used textbooks. In the former, the hematocrit and blood volume are generally increased, whereas in the latter, both are generally very low. In both conditions, however, there is concern about inadequate organ blood flow, oxygenation delivery, and potential for hypoxic injury, especially in the brain. A large body of definitive information on polycythemia is available that allows conclusions to be made as to management and patient outcome. However, the area of fetomaternal hemorrhage has not been as comprehensively investigated and relies mostly on small clinical series and case reports. There are no controlled basic or clinical trials, which hampers our understanding of pathophysiology as well as therapeutic modalities. This leaves us with gaps in our knowledge of this important topic. What is presented here is the most current body of information and recommendations for diagnosis, treatment, and reported outcomes.

Polycythemia

Polycythemia and hyperviscosity were first associated with adverse neurologic events and sequelae in a series of case reports. The first case often referenced was published by Wood in 1952, and this was followed by a small series of infants with polycythemia and hyperviscosity who displayed multiple problems, including cerebral dysfunction [1–5]. Since those early reports it has become clear that polycythemia has multiple etiologies that influence whether and which problems may be associated with it in the newborn period. In addition, more recent animal and human studies have clarified the relationship between polycythemia and alterations in function of various organs [6–33].

Definition

Polycythemia is usually defined in the literature as a hematocrit value of 65% or greater when the blood sample is obtained from a free-flowing, large venous blood vessel such as the inferior vena cava (umbilical vein sample) spun in a centrifuge [34]. Sampling from small vessels with low flow or capillary samples will produce higher values. In addition, hematocrits calculated by a Coulter counter will yield comparatively lower values [35–37]. Independent of sample site or measurement technique, the hematocrit increases over the first 2–4 hours of life, gradually returning to the birth value by 12–24 hours of age [34,38,39].

Incidence

The incidence of polycythemia varies by definition, altitude of the population, pregnancy risk factors, and techniques involved in the delivery of the fetus and timing and sampling sites of blood samples. Studies by Wirth et al. have demonstrated that higher altitude is associated with a higher incidence of polycythemia in the general newborn population. At sea level, the incidence is 1–2%, whereas at 1,600 ft (430 m), it has been documented to be 5% [40,41]. Additionally, the hematocrit increases over the first hours after birth and then returns to the value observed at birth by 24 hours of age. Thus incidence may vary by the time of the blood sampling.

Recently, there has been an increased interest on the issue of placental transfusion by delayed cord clamping and cord milking. Concerns have been raised about whether this intervention may increase the risk of polycythemia. Meta-analysis showed that the incidence of polycythemia in preterm infants who received placental transfusion is similar to that in infants with immediate cord clamping at birth [42]. There is also no difference in the incidence of hyperviscosity in this population who received placental transfusion when compared with those with immediate cord clamping

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Table 28.1 Polycythemia: Etiologies and High-Risk Groups

Delayed cord clamping
Acute hypoxia
Meconium-stained infants
Post-term infants
Chronic hypoxia
Placental insufficiency
Infants of diabetic mothers
Large-for-gestational-age infants
Twin-to-twin transfusion
Other
Trisomy 21
Beckwith-Wiedemann syndrome
Fetal/neonatal hyperthyroidism

[43]. In term infants, a meta-analysis by Hutton et al. showed that neonates with delayed cord clamping were at increased risk of experiencing asymptomatic polycythemia (seven studies [403 neonates]: relative risk [RR] 3.82, 95% confidence interval[CI] 1.11–13.21; two high-quality studies only [281 infants]: RR 3.91; 95% CI 1.00–15.36) [44]. Clinicians should be aware of this potential complication when delayed cord clamping or cord milking is done in term infants.

Causes of Polycythemia

A number of fetal and birth complications are known to increase the hematocrit. These problems can usually be attributed to acute or chronic fetal hypoxia or placental transfusion due to delayed clamping of the umbilical cord (Table 28.1) [2,6,41–57].

Effects of Increased Hematocrit on Organ Blood Flow and Function

Using in vitro techniques, increases in hematocrit are associated with increases in whole-blood viscosity [58,59]. This observation led many to believe that very high hematocrit levels would be associated with decreased organ blood flow, particularly in the brain. It has been hypothesized that this reduction in blood flow would lead to organ hypoxia and damage. A detailed examination of the data from several sources clarify the relationship between hematocrit, blood viscosity, organ blood flow, and oxygenation.

Viscosity

Fluids can be categorized as Newtonian and non-Newtonian [60,61]. Blood is a nonhomogeneous, non-Newtonian fluid. This means that there is not a reciprocal relationship between shear stress and shear rate as with Newtonian fluids such as water [60–62]. Numerous factors affect whole-blood viscosity, including pH, plasma protein concentration, red cell deformity, white blood cell fibrinogen and platelet concentration, blood vessel diameter, and blood velocity [14,59,63–69]. However, in newborns, the single most important factor is red cell concentration, or hematocrit. When measured in vitro by a Wells viscometer, blood viscosity will increase as hematocrit increases [63]. In newborns, the increase becomes exponential at hematocrit values of 65% and higher. However, in small tubes and the capillaries, blood viscosity becomes similar to the viscosity of plasma, independent of the hematocrit [61,62,70,71]. This suggests that changes in organ blood flow are not likely to be affected by hematocrit alone or blood viscosity as determined by in vitro techniques.

Relationship between Polycythemia, Blood Viscosity, and Organ Oxygenation

Based on the stipulation that polycythemia is associated with an increase in blood viscosity that results in decreased blood flow, many individuals have assumed that polycythemia and hyperviscosity result in organ – particularly brain – ischemia and hypoxia. However, a series of experiments performed between 1980 and 1995 has now clarified the changes in blood flow, oxygen delivery, and utilization of the brain of newborns with polycythemia.

Since Wood's first report, it has been assumed that infants with polycythemia had a reduction of brain blood flow due to sludging of red blood cells within the small blood vessels and capillaries of the brain. Using Doppler techniques, we demonstrated that infants with polycythemia did have a reduction in brain blood flow that returned to normal baseline values following a partial exchange transfusion to reduce the hematocrit [9]. In order to understand the factors responsible for the reduction of brain blood flow, our group studied a series of newborn lambs in which hematocrit, whole-blood viscosity, and arterial oxygen content were independently varied [19]. The data demonstrated that the changes in brain blood flow were due to changes in oxygen

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content, which change in parallel with the changes in the hematocrit in newborns. This is a normal physiologic response. Viscosity did not influence brain blood flow in this study. This finding has been confirmed by others [72]. Additional studies found that the usual reciprocal relationship between arterial oxygen content and brain blood flow that results in a consistent delivery of oxygen to the brain existed in conditions of increased hematocrit [18,20,73,74]. Further, brain uptake of oxygen was unaffected by polycythemia. These data strongly suggest that the elevated hematocrit alone cannot account for the neurologic abnormalities observed in infants with polycythemia and hyperviscosity.

Blood Flow and Functional Changes in Other Organs Related to Increases in Hematocrit

As noted earlier, numerous signs and symptoms have been attributed to polycythemia. These are listed in Table 28.2. Cardiac output, as reflected clinically by heart rate, is decreased [7,9,75,76]. Systemic oxygen delivery is normal due to the reciprocal relationship between increased arterial oxygen content and cardiac output. Systemic blood pressure is not affected by polycythemia. The respiratory distress and cyanosis that occur are likely due to decreased pulmonary blood flow [10,21,77]. Decreased pulmonary blood flow and increased pulmonary vascular resistance associated with shunting have been documented in human and animal investigations. Feeding intolerance, as evidenced by poor suck and oral feeding, is probably due to neurologic dysfunction [78]. However, there is an increased risk of lower gastrointestinal dysfunction, including ileus and necrotizing enterocolitis [7,10,23,24,79–82]. Nowicki et al. have documented changes in gastrointestinal blood flow and oxygen delivery and utilization in the unfed and fed states [7]. A study by Black et al. has suggested that partial exchange transfusion may contribute significantly to the development of necrotizing enterocolitis [24]. Renal function is compromised, as evidenced by a decreased renal plasma flow and glomerular filtration rate and decreased urine output in infants with normovolemic polycythemia [13].

Newborn infants with polycythemia are at increased risk for hypoglycemia [26,27]. It is not clear whether this is due to decreased gluconeogenesis or increased glucose utilization. Of concern is the finding that cerebral glucose delivery and uptake are lower at whole-blood or plasma glucose concentrations that are generally accepted as normal [75]. This is due to the fact that glucose exists only in the plasma fraction of the blood. This fraction is reduced in polycythemia. Therefore, the glucose-carrying capacity of the blood is reduced. When taken in combination with the decreased cerebral blood and plasma flow, cerebral glucose delivery, the limiting determinant of cerebral glucose uptake, reaches its lower limit for normal cerebral glucose uptake at higher concentrations of glucose compared with normal infants. This may have some implication for impaired cerebral function in infants with polycythemia.

Table 28.2 Signs and Symptoms Associated with Polycythemia

Cyanosis
Plethora
Tremulousness/jitteriness
Seizures
Respiratory distress
Cardiomegaly
Lethargy
Poor suck and feeding
Hyperbilirubinemia
Thrombocytopenia
Hypoglycemia
Hypocalcemia

Effects of Polycythemia on Neurologic Function

Information about neurologic function is limited by the study design and selection process for subjects. A number of studies have examined neurologic function in the newborn period, whereas others have concentrated on long-term development outcome. Of those examining symptomatic newborns, only two studies have been prospective and randomized. To date, there are no controlled, randomized studies of asymptomatic polycythemic infants to determine their long-term neurologic outcome with reference to treatment. However, as cited in the following discussion, some of the studies, such as those by Bada et al. [78] and Høst and Ulrich [82], included asymptomatic infants as well as those exhibiting signs and symptoms that are associated with polycythemia.

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Symptomatic Infants

Problems in the Newborn Period

Symptoms associated with polycythemia are listed in Table 28.2 [5,79,80,83]. The first controlled study of symptomatic infants and the effects of a partial exchange transfusion to reduce the hematocrit were reported by Goldberg et al. [80]. Prechtl and Brazelton examinations were initially abnormal in the polycythemic population compared with control infants. Normalization of these examinations in the polycythemic infants who received therapy to reduce the hematocrit was not accelerated. Van der Elst et al. performed a study of similar design in which the Brazelton score alone was used to evaluate the infants [81]. While the polycythemic infants were different from control infants, again, therapy to reduce the hematocrit did not alter outcome in the newborn period.

There have been some studies that have specifically examined the outcome of small-for-gestational-age (SGA) infants. As a group, the SGA infants have an increased incidence of polycythemia and an outcome that is inferior to infants who have normal intrauterine growth [53,84]. Polycythemia, likely a compensatory mechanism for chronic hypoxia, does not appear to be an independent factor in the outcome of this group of infants [56,78].

Long-Term Sequelae

Goldberg et al. were able to reexamine a subset of their original study population at 8 months of age [80]. Abnormalities were found in 67% of infants treated with partial exchange transfusion, 50% of untreated infants, and 17% of control infants. These findings are in contrast to those of van der Elst et al., who found that all of the infants had normal neurologic examinations [81]. There were no differences in the developmental scores of the three groups.

Black et al. have performed two studies to determine the long-term outcome of infants with polycythemia. In the first study, 111 infants with polycythemia and 110 control infants were studied [83]. The infants with polycythemia were not randomized as to observation or treatment. Follow-up examinations were performed between 1 and 3 years of age. Control infants had fewer abnormalities than the polycythemia group. The polycythemic infants were characterized by a 25% incidence of motor abnormalities, especially spastic diplegia. Forty percent had some type of handicap. However, there were no differences in outcome when the two subsets of polycythemic infants (observed versus treated) were compared.

In 1985, Black et al. published data on a group of 93 infants with polycythemia who were randomized to treatment or observation [85]. The total population included infants who were symptomatic and asymptomatic in the newborn period. At 1 year, 59% of the infants were available for follow-up, and no differences between the groups were found. At 2 years, 61% of the original group was examined, and the treated group had fewer abnormalities. This same group was called back again at school age (7 years of age) [86]. At that time, only 49 of the original 93 infants were available for evaluation. Significant differences between the control and polycythemic infants persisted. However, the observed and treated polycythemic groups were virtually identical.

Høst and Ulrich revealed the outcome of 635 infants as part of a public health project [82]. Screening in the newborn period revealed that 117 (18%) had a venous hematocrit greater than 60%, 30 (4.7%) had a hematocrit greater than 65%, and 7 had a hematocrit greater than 70%. Only 13 had any symptomatology that could be ascribed to polycythemia. None received an exchange transfusion to reduce the hematocrit. Over 80% of the infants were available for follow-up at age 6 years. Of those restudied, 104 of 113 polycythemic infants were normal. The remainder had minor problems, such as febrile convulsions, that could not be attributed to polycythemia in the newborn period.

Lastly, Bada et al. examined a group of infants with asymptomatic and symptomatic polycythemia and a control group of infants [78]. Follow-up at 30 months of age revealed no differences between the infants. However, when multivariate analysis was performed using multiple perinatal factors, it became clear that these other perinatal risk factors were highly related to outcome in all groups of infants, and polycythemia fell out as a nonsignificant factor.

When the results of these studies are taken together with our current knowledge of adaptive fetal physiology, several conclusions can be made. First, polycythemia appears to be an adaptive mechanism for chronic and acute fetal hypoxia. Hypoxia alone is known to be responsible for irreversible brain injury. Second, exchange transfusion does not appear to have an appreciable influence on the long-term neurologic function of infants with elevated hematocrits at birth, although the polycythemia

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is clearly a marker for increased risk of cerebral dysfunction. The demographic data from the studies of Black et al. and Bada et al. clearly indicate that these infants, particularly those who are symptomatic in the newborn period and in later life, are the ones who experienced an adverse fetal environment [78,85,86]. Therefore, it would appear that the events, particularly hypoxic-ischemic events, that result in an increase in hematocrit are likely to be responsible for the observed cerebral dysfunction. This would explain the failure of postnatal reduction of the hematocrit to alter long-term prognosis.

Asymptomatic Infants

There are still institutions that screen either all or high-risk infants for polycythemia. There are no large population studies of the long-term outcome of this type of population. Based on the findings in the studies cited in the preceding section, as well as a meta-analysis by Dempsey and Barrington [87], these infants may be at some nonquantifiable increased risk for long-term sequelae; however, current data strongly suggest that there is no evidence that an exchange transfusion to reduce the hematocrit will change the outcome because these sequelae appear to be due to other adverse perinatal events. Based on the data from well-designed trials, the American Academy of Pediatrics (AAP) Committee of the Fetus and Newborn made the following statement: "The accepted treatment of polycythemia is partial exchange transfusion. However, there is no evidence that exchange transfusion affects long-term outcome. Universal screening for polycythemia fails to meet the methodology and treatment criteria and also, possibly the natural criterion" [88].

Recommendations for Therapy

Partial exchange transfusion may be of benefit for infants who exhibit signs and symptoms or complications that have been demonstrated to be related to physiologic abnormalities caused by polycythemia. Such manifestations or clinical conditions include respiratory distress with cyanosis, renal failure, and hypoglycemia. Before considering therapy, the infant should be evaluated for other temporal and clinical events that may, in fact, be responsible for the problems observed. A partial exchange transfusion should not be done in the hope of correcting neurologic abnormalities in the immediate newborn period or preventing future neurologic dysfunction.

Because there are no adequate scientific data to demonstrate any benefit for polycythemic infants who are asymptomatic in the newborn period, simple observation alone would seem prudent. In situations when there are subtle signs and symptoms or in the presence of an extremely high hematocrit (e.g., >70%), the decision to perform a partial exchange transfusion may be initiated on individual clinical judgment based on the level of hematocrit, certainty of interpreting clinical symptoms, and the potential risk of the treatment (partial exchange transfusion). For those who develop neurologic abnormalities at a later time, the events during the prenatal and perinatal periods should be examined carefully to verify an etiology, other than polycythemia, that might explain the cerebral dysfunction.

Summary

Since the last version of this chapter, there has not been further original work on polycythemia, hyperviscosity, and outcome [89]. The meta-analyses and the statement from the AAP concur with our thoughts on this topic [87–89]. That is, there are no data to support a direct relationship between polycythemia and neurologic dysfunction. Polycythemia appears to be a marker for adverse prenatal and perinatal events that are known to cause mild to catastrophic neurologic injury. Postnatal exchange transfusion has not been shown to be of long-term benefit to infants who are symptomatic in the newborn period. There are no data to support the efficacy of this therapy in the infant with an elevated hematocrit who is otherwise normal.

Fetomaternal Hemorrhage

Introduction

Fetal cells cross the placental barrier before delivery, during labor, and after delivery during all pregnancies without apparent clinical significance in most cases. [90]. Generally, the volume of fetal cells entering the maternal circulation is quite small, 0.01–0.1 mL in 75% of cases, less than 0.5 mL in 96%, and less than 15 mL in more than 99% [91, 92]. When the mother is Rh negative and the fetus is Rh positive, even a small fetomaternal hemorrhage may lead to maternal antibody production and hemolysis in the fetus. This is a preventable problem with the availability of Rhogram.

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The focus of this section is the passage of a large volume of fetal cells into the maternal circulation (massive fetomaternal hemorrhage [FMH]), which results in either acute anemia and hypovolemia or chronic and progressive anemia in the fetus. An acute FMH is frequently associated with a sudden deterioration in fetal well-being. A more chronic hemorrhage generally allows the fetus to compensate until the hemoglobin concentration becomes so low that the fetus develops hydrops fetalis. A catastrophic outcome secondary to FMH can be prevented if the hemorrhage is detected in a timely fashion so that appropriate intervention can take place that prevents fetal hypoxia. What follows is a discussion of the incidence, presentation, potential interventions, and outcomes of pregnancies complicated by FMH.

Incidence

Although 50–75% pregnancies are associated with some degree of FMH, the volume of transferred cells is usually small, from 0.01 to 0.1 mL. The reported incidence for clinically significant FMH in many series has focused on a volume of 30 mL because this is the amount of fetal red blood cells (RBCs) covered by the standard 300-μg Rh immune globulin dose administered for the prevention of Rh sensitization [93]. This value does not necessarily correlate with the risk of fetal morbidity and mortality. At a volume of 30 mL, the incidence of FMH has been estimated to be approximately 3/1,000 births [92]. From a series of more than 30,000 unselected births evaluated for FMH, the incidence of FMH was 0.9/1,000 and 0.2/1,000 at volumes of more than 80 mL and more than 150 mL, respectively [94]. *Massive* FMH is defined as the presence of 20–60 mL or more of fetal blood in the maternal circulation. FMHs of this size are reported to occur in 1–6/1,000 births [95–97]. A more objective method for assessing the magnitude of FMH is to estimate the percentage of fetal blood volume represented by FMH. Defining a massive FMH as the transfer of 20 mL/kg, which represents 20% of fetoplacental blood volume, may be most appropriate because it has been associated with significant fetal morbidity and mortality [95]. Large hemorrhages with clinical impact on the fetus and newborn are so uncommon that most of the information is based on case reports and a few small series [92,95–98]. Most of this data is retrospective. Lastly, the diagnosis may be affected by the method used to detect fetal cells in the maternal circulation.

Etiology

FMH has been associated with a maternal history of vaginal bleeding, abdominal trauma, placenta previa, placental abruption, and cord compression [95,99]. Massive FMH can also occur spontaneously. One of the largest series of FMH greater than 50 mL reported that the cause could not be determined in 82%, suggesting that most FMHs are spontaneous. Traumatic injuries to the placental interface are typically caused by invasive diagnostic procedures such as amniocentesis, chorionic villus biopsy, and versions [100]. There are contradictory reports regarding mode of delivery. Ness et al. reported a higher incidence with cesarean section, and Salim et al reported no difference for a large FMH between cesarean section and vaginal deliveries between singleton and multiple deliveries [101,102]. Emergency cesarean delivery, cord around the neck, and low birth weight were associated with larger FMHs [97]. Large FMHs have also been described with external cephalic version with anterior placenta and placental tumors such as chorioangiomata and choriocarcinoma [102–106].

Pathophysiology

In most studies done to date, not much attention has been paid to why FMH occurs. A disruption in the trophoblast must exist to allow fetal red blood cells from the higher-pressure fetal circulation to enter the intervillous space and then maternal circulation. It is unclear if this breach heals, remains small, or grows to lead to massive blood loss or what causes it. Evaluation of several hundred placentas from both normal and abnormal deliveries revealed that certain placental lesions such as intraplacental hemorrhage, intervillous thrombosis, placental infarction, and retroplacental hematoma were associated with FMH, as determined by Kleihauer-Betke test. The greater the number of placental lesions, the larger is the transplacental hemorrhage [100].

Diagnosis

The diagnosis of FMH is made by detecting fetal RBCs in maternal blood. The Kleihauer-Betke (KB) test has been used as the standard since it was described in 1957 [107]. The principle of the KB test is that fetal hemoglobin (HbF) is resistant to elution by an acidic buffer, whereas adult hemoglobin HbA is eluted by the acid buffer. When the blood film is fixed and

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stained, the fetal cells containing HbF are stained, and the maternal cells appear as *ghost cells*.

The extent of the FMH can only be estimated accurately if done before delivery because postpartum estimates may be falsely elevated from extra fetal blood extravasated into the maternal circulation with delivery of the placenta. There may also be false-positive results in mothers with increased fetal hemoglobin synthesis due to sickle cell disease, thalassemia, and hereditary persistence of HbF or false-negative results if some fetal cells fail to stain or fetal cells are cleared from maternal circulation due to maternal antibodies such as ABO or Rh incompatibility. The KB test does not reflect timing of the bleeding [108]. Using the KB test and basic physiologic principles, FMH can be calculated using the following formula [109]:

$$\text{Fetal RBCs} = \frac{\text{maternal blood volume} \times \text{maternal hematocrit} \times \%\ \text{fetal RBCs (KB)}}{\text{infant hematocrit}}$$

$$\text{Maternal blood volume} = 5,000\ \text{mL}$$
$$\text{Maternal hematocrit at term} = 35\%$$
$$\text{Neonate hematocrit} = 50\%$$

Flow cytometry is a new technology that is also available for the estimation of FMH. It quantifies the number of fetal cells by measuring the fluorescence intensity of monoclonal antibodies binding to hemoglobin F. The florescent intensity of fetal HbF-containing cells has been demonstrated to be greater than adult HbF-containing cells, and it also measures the size of the RBCs by forward light scatter, allowing distinction of fetal from adult cells based on the higher mean volume [110]. Some commercial kits also have antibodies against RBC surface antigens such as carbonic anhydrase II expressed on fetal erythrocytes [111]. Flow cytometry has been shown to be accurate and more sensitive and reproducible than the KB test [112,113]. Because it is more expensive, it is not done routinely in all hospitals. It has been used in Rh-incompatible pregnancies as an alternative to the KB test to decide an accurate dosage of anti-D immunoglobulin.

Clinical Presentation

Massive FMH occurs in the second or third trimester and can be acute, chronic, or intermittent recurrent. The mother is usually asymptomatic but can sometimes have symptoms suggestive of a transfusion reaction such as fever, chills, or nausea [114,115]. Presentation of the neonate depends on the amount and timing of the FMH [99]. The most common presentation appears to be an acute event. In this situation, a large FMH is associated with decreased fetal movement or loss of fetal movements and sinusoidal fetal heart rate pattern or recurrent late decelerations or fetal tachycardia. Giacoia reviewed these variables to see if there was a correlation with the amount of hemorrhage [96]. One hundred and thirty-four cases were evaluated, and 17 had absent fetal movements from 1–7 days. A sinusoidal heart rate pattern was found in 21% and decreased fetal movements in 40%. No difference was found between cases with FMHs less than 200 mL or more than 200 mL. Others have found that the absolute blood flow velocity of the middle cerebral artery in the fetus correlates with the degree of fetal anemia [116]. To preserve oxygen to the brain, cerebral blood flow increases. As such, there is an increased peak systolic velocity in the middle cerebral artery. Values greater than 1.5 multiples of the median are suspicious for significant fetal anemia [117].

Infants born after an acute hemorrhage are often tachycardic and tachypneic. The infant's hemoglobin can be as low as 4–6 g/dL [98]. In cases of acute massive FMH, the newborn presents with hypovolemic shock, acidosis, respiratory distress, persistent pulmonary hypertension, hypoxic ischemic encephalopathy, and mulitorgan failure.

If the FMH is a slow, chronic process, the neonate may presents with pallor but is otherwise hemodynamically stable because there has been time for the fetus to compensate. If the hemoglobin reaches very low levels, then the fetus will develop hydrops fetalis. The triad of decreased fetal movements, sinusoidal fetal heart rate, and hydrops fetalis is a late sign of chronic massive FMH [96].

There have been reports of fetal transfusion in instances when the fetus is still very premature. The correction of fetal anemia leads to resolution of the hydrops and allows continuation of the pregnancy [118].

Treatment

Newborn infants with significant hemorrhage require rapid assessment and treatment. Treatment consists of volume replacement with crystalloids and/or packed RBCs under close monitoring. These infants will also need assessment and treatment for metabolic acidosis, respiratory distress, and ongoing hypotension. Evaluation and therapy for possible hypoxic-ischemic encephalopathy and seizures are also required. For infants with chronic anemia and symptoms of hydrops, exchange transfusion is a more appropriate means of correcting the anemia because these infants will have a normal blood volume. These infants will often need additional therapy for respiratory distress and congestive heart failure [119].

Outcomes

In the study by Giacoia, six infants survived, five were stillborn, and five died in the neonatal period [96]. Kecskes found that only the postnatal presentation and an initial hemoglobin of less than 4 g/dL were associated with a poor outcome. Rubod et al. studied the long-term prognosis for infants after massive FMH and concluded that FMH of 20 mL/kg or more significantly increased the risk of death and preterm delivery, but long-term follow-up of survivors was not associated with neurologic sequelae [95]. However, a detailed review of documented cases of FMH revealed that a significant number of survivors developed cerebral changes including intraventricular hemorrhage, cerebral infarction, ventriculomegaly, perventricular leukomalacia, and cerebral atrophy. There are also some infants with a normal neurologic examination and imaging studies in the newborn period who go onto develop cerebral palsy [92,94,95]. Therefore, the outcome may depend on multiple factors including the size of the FMH, the time between the FMH and delivery, and recognition of the anemia and hypotension and timely therapy [120].

Conclusion

Massive FMH is not as uncommon as previously believed. It is an important cause of fetal morbidity and mortality in low-risk pregnancies. The KB test and flow cytometry are the two diagnostic tools available to establish the diagnosis. Outcomes appear to be related to the degree of fetal/neonatal anemia, a high index of suspicion leading to prompt diagnosis, and rapid evaluation and treatment of the newborn. In all cases of unexplained fetal demise, a KB test should be performed.

References

1. Wood JL. Plethora in the newborn infant associated with cyanosis and convulsions. *J Pediatr* 1952; **54**: 143–51.
2. Michael A, Mauer AM. Maternal-fetal transfusion as a cause of plethora in the neonatal period. *Pediatrics* 1961; **28**: 458–61.
3. Minkowski A. Acute cardiac failure in connection with neonatal polycythemia in monovular twins and single newborn infants. *Biol Neonate* 1962; **4**: 61–74.
4. Danks DM, Stevens LH. Neonatal respiratory distress associated with a high haematocrit reading. *Lancet* 1964; **2**: 499–500.
5. Gross CP, Hathaway WE, McCaughey HR. Hyperviscosity in the neonate. *J Pediatr* 1973; **82**: 1004–12.
6. Oh W, Oh MA, Lind J. Renal function and blood volume in newborn infants related to placental transfusion. *Acta Paediatr Scand* 1966; **56**: 197–210.
7. Nowicki P, Oh W, Yao A, et al. Effect of polycythemia on gastrointestinal blood flow and oxygenation in piglets. *Am J Physiol* 1984; **247**: G220–5.
8. Surjadhana A, Rouleau J, Boerboom L, et al. Myocardial blood flow and its distribution in anesthetized polycythemic dogs. *Circ Res* 1978; **43**: 619–31.
9. Rosenkrantz TS, Oh W. Cerebral blood flow velocity in infants with polycythemia and hyperviscosity: effects of partial exchange transfusion with plasmanate. *J Pediatr* 1982; **101**: 94–8.
10. Fouron JC, Hebert F. The circulatory effects of hematocrit variations in normovolemic newborn lambs. *J Pediatr* 1973; **82**: 995–1003.
11. Gatti RA, Muster AJ, Cole RB, et al. Neonatal polycythemia with transient cyanosis and cardiorespiratory abnormalities. *J Pediatr* 1966; **69**: 1063–72.
12. Kotagal VR, Keenan WJ, Reuter JH, et al. Regional blood flow in polycythemia and hypervolemia. *Pediatr Res* 1977; **11**: 394.
13. Kotagal VR, Kleinman LI. Effect of acute polycythemia on newborn renal hemodynamics and function. *Pediatr Res* 1982; **16**: 148–51.
14. Bergqvist G, Zetterman R. Blood viscosity and peripheral circulation in newborn infants. *Acta Paediatr Scand* 1974; **63**: 865–8.
15. Linderkamp O, Strohhacker I, Versmold HT, et al. Peripheral circulation in the newborn: interaction of peripheral blood flow, blood pressure, blood volume and blood viscosity. *J Pediatr* 1978; **129**: 73–81.
16. Gustafsson L, Applegren L, Myrvold HE. The effect of polycythemia on blood flow in working and

non-working skeletal muscle. *Acta Physiol Scand* 1980; **109**: 143–8.

17. Waffarn F, Cole CD, Huxtable RF. Effects of polycythemia on cutaneous blood flow and transcutaneous PO_2 and PCO_2 in the hyperviscosity neonate. *Pediatrics* 1984; **74**: 389–94.
18. Jones MD, Traystman RJ, Simmons MA, et al. Effects of changes in arterial O_2 content on cerebral blood flow in the lamb. *Am J Physiol* 1981; **240**: H209–15.
19. Rosenkrantz TS, Stonestreet BS, Hansen NB, et al. Cerebral blood flow in the newborn lamb with polycythemia and hyperviscosity. *J Pediatr* 1984; **104**: 276–80.
20. Rosenkrantz TS, Philipps AF, Skrzypczak PS, et al. Cerebral metabolism in the newborn lamb with polycythemia. *Pediatr Res* 1988; **23**: 329–33.
21. Oh W, Wallgren G, Hanson JS, et al. The effects of placental transfusion on respiratory mechanics of normal term newborn infants. *Pediatrics* 1967; **40**: 6–12.
22. Hakanson DO, Oh W. Necrotizing enterocolitis and hyperviscosity in the newborn infant. *J Pediatr* 1977; **90**: 458–61.
23. LeBlanc MH, D'Cruz C, Pate K. Necrotizing enterocolitis can be caused by polycythemic hyperviscosity in the newborn dog. *J Pediatr* 1984; **105**: 804–9.
24. Black VD, Rumack CM, Lubchenco LO, et al. Gastrointestinal injury in polycythemic term infants. *Pediatrics* 1985; **76**: 225–31.
25. Herson VC, Raye JR, Rowe JC, et al. Acute renal failure associated with polycythemia in a neonate. *J Pediatr* 1982; **100**: 137–9.
26. Leake RD, Chan GM, Zakauddin S, et al. Glucose perturbation in experimental hyperviscosity. *Pediatr Res* 1980; **14**: 1320–3.
27. Creswell JS, Warburton D, Susa JB, et al. Hyperviscosity in the newborn lamb produces perturbation in glucose homeostasis. *Pediatrics* 1981; **15**: 1348–50.
28. Rivers RPA. Coagulation changes associated with a high haematocrit in the newborn infant. *Acta Paediatr Scand* 1975; **64**: 449–56.
29. Katz J, Rodriquez E, Mandani G, et al. Normal coagulation findings, thrombocytopenia, and peripheral hemoconcentration in neonatal polycythemia. *J Pediatr* 1982; **101**: 99–102.
30. Henriksson P. Hyperviscosity of the blood and haemostasis in the newborn infant. *Acta Paediatr Scand* 1979; **68**: 701–4.
31. Shaikh BS, Erslev AJ. Thrombocytopenia in polycythemic mice. *J Lab Clin Med* 1978; **92**: 765–71.
32. Jackson CW, Smith PJ, Edwards CC, et al. Relationship between packed cell volume platelets and platelet survival in red blood cell–hypertransfused mice. *J Lab Clin Med* 1979; **94**: 500–9.
33. Meberg A. Transitory thrombocytopenia in newborn mice after intrauterine hypoxia. *Pediatr Res* 1980; **14**: 1071–3.
34. Rosenkrantz TS, Oh W. Neonatal polycythemia and hyperviscosity. In Milunsky A, Friedman EA, Gluck L, eds., *Advances in Perinatal Medicine*, vol. **5**. New York: Plenum, 1986: 93–123.
35. Cornbleet J. Spurious results from automated hematology cell counters. *Lab Med* 1983; **14**: 509–14.
36. Penn D, Williams PR, Dutcher TF, et al. Comparison of hematocrit determination by microhematocrit electronic particle counter. *Am J Clin Pathol* 1979; **72**: 71–4.
37. Pearson TC, Guthrie L. Trapped plasma in the microhematocrit. *Am J Clin Pathol* 1982; **78**: 770–2.
38. Oh W, Lind J. Venous and capillary hematocrit in newborn infants and placental transfusion. *Acta Paediatr Scand* 1966; **55**: 38–40.
39. Shohat M, Reisner SH, Mimouni F, et al. Neonatal polycythemia II. Definition related to time of sampling. *Pediatrics* 1984; **73**: 11–13.
40. Wirth FH, Goldberg KE, Lubchenco LO. Neonatal hyperviscosity. I. Incidence. *Pediatrics* 1979; **63**: 833–6.
41. Stevens K, Wirth FH. Incidence of neonatal hyperviscosity at sea level. *J Pediatr* 1980; **97**: 118–19.
42. Ghavam S, Batra D, Mercer J, et al. Effects of placental transfusion in extremely low birthweight infants: meta-analysis of long- and short-term outcomes. *Transfusion* 2014; **54**(4): 1192–8.
43. Christensen R, Baer V, Gerday E, et al. Whole blood viscosity in the neonate: effects of gestational age, hematocrit, mean corpuscular volume, and umbilical cord milking. *J Perinatol* 2014; **34**(1): 16–21.
44. Hutton EK, Hassan ES: Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. *JAMA*. 2007; **297**(11): 1241–52.
45. Oh W, Blankenship W, Lind J. Further study of neonatal blood volume in relation to placental transfusion. *Ann Paediatr* 1966; **207**: 147–59.
46. Yao AC, Moinian M, Lind J. Distribution of blood between infants and placenta after birth. *Lancet* 1969; **2**: 871–3.
47. Linderkamp O. Placental transfusion: determinants and effects. *Clin Perinatol* 1981; **9**: 559–92.
48. Saigal S, Usher RH. Symptomatic neonatal plethora. *Biol Neonate* 1977; **32**: 62–72.

49. Philip AGS, Yee AB, Rosy M, et al. Placental transfusion as an intrauterine phenomenon in deliveries complicated by fetal distress. *BMJ* 1969; **2**: 11–13.
50. Flod NE, Ackerman BD. Perinatal asphyxia and residual placenta blood volume. *Acta Paediatr Scand* 1971; **60**: 433–6.
51. Yao AC, Lind J. Effect of gravity on placental transfusion. *Lancet* 1969; **2**: 505–8.
52. Oh W, Omori K, Emmanouilides GC, et al. Placenta to lamb fetus transfusion *in utero* during acute hypoxia. *Am J Obstet Gynecol* 1975; **122**: 316–21.
53. Sacks MO. Occurrence of anemia and polycythemia in phenotypically dissimilar single ovum human twins. *Pediatrics* 1959; **24**: 604–8.
54. Schwartz JL, Maniscalco WM, Lane AT, et al. Twin transfusion syndrome causing cutaneous erythropoiesis. *Pediatrics* 1984; **74**: 527–9.
55. Humbert JR, Abelson H, Hathaway WE, et al. Polycythemia in small for gestational age infants. *J Pediatr* 1969; **75**: 812–19.
56. Widness JA, Garcia JA, Oh W, et al. Cord serum erythropoietin values and disappearance rates after birth in polycythemic newborns. *Pediatr Res* 1982; **16**: 218A.
57. Philipps AF, Dubin JW, Matty PJ, et al. Arterial hypoxemia and hyperinsulinemia in the chronically hyperglycemic fetal lamb. *Pediatr Res* 1982; **16**: 653–8.
58. Wells RE, Penton R, Merrill EW. Measurements of viscosity of biologic fluids by core plate viscometer. *J Lab Clin Med* 1961; **57**: 646–56.
59. Linderkamp O, Versmold HT, Riegel KP, et al. Contributions of red cells and plasma to blood viscosity in preterm and full-term infants and adults. *Pediatrics* 1984; **74**: 45–51.
60. Poiseuille JLM. Recherches expérimentales sur le mouvement des liquides dans les tubes de très petits diameters. *C R Acad Sci* 1840; **11**: 961–1041.
61. van der Elst CW, Malan AF, de Heese HV. Blood viscosity in modern medicine. *S Afr Med J* 1977; **52**: 526–8.
62. Dintenfass L. Blood viscosity, internal fluidity of the red cell, dynamic coagulation and the critical capillary radius as factors in the physiology and pathology of circulation and microcirculation. *Med J Aust* 1968; **1**: 688–96.
63. Wells RE, Merrill EW. Influence of flow properties of blood upon viscosity-hematocrit relationships. *J Clin Invest* 1962; **41**: 1591–8.
64. Bergqvist G. Viscosity of the blood in the newborn infants. *Acta Paediatr Scand* 1974; **63**: 858–64.
65. Wells R. Syndromes of hyperviscosity. *N Engl J Med* 1970; **283**: 183–6.
66. Smith CM, Prasler WJ, Tukey DP, et al. Fetal red cells are more deformable than adult red cells. *Blood* 1981; **58**: 35a.
67. Lichtman MA. Cellular deformability during maturation of the myeloblast: possible role in marrow egress. *N Engl J Med* 1970; **283**: 943–8.
68. Lichtman MA. Rheology of leukocytes, leukocyte suspensions, and blood in leukemia. *J Clin Invest* 1973; **52**: 350.
69. Miller ME. Developmental maturation of human neutrophil motility and its relationship to membrane deformability. In Bellanti UA, Dayton DH, eds., *The Phagocytic Cell in Host Resistance*. New York: Raven Press, 1975: 295.
70. Burton AC. Role of geometry, of size and shape, in the microcirculation. *Fed Proc* 1966; **25**: 1753–60.
71. Fahraeus R, Lindqvist T. The viscosity of the blood in narrow capillary tubes. *Am J Physiol* 1931; **96**: 561–8.
72. Goldstein M, Stonestreet BS, Brann BS, et al. Cerebral cortical blood flow and oxygen metabolism in normocythemic hyperviscous newborn piglets. *Pediatr Res* 1988; **24**: 486–9.
73. Massik J, Tang YL, Hudak ML, et al. Effect of hematocrit on cerebral blood flow with induced polycythemia. *J Appl Physiol* 1987; **62**: 1090–6.
74. Rosenkrantz TS, Philipps AF, Knox I, et al. Regulation of cerebral glucose metabolism in normal and polycythemic newborns. *J Cereb Blood Flow Metab* 1992; **12**: 856–65.
75. LeBlanc MH, Kotagal UR, Kleinman LI. Physiological effects of hypervolemic polycythemia in newborn dogs. *J Appl Physiol* 1982; **53**: 865–72.
76. Murphy DJ, Reller MD, Meyer RA, et al. Effects of neonatal polycythemia and partial exchange transfusion on cardiac function: an echocardiographic study. *Pediatrics* 1985; **76**: 909–13.
77. Brashear RE. Effects of acute plasma for blood exchange in experimental polycythemia. *Respiration* 1980; **40**: 297–306.
78. Bada HS, Korones SB, Pourcyrous M, et al. Asymptomatic syndrome of polycythemic hyperviscosity: effect of partial plasma exchange transfusion. *J Pediatr* 1992; **120**: 579–85.
79. Ramamurthy RS, Brans YW. Neonatal polycythemia. I. Criteria for diagnosis and treatment. *Pediatrics* 1981; **68**: 168–74.
80. Goldberg K, Wirth FH, Hathaway WE, et al. Neonatal hyperviscosity. II. Effect of partial plasma exchange transfusion. *Pediatrics* 1982; **69**: 419–25.

81. van der Elst CW, Molteno CD, Malan AF, et al. The management of polycythemia in the newborn infant. *Early Hum Dev* 1980; **4**: 393–403.

82. Høst A, Ulrich M. Late prognosis in untreated neonatal polycythemia with minor or no symptoms. *Acta Paediatr Scand* 1982; **71**: 629–33.

83. Black VD, Lubchenco LD, Luckey DW, et al. Developmental and neurologic sequelae of neonatal hyperviscosity syndrome. *Pediatrics* 1982; **69**: 426–31.

84. Hakanson DO, Oh W. Hyperviscosity in the small-for-gestationa1 age infant. *Biol Neonate* 1980; **37**: 109–12.

85. Black VD, Lubchenco LO, Koops BL, et al. Neonatal hyperviscosity: randomized study of effect of partial plasma exchange on long-term outcome. *Pediatrics* 1985; **75**: 1048–53.

86. Black VD, Camp BW, Lubchenco LO, et al. Neonatal hyperviscosity is associated with lower achievement and IQ scores at school age. *Pediatr Res* 1988; **23**: 442A.

87. Dempsey EM, Barrington K. Short and long term outomes following partial exchange transfusion in the polycythemic newborn: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2006; **91**: F2–6.

88. American Academy of Pediatrics Committee on the Fetus and Newborn. Routine evaluation of blood pressure, hematocrit and glucose in newborns. *Pediatrics* 1993; **92**: 474–6.

89. Rosenkrantz TS. Polycythemia and hyperviscosity in the newborn. *Semin Thromb Hemost* 2003; **29**: 515–27.

90. Bowman JM, Pollock JM, Penston LE. Fetomaternal transplacental hemorrhage during pregnancy and after delivery. *Vox Sang* 1986; **51**: 117–21.

91. Scott JR, Warenski JC. Tests to detect and quantitate fetal maternal bleeding. *Clin Obstet Gynecol* 1982; **25**: 277.

92. Sebring ES, Polesky HF. Fetomaternal hemorrhage: Incidence, risk factors, time of occurrence and clinical effects. *Transfusion* 1990; **30**: 344–57.

93. Pollack W, Ascari WQ, Kochesky RJ et al. Studies on Rh prophylaxis. 1. Relationship between dose of anti-Rh and size of antigenic stimulus. *Transfusion* 1971; **11**: 333–9.

94. De Almeida V, Bowman JM. Massive fetomaternal hemorrhage: Manitoba experience. *Obstet Gynecol* 1994; **83**: 323–8.

95. Rubod C, Deruelle P, Le Goueff F, et al. Long term prognosis for infants after massive fetomaternal hemorrhage. *Obstet Gynecol* 2007; **110**(2 pt 1): 256–60.

96. Giacoia GP. Severe fetomaternal hemorrhage: a review. *Obstet Gynecol Surv* 1997; **52**: 372.

97. Salim R, Ben- Shlomo I, Nachum Z et al. The incidence of large fetomaternal hemorrhage and Kleihauer-Betke test. *Obstet Gynecol* 2005; **105**(5 Pt 1): 1039–44.

98. Kosasa T, Ebesugawa I, Nakayama R, Hale R. Massive fetomaternal hemorrhage precedes by decreased fetal movement and a nonreactive fetal heart rate pattern. *Obstet Gynecol* 1993; **82**: 711–14

99. Markham LA, Charsha DS, Peelmuter B. Case report of massive fetomaternal hemorrhage and a guideline for acute neonatal management. *Adv Neonat Care* 2006, **6**: 197–207.

100. Devi B, Jennison RF, Langley FA. Significance of placental pathology in transplacental hemorrhage. *J Clin Pathol* 1968; **21**: 322–31.

101. Ness PM, Baldwin ML, Niebyl JR. Clinical high risk designation does not predict excess fetal-maternal hemorrhage. *Am J Obstet Gynecol* 1987; **156**: 154–8.

102. Banninger V, Schmid J. External cephalic version close to term in the management of breech presentation. *Z Geburtshilfe Perinatol* 1977; **181**: 189–192.

103. Blom AH, Gevers RH. Een patient met diffuse choriangiomatosis placenta. *Ned Tijdschr Geneeskd* 1974; **118**: 7–10.

104. Blackburn GK. Massive fetomaternal hemorrhage due to choricarcinoma of the uterus. *J Pediatr* 1976; **89**: 680–681.

105. Shankar M, Gough GW, Chakravarti S, Vellacott ID. Massive feto-maternal haemorrhage with good perinatal outcome following failed external cephalic version. *Fetal Diang Ther* 2004; **19**: 68–71.

106. Lam CM, Wong SF, Lee DW, et al. Massive feto-maternal hemorrhage: an early presentation of women with gestational choriocarcinoma. *Acta Obstet Gynecol Scand* 2002; **81**: 573–76.

107. Kleihauer E, Betke K. Practical use of the demonstration of cells containing hemoglobin F in fixed blood smears (in German). *Izv Mikrobiol Inst* 1960; **1**: 292–5.

108. Polesky HF, Sebring ES. Evaluation of methods for detection and quantitation of fetal cells and their effect on RhIG usage. *Am J Clin Pathol* 1981; **76**: 525–9.

109. Cunningham FG, Gant NF, Leveno KJ et al. Disease and injuries of the fetus and newborn. In *Williams Obstetrics*, 21st ed. New York: McGraw- Hill, 2001: 1039–91.

110. Chen JC, Bigelelow NC, Davis BH. Proposed flow cytometric reference method for the determination of erythroid F-cell counts. *Cytometry* 2000; **42**: 239–46.

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111. Porra V, Bernaud J, Gueret P, et al. Identification and quantification of fetal RBCs in maternal blood by a dual-color flow cytometric method: evaluation of fetal cell count kit. *Transfusion* 2007; **47**: 1281–9.

112. Bromilow IM, Duguid JK. Measurement of feto-maternal haemorrhage: a comparative study of three Kleihauer techniques and two flow cytometry methods. *Clin Lab Haemtol* 1997; **19**: 137–42.

113. Fong EA, Davies JI, Grey DE, et al. Detection of massive transplacental haemorrhage by flow cytometry. *Clin Lab Haemtol* 2000; **22**: 325–7.

114. Murphy KW, Venkatraman N, Stevens J. Limitations of ultrasound in the diagnosis of fetomaternal hemorrhage. *BJOG* 2000; **107**: 1317.

115. Glasser L, West JH, et al. Incompatible fetomaternal transfusion with maternal intravascular lysis. *Transfusion* 1970; **10**: 322.

116. Malcus P, Bjorklund LJ, Lilja M, et al. Massive feto-maternal Hemorrhage: diagnosis by cardiotocography, Doppler ultrasonography and ST waveform analysis of fetal electrcardiography. *Fetal Diagn Ther* 2006; **21**: 8–12.

117. Moise KJ Jr. The usefulness of middle cerebral artery Doppler assessment in the treatment of the fetus at risk for anemia. *Am J Obstet Gynecol* 2008; **161**: el–4.

118. Rubod C, Houfflin V, Belot F, et al. Successful in utero treatment of chronic and massive fetomaternal hemorrhage with fetal hydrops. *Fetal Diagn Ther* 2006; **21**: 410–13.

119. Wylie JW, D'Alton ME. Fetomaternal hemorrhage. *Obstet Gynecol* 2010; **115**: 1039–51.

120. Kecskes Z. Large fetomaternal hemorrhage: clinical presentation and outcome. *J Maternal-Fetal and Neonatal Medicine*. 2003; **13**: 128–32.

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Chapter 29

Hydrops Fetalis

Carlo Bellini and Luca A. Ramenghi

Definition

Hydrops fetalis (HF) is a severe and challenging fetal condition. It is the nonspecific end stage of a wide variety of disorders and usually refers to an excessive accumulation of fetal fluid within the fetal extravascular compartments and body cavities that manifests as edema, pleural and pericardial effusions and ascites, generalized skin thickness greater than 5 mm, and placental enlargement [1,2]. When fluid accumulation is limited to one cavity, for example, isolated ascites or pleural effusion, it should be described in terms of the involved site because this could help to pin down the differential diagnosis. Hydrops is a continuously evolving condition, and thus the involvement of only one visceral cavity may be transient and may be followed by involvement of several other visceral cavities. A basic dichotomy in the hydrops classification is in immune (IHF) and nonimmune hydrops fetalis (NIHF) [2]. Previously, IHF was caused by Rhesus or ABO isoimmunization, but prophylaxis against Rhesus isoimmunization since the 1970s has led to a significant decline in the prevalence of IHF. NIHF indicates significant fetal compromise and is associated with high rates of perinatal mortality and neonatal morbidity. The incidence is estimated to be at about 1/1,500 to 1/3,750 births; IHF accounts for about 10–20% of all cases of HF. IHF presents during the gestational period (50% between 18–34 weeks of gestation, 50% between 34 weeks and term). The prevalence of NIHF is unknown and difficult to determine because many cases are not diagnosed before intrauterine death or may resolve spontaneously antenatally. It is estimated at around 3/10,000 births. Currently, NIHF constitutes up to 85–90% of all HF cases [1–4].

Etiology

In 2009, a systematic review established the etiology of NIHF based on the literature up to December 2007 [2]. Since then, a considerable number of papers have been published on the etiologic findings in NIHF, thus revealing the need for an update of the previous review that was recently published [2,5] (Table 29.1).

These studies [2,5] demonstrated that it is often difficult or even impossible to correctly classify patients with, for example, a chromosome imbalance because they can be classified either in the chromosomal category or in the category related to the (presumed) pathogenetic mechanisms leading to HF. Trisomy 21 and 18 are clear examples. Another example of the difficulty in systematizing the etiology of NIHF lies in evaluating the percentage of cases assigned to the lymphatic dysplasia category, which showed a remarkable increase in the second review compared with the first (Table 29.1). An increase in the number of papers in the recent literature describing the relationship between NIHF and congenital lymphatic dysplasia was observed, thus implying that awareness of the role of lymphatic system disorders in NIHF is increasing [6–10]. Some differences in the strategies that are used to deal with NIHF may be observed between the first review [2] and the second one [5]. As 2015 approached, it became more evident that greater attention was being paid to pathophysiology than to simple etiologic classification.

Despite the increase in the number of reported NIHF cases in the literature, the percentage of cases in the idiopathic category has basically remained unchanged, and to some extent, it has actually increased [2,5] (Table 29.1). This negative result highlights the need for a careful and detailed diagnostic workup of NIHF cases using the idiopathic category. It is quite impossible to draft a table that can be all-embracing, that is, that includes every possible (described) cause, disease, or disorder linked to NIHF.

Pathophysiology

The cornerstone of hydrops fetalis is the pathophysiology, that is, the imbalance of the regulation of fluid

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Table 29.1 Etiology of NIHF

Categories	1979–2007 [1]		2008–2013 [4]		1979–2013 [1, 4]	
	No. of cases	Percent	No. of cases	Percent	No. of cases	Percent
Cardiovascular	1,181	21.7	269	20.1	1,450	21.4
Hematologic	564	10.4	124	9.3	688	10.1
Chromosomal	727	13.4	120	9.0	847	12.5
Syndromic	237	4.4	74	5.5	311	4.6
Lymphatic dysplasia	310	5.7	201	15.0	511	7.5
Inborn errors of metabolism	60	1.1	18	1.3	78	1.1
Infections	366	6.7	93	7.0	459	6.8
Thoracic	327	6.0	31	2.3	358	5.3
Urinary tract malformations	127	2.3	12	0.9	139	2.0
Extrathoracic tumors	39	0.7	10	0.7	49	0.7
TTTF, placental	304	5.6	55	4.1	359	5.3
Gastrointestinal	29	0.5	18	1.3	47	0.7
Miscellaneous	200	3.7	48	3.6	248	3.7
Idiopathic	966	17.8	265	19.8	1,231	18.2
Total	**5,437**		**1,338**		**6,775**	

Note: This table shows the results of two reviews on NIHF [1,4], with overall results from 1979 to 2013. Data were categorized on the basis of 14 etiologic classification groups.

movements between vascular and interstitial spaces (Figure 29.1). Extracellular fluid volume changes markedly during intrauterine life and in the neonatal period. Hormonal, renal, and cardiovascular mechanisms are the main factors strongly influencing the regulation of extracellular fluid volume in the fetus and neonate [10]. Very little is known about lymphatic function during the fetal or neonatal period, and there is a great deal more to learn about its regulation. Figure 29.1 shows the pathophysiologic pathways.

Distribution of Fluids in the Fetus and Neonate

Total-body water (TBW) as a percentage of body weight varies with age, showing values of approximately 95% of the total body weight in early gestation, 75% at term, and 62% by 9 months of age. TBW is divided into two main compartments, intracellular fluid (ICF) and extracellular fluid (ECF), and ECF is greater than ICF in both the fetus and the newborn. As gestation proceeds and then throughout life, the proportion of body water in the ECF drops, whereas the proportion in the ICF increases slightly (Figure 29.2) [7,11,12].

Changes during Intrauterine Development

In early gestation, body composition is characterized by a high proportion of TBW and large extracellular compartments. As gestation progresses, the rapid cellular growth and increase in body solids and fat stores lead to a gradual decrease in TBW content and extracellular water volume, while the intracellular fluid compartment increases (Figure 29.2) [7,11,12].

Changes during Labor and Delivery

Labor and delivery cause acute changes in TBW and its distribution. Arterial blood pressure increases due to higher catecholamine, vasopressin, and cortisol plasma levels. Thus the translocation of blood from the placenta to the fetus, together with intrapartum

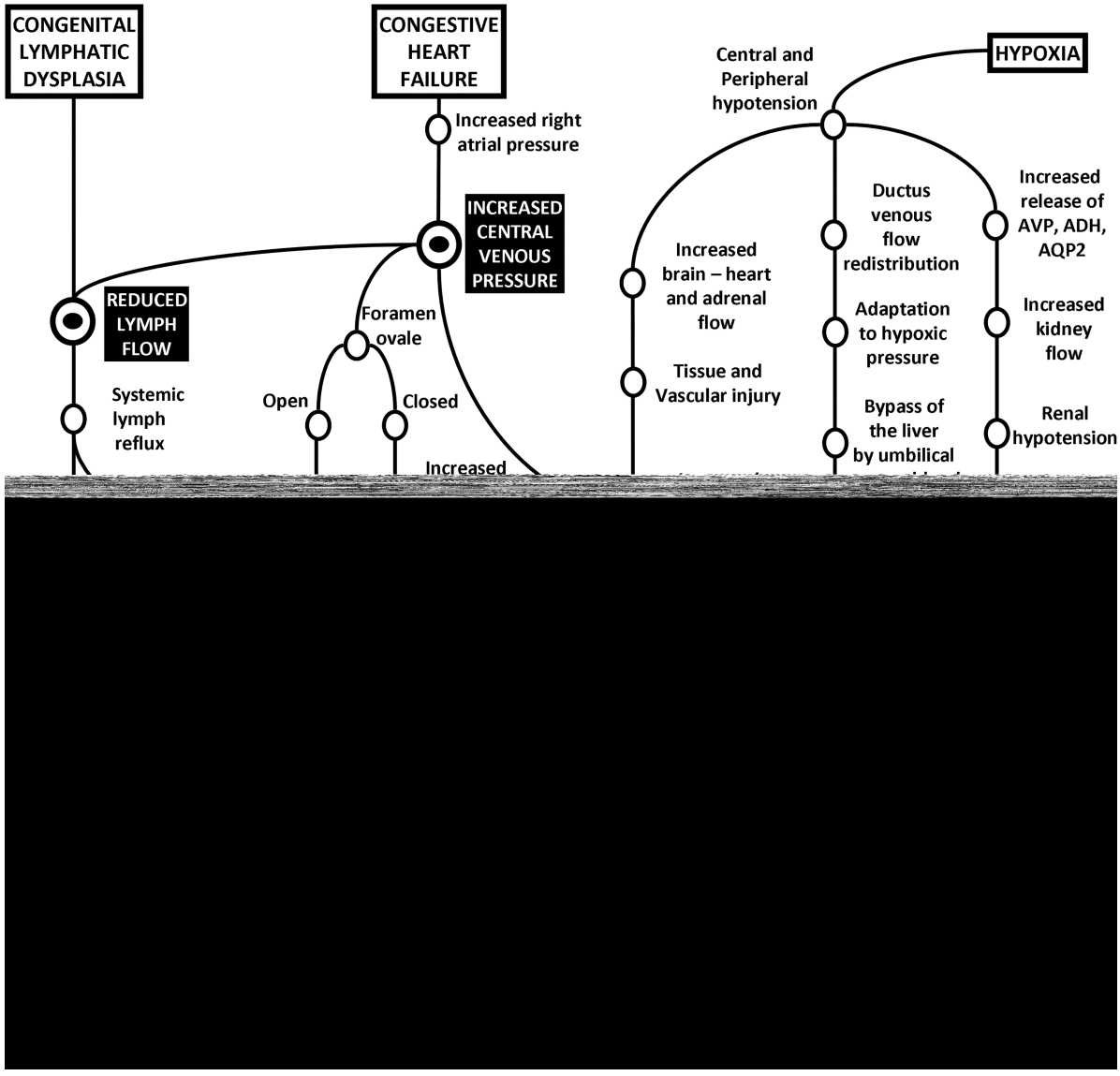


Figure 29.1 Pathophysiology of hydrops. Flowchart indication of the various possibilities in the pathophysiology of NIHF.

hypoxia, generates a shift of fluid from the intravascular to the interstitial compartments. In turn, this generates a reduction of approximately 25% in circulating plasma volume in the fetus during labor and delivery (Figure 29.2) [7,11,12].

Changes in the Postnatal Period

During the early transitional period, the healthy newborn loses weight. It is generally accepted that this postnatal weight loss is mainly due to the contraction of the expanded ECF compartment and that it approximates the total-body fluid loss. Water loss from the intracellular space may also contribute to the physiologic weight loss (Figure 29.2) [7,11,12].

Lymphatic Flow

Very little is known about lymphatic function during the fetal and neonatal periods. We can highlight some

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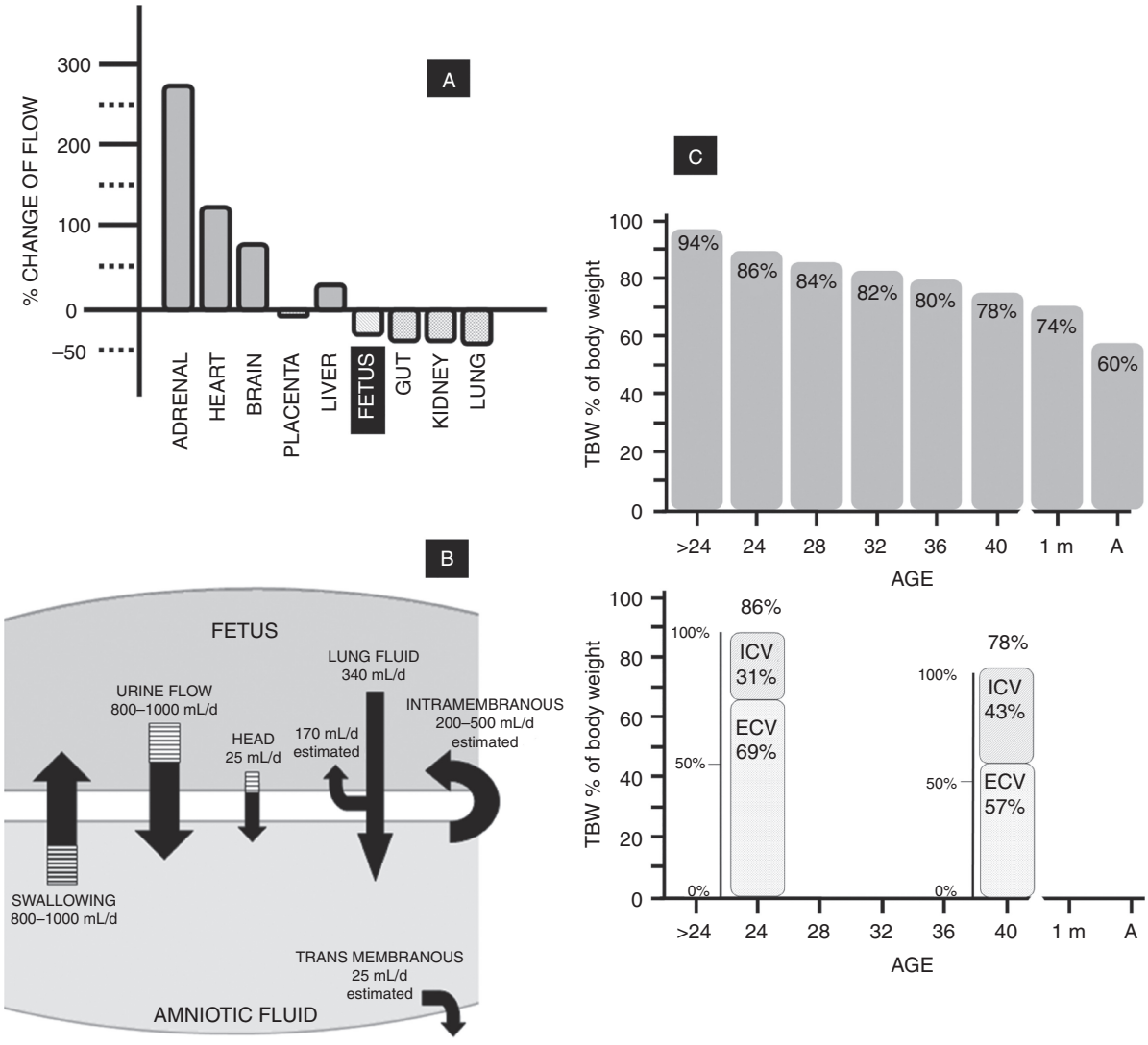


Figure 29.2 Water distribution. (a) Redistribution of fetal combined cardiac output during acute hypoxemia (reduced uterine blood flow). (b) Schematic diagram of the known pathways for fluid and solute entry and exit from the amniotic fluid in the fetus in late gestation. Volume flow in milliliters per day. (c) (Above) Distribution of TBW related to total weight relating to gestational age. (Below) Distribution of intracellular and extracellular volume relating to gestational age.

peculiar circumstances that may be observed early in life; that is, lymphatics must cope with increased interstitial fluid, fetal lymph flow is five times greater than in adults, flow depends on outflow pressure, a slight increase in central venous pressure results in a dramatic decrease in lymph flow, and lastly, lung liquid removal is significantly linked to lung lymph flow and lung tidal volume [7,10–12]. The lack of a classic lymphatic drainage system in the CNS is a weaker assumption because it was recently discovered that meningeal lymphatic vessels and not nasal mucosa lymphatic vessels alone represent the primary CSF drainage route [13].

The volume of fluid within the lymphatic system is small and averages only 1 mL/kg of body weight in adult dogs, as estimated by lymph flow dynamics. Lymphatic flow has never been measured in the human fetus or neonate, and it is reasonable to speculate that there are developmental changes in lymphatic volume. Studies in animals have shown higher flow rates in the fetus and

newborn than in the adult. Basal lymph flow rates in the fetus are higher than in the newborn, and lymph flow rates in the newborn are higher than in the adult. Thus a possible consequence of reduced lymph flow in the fetus is fluid retention and the gradual formation of generalized fetal tissue edema, that is, HF (Figure 29.1) [7,10–14].

Interstitial Fluid Balance: Starling Equation

The regulation of fluid movement between vascular and interstitial spaces is linked to transcapillary filtration; the rate of fluid filtration across the capillary wall is calculated by the Starling equation: $J_v = K_f (\Delta P - \sigma\Delta\pi)$ (Figure 29.3). A high value indicates a highly water-permeable capillary; a low value indicates low capillary permeability. The Starling equation is an equation that illustrates the role of hydrostatic and oncotic forces (the so-called Starling forces) in the movement of fluid across capillary membranes [7,15].

Amniotic Fluid Balance

The ratio of amniotic fluid volume to fetal volume changes during pregnancy. In early pregnancy, amniotic fluid volume is many times greater than fetal volume. In the subsequent period, amniotic fluid volume and fetal volume increase from 25 mL at 10 weeks to 400 mL at 20 weeks, when both volumes become equal. Thereafter, fetal volume becomes greater than amniotic volume: at 30 weeks, the amniotic fluid volume is half the fetal volume, and at term, it is a one-quarter [16,17].

Role of Fetal Circulation

For a long time it was believed that the fetal blood flow pattern with shunts in the foramen ovale and ductus arteriosus allowed the fetus to tolerate heart malformations [18]. More recently, ultrasound evaluation of fetal lambs with congenital heart defects indicated that fetal circulation and development are more strongly influenced by cardiac malformations than expected. Various mechanisms have been suggested to explain these effects, such as altered flow volume, altered tissue oxygenation, and altered fetal venous pressure (Figure 29.1) [19]. The altered flow volume is thought to be the main mechanism leading to (cardiogenic) NIHF.

Elevated systemic venous pressure is a well-known event linked to congenital heart defects that eventually lead to HF. In this condition, increased end-diastolic pressure and limited ventricular compliance lead to congestive heart failure; thus high right atrial pressure increases both central venous pressure and hydrostatic pressure at the capillary level and decreases lymphatic flow. Fluid extravasation into the interstitium and impaired interstitial fluid reuptake by lymphatics are closely linked to HF formation [7,10,11].

Role of Acute Fetal Hypoxia

It was observed that experimental severe asphyxia obtained by 30 seconds ofocclusion of the umbilical cord in midgestation fetal sheep (90 days, term 150 days) leads to hydrops [20]. This observation confirmed a similar, previous report [21]. It was established that marked activation of the rennin-angiotensin system (RAS) was present in fetuses with hydrops (Figure 29.1). If an asphyxial insult occurs, fetal ventricular output shunts away from the kidney to the brain, heart, and adrenals and may cause renal tubular ischemic damage. During an asphyxial insult, the placenta can increase salt and water transport to the fetus; if fetal kidney function is impaired, leading to oliguria-anuria, then hydrops may develop [21,22]. There is no general agreement on these findings. It is not clear how the fetal kidney can regulate the excretion of fluid load. Hydrops can also occur in the absence of significant renal damage, with a normal rate of urine production. A combination of renal impairment and high levels of angiotensin may play a significant role in the etiology of NIHF [10,23,24].

Conclusion

The number of published papers in the field of hydrops-related disorders is on the rise. Although the level of knowledge in the field has improved significantly, many questions are still pending. Decreased cardiac output, as well as high cardiac output failure, decreased colloid oncotic plasma pressure associated with increased fetal capillary permeability, severe adverse tissue effects of hypoxia or sepsis, obstruction of venous flow leading to increased central venous pressure resulting in secondary lymphatic imbalance, and, again, primary lymphatic dysplasia are conditions that have been extensively reviewed in this section. Less is known about the fetal neural and hormonal mechanisms that are responsible for the fetal protective action of blood flow redistribution. Metabolic conditions are probably underestimated due to the difficult diagnosis. Finally, many experimental studies are conducted on animal models due to easily understandable limitations in human fetus studies, thus obtaining results that may not be readily transferable to the human fetus.

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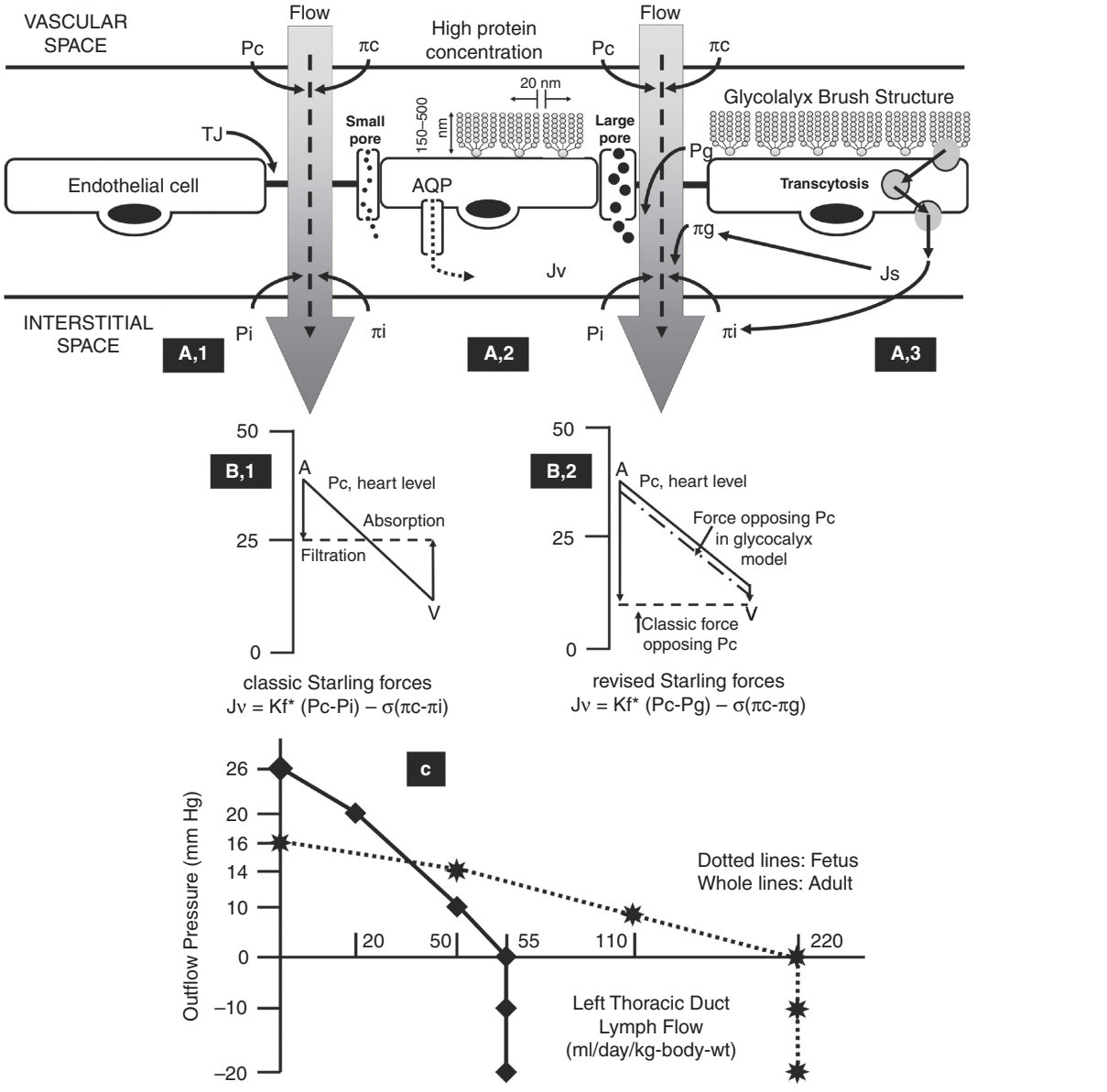


Figure 29.3 Starling law and thoracic lymph flow. (a) Comparison of traditional and revised views of the endothelial semipermeable membrane: (a, 1) traditional view of continuous endothelium as a semipermeable membrane; (a, 2) pore theory of capillary permeability showing large and small pores and the role of aquaporin (AQP); (a, 3) revised Starling model; the main barrier to fluid permeability is the glycocalyx network that restricts fluid entry to the intercellular space. (b). Imbalance of the classic Starling pressures: (b, 1) traditional filtration-reabsorption model; (b, 2) the imbalance when all four classic Starling forces are measured. (c). Relationship between left thoracic duct lymph flow and rising outflow pressure in unanesthetized fetal and adult sheep.

Prenatal and Postnatal Diagnostic Workup for HF

We previously suggested a diagnostic flowchart for NIHF [25]; Figure 29.4 and Table 29.2 summarize the recent suggestions on prenatal and postnatal diagnostic workup for hydrops, outlining the baseline investigations for all HF cases (references inside the table). In general, in case of HF, urgent referral to a maternal-fetal medicine specialist for rapid evaluation is mandatory because some situations must be considered true prenatal medical emergencies. Waiting for complete results

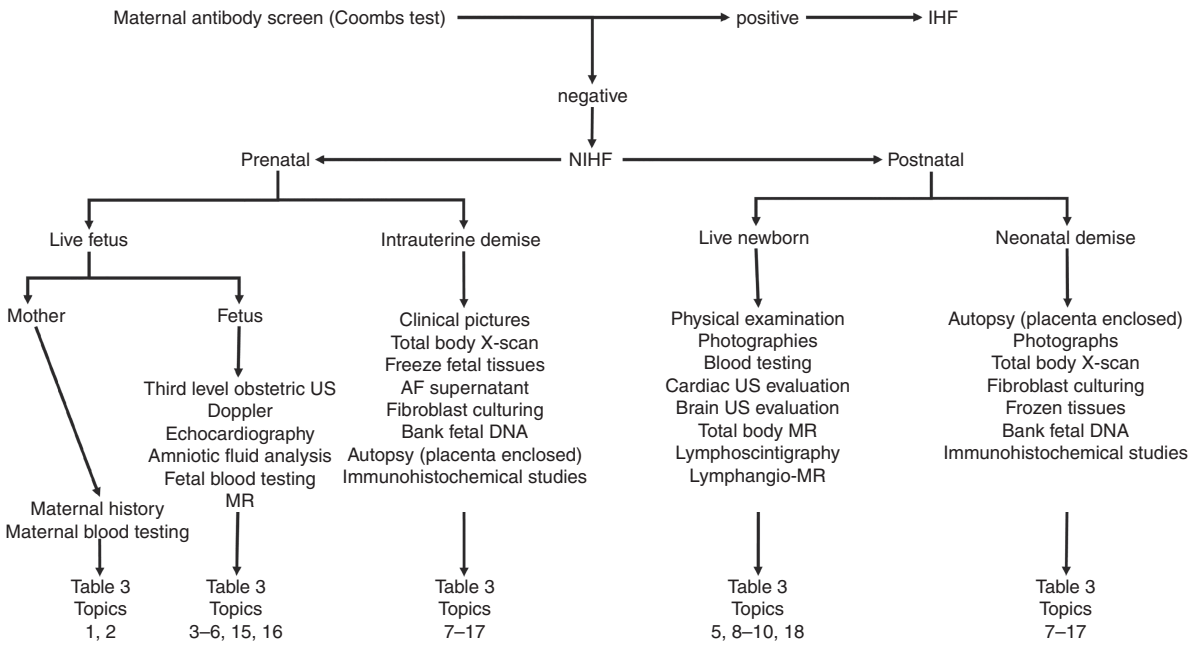


Figure 29.4 Diagnostic flowchart for prenatal and postnatal hydrops fetalis. For details, see Table 29.2.

before initiating referral, invasive diagnostic procedures, or treatment is not recommended.

Fetal Treatment

Fetal hydrops is a challenging medical emergency that must be referred immediately to a maternal-fetal medicine specialist and a medical geneticist for rapid evaluation. Recently, many effective therapeutic options have become available (Table 29.3) [26,27,60,61], resulting in significantly improved outcomes for many patients. The currently accepted list of fetal conditions for which antenatal surgery is taken into consideration includes twin-twin transfusion syndrome, congenital diaphragmatic hernia, lower urinary tract obstruction, myelomeningocele, neck masses occluding the trachea, and tumors such as congenital cystic adenomatoid malformation or sacrococcygeal teratoma, though only if associated with developing fetal hydrops in the latter two cases. Fetal therapy can potentially improve perinatal outcomes for fetuses with many conditions leading to hydrops fetalis, but it is often complicated by intrauterine death and preterm birth [26,27,60–62]. Uncertainties still trouble physicians in this fascinating field of perinatal medicine, including the difficulty involved in identifying the ideal fetal candidates for antenatal therapy, determining the optimal timing of intervention, and preventing preterm birth after fetal surgery [61]. Fetal treatment options for NIHF depend on the etiology and the gestational age at diagnosis. A maternal-fetal specialist should undertake this evaluation.

Timing and Mode of Delivery

There are no management trials regarding delivery timing in the setting of NIHF on which to base recommendations. Based on expert opinion, about 34 weeks' gestational age would seem a reasonable indication for delivery in case of worsening NIHF. Depending on the degree of associated effusions and anasarca, the real risk of dystocia must be taken into account; thus cesarean delivery may be indicated. Although there are no definitive data regarding the usefulness of antepartum corticosteroid therapy, the high rate of preterm births among NIHF fetuses makes it reasonable to take such preventive treatment into consideration [26].

At-Birth Management

Postnatal therapy is challenging [63]. Vigorous resuscitation including thoracocentesis and/or paracentesis [56,63,64] is usually performed in an effort to

Table 29.2 Diagnostic Flowchart for Prenatal and Postnatal Diagnosis of Nonimmune Hydrops Fetalis

Topic	Suggestions	Refs
1. Maternal history	Consider: collagen-vascular diseases, organ transplant, blunt abdominal trauma, coagulopathies, sexually transmitted diseases, thyroid disorders, diabetes mellitus, viral infections, teratogenics through occupation, pets, or place of living, and jaundice in other family members. Consider maternal medication use: indomethacin, sodium diclofenac, or potentially teratogenic drugs during pregnancy; prior administration of blood products; risks of illicit drug use. Determine ethnicity and probability of hemoglobinopathies in the population from which parents originate. Exclude immune hydrops. Check history of previous pregnancies: jaundice in previous children, twin-to-twin transfusion syndrome (TTTS), genetic disorders in earlier fetuses and children, chromosomal abnormalities, inborn errors of metabolism, congenital malformations, cardiac defects, fetal death, polyhydramnios; TORCHES-CLAP.	[25–27]
2. Maternal blood and invasive testing	Blood cell count, blood grouping and Rh, Hb electrophoresis, Kleihauer-Betke test, erythrocyte enzymes (include at least G6PD, pyruvate kinase, and glucose phosphate isomerase), TORCHES-CLAP, serum alpha-fetoprotein, maternal anti-SSA/SSB antibodies (fetal bradyarrhythmia), karyotype, DNA storage, inborn errors of metabolism, total-body scan, and MRI.	[28–30]
3. Fetal imaging	Detailed morphologic obstetric ultrasound study in a tertiary center; assessment of the fetal venous and arterial circulations; venous and arterial MCA Doppler; fetal echocardiogram.	[26,27]
4. TTTS	Twin-to-twin transfusion syndrome, including a cardiac parasitic twin.	[31–33]
5. Fetal blood testing	Consider: fetal karyotype, fetal complete blood count, hemoglobin electrophoresis, TORCHES-CLAP, fetal albumin, and inborn errors of metabolism.	[34]
6. TORCHES-CLAP	*Toxoplasma gondii*; rubella virus; cytomegalovirus; herpes simplex virus; enterovirus; syphilis; chickenpox (varicella-zoster) virus; Lyme disease (*Borrelia burgdoferi*); AIDS; parvovirus B19.	[26,27,35–37]
7. Autopsy	The value of autopsy cannot be overestimated. If consent to autopsy is refused, a total-body MRI may be a noninvasive and acceptable alternative for the family.	[38–43]
8. Photographic documentation	A full-body picture, facial pictures in two directions, and pictures of any other structure that seems abnormal can be an important tool in diagnosis. Digital photographs are advisable because such pictures can be more easily used in consultations.	[25–27]
9. Fetal measurements	Length, weight, and skull circumference are obligatory. Foot length can be used to determine gestational age. Other useful measurements can be inner canthal distance, outer canthal distance, philtrum length, and ear length. In severe hydrops, some of the values obtained may be unreliable.	[25–27]
10. Total-body x-ray scan	A total-body radiograph in two directions is useful and will allow diagnosis of most skeletal dysplasias and dysostoses. Detailed views of the hands and feet should be made if the suspicion of a skeletal dysplasia or dysostosis is high.	[25–27]
11. Skin for fibroblast culturing	A skin specimen (diameter 3–5 mm) should be collected and placed in culture medium. If culture media are unavailable, the skin specimen	[25–27]

Table 29.2 (cont.)

Topic	Suggestions	Refs
	can be placed in sterile saline for a short time only. Do not allow specimen to freeze. Ear cartilage is usually the tissue that remains viable the longest; useful if fetal demise > 96 hours. If there is intrauterine demise and delivery will be induced using prostaglandins, it is advisable to obtain amnion cells before induction of delivery because growth of fibroblasts is usually very poor after prostaglandins.	
12. Frozen tissue storage	Include specimens from muscle, heart, brain, liver, intestine, kidney, peripheral nerve, bone marrow, conjunctiva, amniocytes, and placenta. The specimens should be frozen as soon as possible at −70°C, if available, or otherwise at −20°C. Tissue specimens should be stored in a nonfixed way and not treated with a preservative.	[25–27]
13. Fluid storage	Parental informed consent. Include plasma, blood, urine, visceral effusion, bile, and cerebrospinal fluid. Use filter paper for adjunctive storage; the specimen should be allowed to dry. Postmortem blood specimen collection is possible for several hours after demise by intracardiac puncture. Urine may be obtained by swabbing the bladder. Bile collection is obtained by direct gallbladder puncture. Cerebrospinal fluid collection is obtained by anterior fontanel puncture.	[25–27,44]
14. Immuno histochemical studies	Indication: diagnosing and searching for the cause of death in fetuses or newborns who present clinically evident signs or findings of possible lymphatic dysplasia, such as hydrops itself, pleural, pericardial, or abdominal effusions, cystic hygroma, or prenatal, unexplained, increased NT. Routine staining on five microtome sections; the following monoclonal antibodies are recommended: CD-31, CD-34, D2-40 (or podoplanin), smooth muscle actin (SMA). Inclusion of specimens from the nuchal region is recommended.	[40,45–47]
15. Inborn errors of metabolism testing.	Consider lysosomal storage diseases: lysosomal enzyme and molecular analysis in cultured amniocytes or cell lines from trophoblasts. Hydrops fetalis has been described in Gaucher disease, type II, Morquio disease, Hurler syndrome, Sly syndrome, Farber disease, GM1 gangliosidosis, I-cell disease, Niemann-Pick disease type A and type C, infantile sialic acid storage disorder, alpha-neuroaminidase deficiency, multiple sulfatase deficiency, and Wolman disease. Consider also nonlysosomal diseases, including glycogenosis type IV, long-chain hydroxy-acylCoA dehydrogenase deficiency, CDG type1a, CDG type I/IX, hypothyroidism, Carnitine deficiency, and Smith-Lemli-Opitz syndrome.	[48–51]
16. Amniotic fluid	FISH or QF-PCR on uncultured amniocytes; karyotype or microarray analysis; PCR for CMV, parvovirus B19, toxoplasmosis; bacterial culture; store amniotic cells; DNA extraction for alpha-thalassemia.	[52]
17. Placenta	Clinical pictures; placental pathology; store tissue (see also topics 11–15).	[42,43,53]
18. Lymphatic dysplasia	Lymphoscintigraphy, lymphangio-MR, molecular genetics analysis of genes involved in lymphatic dysplasia. Consider pulmonary and intestinal lymphangiectasia.	[45,54–59]

Note: The text of this table must be read with the integration of Figure 29. 4 showing the diagnostic flowchart for prenatal and postnatal hydrops fetalis (see references inside the table).

Table 29.3 Available Fetal Therapies for Treatable Fetuses with Hydrops

Disease(s)	Possible fetal therapies, complications, and outcome
Maternal acquired pure red cell aplasia	Intrauterine transfusion, possible intrauterine fetal demise, survival hydrops estimated around 74%
Maternal fetal hemorrhage	
Fetal massive hemolysis	
Viral infection	
Pleural effusion	Thoracoamniotic shunting
Ascites	Possible shunt dislodgment, survival hydrops estimated around 55%
Pulmonary lymphangiectasia	
Cystic adenomatoid malformation	Vaso-occlusive techniques, fetal lobectomy, steroidal drugs, minimally invasive techniques are recommended: interstitial laser, radiofrequency ablation, cyanoacrylate injection into the mass; shunt is preferred, but only in the presence of hydrops
Pulmonary sequestration	
Laryngeal atresia	Ex utero intrapartum therapy (EXIT procedure)
Congenital diaphragmatic hernia	Tracheal occlusion, just below the vocal cords; possible balloon deflation; survival hydrops estimated around 50%
Hypoplastic left heart syndrome	Balloon valvuloplasty in case of aortic critical stenosis; in case of restrictive foramen ovale, the use of stent is indicated; possible intrauterine fetal demise; possible shunt dislodgement; survival 30–40%
Fetal tachyarrhythmia	Antiarrhythmic drugs administered to the mother; in case of atrioventricular block, use salbutamol if heart rate < 55 beats/minute
Atrioventricular block (anti-SS-A/SS-B)	
Twin-to-twin transfusion, TRAP	Laser ablation of anastomosis; possible intrauterine fetal demise of one fetus; twin anemia polycythemia sequence; TRAP, cord clamp; double survival 70%, one fetus 90%
Chorioangioma	Laser photocoagulation of placental vessels
Myelomeningocele	In spina bifida, open surgery and repair; in sacrococcygeal teratoma, percutaneous drainage of large cysts may alleviate dystocia at delivery
Sacrococcygeal teratoma	
Posterior urethral valves	Vescicoamniotic shunting; laser ablation; possible shunt dislodgment

Note: Fetal treatment options for NIHF depend on the etiology and gestational age at diagnosis. A maternal-fetal specialist should undertake this evaluation [26,27,60–62].

establish adequate lung expansion. After stabilizing the patient, every effort must be made to determine the cause and correct the condition responsible for the hydrops. Extensive cardiorespiratory support is necessary, including mechanical ventilation, as is high-frequency oscillatory ventilation and possibly extracorporeal membrane oxygenation (ECMO). Intravenous fluid management is difficult; a balance between the need to obtain sodium and water loss during the first week after birth and the need for parenteral nutrition is the target. Many specific treatments may be useful depending on the condition that led to hydrops. Therapeutic hypothermia, which is widely dealt with in other parts of this book, is now a standard of care for term newborns with moderate or severe perinatal asphyxia, often complicating hydrops at birth [65]. Coagulopathy complicating asphyxia, hypoproteinemia, hypoalbuminemia, massive hemolysis,

thrombocytopenia, and hypoglycemia are but a few examples of the multitude of complications that may be observed at birth [63].

References

1. Bukowski R, Saade GR. Hydrops fetalis. *Clin Perinatol* 2000; **27**: 1007–31.
2. Bellini C, Hennekam RCM, Fulcheri E, et al. Etiology of nonimmune hydrops fetalis: a systematic review. *Am J Med Genet A* 2010; **152A**: 1189–96.
3. Bellini C. Immune hydrops fetalis. Available at www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=364013.
4. Bellini C. Nonimmune hydrops fetalis. Available at www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=363999.
5. Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. *Am J Med Genet A* 2015; **167**: 1082–8.
6. Rodríguez MM, Chaves F, Romaguera RL, et al. Value of autopsy in nonimmune hydrops fetalis: series of 51 stillborn fetuses. *Pediatr Dev Pathol* 2002; **5**: 365–74.
7. Bellini C, Boccardo F, Bonioli E, et al. Lymphodynamics in the fetus and newborn. *Lymphology* 2006; **39**: 110–11.
8. Randenberg AL. Nonimmune hydrops fetalis. I. Etiology and pathophysiology. *Neonatal Netw* 2010; **29**: 281–95.
9. Randenberg AL. Nonimmune hydrops fetalis. II. Does etiology influence mortality? *Neonatal Netw* 2010; **29**: 367–80.
10. Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. *Am J Med Genet A* 2012; **158A**: 597–605.
11. Bauer k, Brace RA, Stonestreet BS. Fluid distribution in the fetus and neonate. In Polin RA, Fox WW, Abman SH, eds., *Fetal and Neonatal Physiology*, 4th edn. Philadelphia: Elsevier Saunders, 2011: 1436–44.
12. Lorenz JM. Fetal and neonatal body water compartment volumes with references to growth and development. In Polin RA, Fox WW, Abman SH, eds., *Fetal and Neonatal Physiology*, 4th edn. Philadelphia: Elsevier Saunders, 2011: 1445–50.
13. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; **523**(7560):337–41.
14. Brace RA. Fetal thoracic duct lymph flow response to intravascular saline infusion. *Am J Physiol* 1988; **254**: 1007–10.
15. Levick JR1, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* 2010; **87**: 198–210.
16. Gilbert WM, Brace RA. Amniotic fluid volume and normal flows to and from the amniotic cavity. *Semin Perinatol* 1993; **17**: 150–7.
17. Magann EF, Sandlin AT, Ounpraseuth ST. Amniotic fluid and the clinical relevance of the sonographically estimated amniotic fluid volume: oligohydramnios. *J Ultrasound Med* 2011; **30**: 1573–85.
18. Kiserud T. Physiology of the fetal circulation. *Semin Fetal Neonatal Med* 2005; **10**: 493–503.
19. Rudolph AM. Congenital cardiovascular malformations and the fetal circulation. *Arch Dis Child Fetal Neonatal Ed.* 2010:**95**(2): F132–6.
20. Lumbers ER, Gunn AJ, Zhang DY, et al. Nonimmune hydrops fetalis and activation of the renin-angiotensin system after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R1045–51.
21. Keunen H, Blanco CE, van Reempts JL, et al. Absence of neuronal damage after umbilical cord occlusion of 10, 15, and 20 minutes in midgestation fetal sheep. *Am J Obstet Gynecol* 1997; **176**: 515–20.
22. O'Connell AE, Boyce AC, Lumbers ER, et al. The effects of asphyxia on renal function in fetal sheep at midgestation. *J Physiol* 2003; **552**: 933–43.
23. Nathanielsz PW, Hanson MA. The fetal dilemma: spare the brain and spoil the liver. *J Physiol* 2003; **548**: 333.
24. Tchirikov M, Kertschanska S, Schröder HJ. Differential effects of catecholamines on vascular rings from ductus venosus and intrahepatic veins of fetal sheep. *J Physiol* 2003; **548**: 519–26.
25. Bellini C, Hennekam RC, Bonioli E. A diagnostic flow chart for non-immune hydrops fetalis. *Am J Med Genet A* 2009; **149A**: 852–53.
26. Norton ME, Chauhan SP, Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline 7: nonimmune hydrops fetalis. *Am J Obstet Gynecol* 2015; **212**: 127–39.
27. Désilets V1, Audibert F. Investigation and management of non-immune fetal hydrops. Society of Obstetrician and Gynaecologists of Canada. *J Obstet Gynaecol Can* 2013; **35**: 923–38.
28. Jaeggi E, Laskin C, Hamilton R, et al. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol* 2010; **55**: 2778–84.

29. Winichagoon P, Kumpan P, Holmes P, et al. Validation of the immunochromatographic strip for α-thalassemia screening: a multicenter study. *Transl Res* 2014; **5**: S1931–52.
30. Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation*. 2011; **124**: 1927–35.
31. Bebbington M. Twin-to-twin transfusion syndrome: current understanding of pathophysiology, in-utero therapy and impact for future development. *Semin Fetal Neonatal Med* 2010; **15**: 15–20.
32. Mosquera C1, Miller RS, Simpson LL. Twin-twin transfusion syndrome. *Semin Perinatol* 2012; **36**: 182–9.
33. Benoit RM, Baschat AA. Twin-to-twin transfusion syndrome: prenatal diagnosis and treatment. *Am J Perinatol* 2014; **31**: 583–94.
34. Berry SM, Stone J, Norton ME, et al. Fetal blood sampling. Society for Maternal-Fetal Medicine (SMFM). *Am J Obstet Gynecol* 2013; **209**: 170–80.
35. Tudor Car L, van-Velthoven MH, Brusamento S, et al. Integrating prevention of mother-to-child HIV transmission (PMTCT) programmes with other health services for preventing HIV infection and improving HIV outcomes in developing countries. *Cochrane Database Syst Rev* 2011; **6**: CD008741.
36. Shahrook S, Mori R, Ochirbat T, et al. Strategies of testing for syphilis during pregnancy. *Cochrane Database Syst Rev* 2014; **10**: CD010385.
37. Neu N, Duchon J, Zachariah P. TORCH infections. *Clin Perinatol* 2015; **42**: 77–103.
38. Rodríguez MM, Chaves F, Romaguera RL, et al. Value of autopsy in nonimmune hydrops fetalis: series of 51 stillborn fetuses. *Pediatr Dev Pathol* 2002; **5**: 365–74.
39. Wainwright HC. My approach to performing a perinatal or neonatal autopsy. *J Clin Pathol* 2006; **59**: 673–80.
40. Bellini C, Fulcheri E, Rutigliani M, et al. Immunohistochemistry in non-immune hydrops fetalis: a single center experience in 79 fetuses. *Am J Med Genet A* 2010; **152A**: 1189–96.
41. Désilets V, Oligny LL. Fetal and perinatal autopsy in prenatally diagnosed fetal abnormalities with normal karyotype. *J Obstet Gynaecol Can* 2011; **33**: 1047–57.
42. Heller DS, Faye-Petersen OM. Pathology of the stillborn infant for the general pathologist, part 1. *Adv Anat Pathol* 2015; **22**: 1–28.
43. Faye-Petersen OM, Heller DS. Pathology of the stillborn infant for the general pathologist, part 2. *Adv Anat Pathol* 2015; **22**: 71–93.
44. Dreux S, Salomon LJ, Rosenblatt J, et al. Biochemical analysis of ascites fluid as an aid to etiological diagnosis: a series of 100 cases of nonimmune fetal ascites. *Prenat Diagn*. 2015; **35**: 214–20.
45. Bellini C, Rutigliani M, Boccardo FM, et al. Nuchal translucency and lymphatic system maldevelopment. *J Perinat Med* 2009; **37**: 673–6.
46. Bellini C, Rutigliani M, Boccardo F, et al. Perinatal deaths and lymphatic system involvement: a diagnostic flow-chart applying immunohistochemical methods. *Lymphology* 2011; **44**: 131–3.
47. Bellini C, Hennekam RC. Clinical disorders of primary malfunctioning of the lymphatic system. *Adv Anat Embryol Cell Biol* 2014; **214**: 187–204.
48. Kooper AJ, Janssens PM, de Groot AN, et al. Lysosomal storage diseases in non-immune hydrops fetalis pregnancies. *Clin Chim Acta* 2006; **371**: 176–82.
49. Gort L, Granell MR, Fernández G, et al. Fast protocol for the diagnosis of lysosomal diseases in nonimmune hydrops fetalis. *Prenat Diagn* 2012; **32**: 1139–42.
50. Whybra C, Mengel E, Russo A, et al. Lysosomal storage disorder in non-immunological hydrops fetalis (NIHF): more common than assumed? Report of four cases with transient NIHF and a review of the literature. *Orphanet J Rare Dis* 2012; **7**: 86.
51. Surmeli-Onay O, Yakarisik S, Korkmaz A, et al. Prenatal-onset Niemann-Pick type C disease with nonimmune hydrops fetalis. *Pediatr Neonatol* 2013; **54**: 344–47.
52. Adams LL, Gungor S, Turan S, et al. When are amniotic fluid viral PCR studies indicated in prenatal diagnosis? *Prenat Diagn* 2012; **32**: 88–93.
53. Andescavage NN, du Plessis A, Limperopoulos C. Advanced MR imaging of the placenta: exploring the in utero placenta-brain connection. *Semin Perinatol* 2015; **39**: 113–23.
54. Bellini C, Boccardo F, Taddei G, et al. Diagnostic protocol for lymphoscintigraphy in newborns. *Lymphology* 2005; **38**: 9–15.
55. Bellini C, Boccardo F, Campisi C, et al. Lymphatic dysplasias in newborns and children: the role of lymphoscintigraphy. *J Pediatr* 2008; **152**: 587–9.
56. Bellini C, Di Battista E, Boccardo F, et al. The role of lymphoscintigraphy in the diagnosis of lymphedema in Turner syndrome. *Lymphology* 2009; **42**: 123–9.
57. Bellini C, Ergaz Z, Radicioni M, et al. Congenital fetal and neonatal visceral chylous effusions: neonatal chylothorax and chylous ascites revisited. A multicenter retrospective study. *Lymphology* 2012; **45**: 91–102.
58. Bellini C, Villa G, Sambuceti G, et al. Lymphoscintigraphy patterns in newborns and children with congenital lymphatic dysplasia. *Lymphology* 2014; **47**: 28–39.

59. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. *J Clin Invest* 2014; **124**: 898–904.

60. Adzick NS. Prospects for fetal surgery. *Early Hum Dev* 2013; **89**: 881–6.

61. Van Mieghem T, Al-Ibrahim A, Deprest J, et al. Minimally invasive therapy for fetal sacrococcygeal teratoma: case series and systematic review of the literature. *Ultrasound Obstet Gynecol* 2014; **43**: 611–9.

62. Wenstrom KD, Carr SR. Fetal surgery: principles, indications, and evidence. *Obstet Gynecol* 2014; **124**: 817–35.

63. Carlton DP. Hydrops fetalis. In Stevenson DK, Benitz WE, Sunshine P, et al., eds., *Fetal and Neonatal Brain Injury*, 4th edn. Cambridge University Press, 2009: 325–30.

64. Bellini C, Hennekam RC, Boccardo F, et al. Nonimmune idiopathic hydrops fetalis and congenital lymphatic dysplasia. *Am J Med Genet A* 2006; **140A**: 678–84.

65. Thoresen M. Who should we cool after perinatal asphyxia? *Semin Fetal Neonatal Med* 2015; **20**: 66–71.

Chapter 30

Bacterial Sepsis in the Neonate

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Introduction

Bacterial sepsis in the neonate is a significant cause of morbidity and mortality. More than half of all admissions to a neonatal intensive care unit (NICU) are for infants with or who are at risk of developing sepsis. Diagnosis is challenging because clinical signs are nonspecific, supportive rapid screening laboratory assays lack good positive predictive value (PPV), and sepsis carries a high mortality rate. As a result, a conservative approach to these patients has evolved, with many infants who are not septic receiving antibiotics. This chapter discusses the epidemiology, diagnosis, treatment, and prevention of neonatal sepsis with a focus on high-income settings such as the United States but with reference to low- and middle-income countries (LMICs) as well.

Meningitis accompanies sepsis in approximately one-quarter of cases of neonatal disease, and thus the two processes share a common etiology and pathogenesis. Similarly, in the neonate, signs of illness overlap between sepsis and pneumonia, as does treatment. This chapter, however, covers only bacterial sepsis of the term infant. Meningitis is covered elsewhere (Chapter 31). Further, prematurity and residence in an intensive care unit are independent though often coexisting risk factors for bacterial sepsis that also are covered in another chapter (Chapter 5). In addition, the emphasis of this chapter will be on early-onset neonatal disease, with less of a concentration on late-onset sepsis.

Epidemiology

Although the ability to diagnose bacterial sepsis has improved, septicemia remains a frequent cause of neonatal morbidity and mortality. The first records of positive blood cultures were reported from Yale in 1928 [1]. Since then, the predominant bacterial organisms that cause sepsis in the neonate continue to change [1–5]. The causes of these variations are complex and often undefined, but recent patterns most strongly reflect the use of intrapartum antibiotic prophylaxis (IAP), among other influences [2,3,6–11].

Two distinct patterns of neonatal sepsis have been described, differentiated by time of disease onset, predominant organism(s), and associated risk factors [3,6,11–16]. Early-onset disease (EOD) has been variably defined but is defined here as occurring 7 days or less postnatally with a strong association with obstetric complications or risk factors. Therefore, disease is caused predominantly by microorganisms that colonize the maternal genital tract [13,15]. Some clinicians argue for a further stratification into "very early onset," also variably defined but generally defined as occurring within 48 or 72 hours of birth, because the pathophysiology may be different. It is believed that this group acquires infection in utero at a particularly susceptible stage, accounting for the very high mortality in these infants. Acquisition in utero can be through ascending spread from the lower genital tract or through transplacental transmission after maternal bacteremia [15,17]. In contrast, infants with EOD acquire the infecting organism at the time of delivery and have a lower case-fatality rate [17].

Late-onset disease (LOD) presents at more than 7 days of life and involves organisms that could be acquired perinatally as well as postnatally [15,18]. Therefore, these infections are acquired through passage in the birth canal, horizontally in the hospital, or in the community [15].

The incidence of neonatal sepsis has been difficult to gauge because sepsis is a clinical diagnosis and some septic episodes are culture negative. In the age of IAP, culture-negative sepsis rates will rise, making incidence rates more difficult to evaluate. In addition, with increases in numbers of preterm infants, the rates of sepsis have been influenced by this population's high susceptibility to infection. Several reports have attempted to characterize the incidence of neonatal sepsis (Figure 30.1) [1,3,5,6,13,14,17,19–21].

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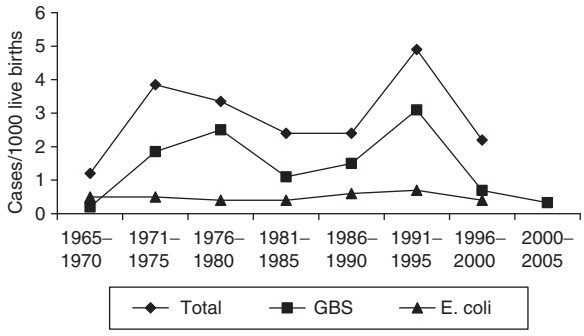


Figure 30.1 Sepsis rates for early-onset neonatal disease in the United States from 1965 to 2005. (Adapted from refs. [1–4]and [10].)

The longest running record, dating to the 1960s, shows incidence rates of EOD at 1/1,000 live births in the United States, with rates peaking at 3.89/1,000 live births in 1978 [1], followed by a subsequent decline and stabilization throughout the 1980s to rates of approximately 2.2–2.8/1,000 live births [1,5]. Enhanced surveillance since the 1990s has provided varying rates, with reports of 7.1–19/1,000 live births, with trends in the early and late 1990s indicating no overall changes in the incidence of EOD despite advances in prevention practices [3,19]. More recent reports concentrating on EOD have shown a dramatic decline in neonatal sepsis owing to the decreased rates attributable to group B *Streptococcus* (GBS) infection, with rates from other organisms remaining unchanged or increasing [2–4,6,11,14,19,20]. A recent update from Yale, which holds the longest running records from a single center, reports that overall EOD rates in term infants declined between 1979 and 2013 to 0.3/1,000 live births [4].

There are discrepant reports for LOD rates, but these appear to be unchanged overall, with some reports showing increased rates secondary to *Escherichia coli* [2,3]. Current reports show overall rates of neonatal sepsis of 0.8–8.2/1,000 live term births in developed countries [2,3,6,14,19]. LOD has an annual incidence of 1.9–8.23/1,000 live births [2,3]. From the Yale study, overall rates of LOD peaked in 2005 and have been declining since then, mostly due to enhanced efforts in NICUs to prevent line infections. This therefore shows the confounding nature of these data given that few report on only term infants who are outside the intensive care unit [4]. The incidence rates for the major individual organisms are described below.

In LMICs, the incidence of possible severe bacterial infection (pSBI) – based on clinical suspicion of sepsis, meningitis or pneumonia in neonates at more than 32 weeks' gestation (or >1,500 g) – is estimated to be 7.6/100 live births (95% confidence interval [CI] 6.1–9.2) or 6.7 million (uncertainty range 5.4–8.1 million) infants; a higher risk was found for male babies (risk ratio [RR] 1.12, 95% CI 1.06–1.08) [22]. Among these cases, 1.7 million (about 25%) globally are estimated to be due to neonatal sepsis. The incidence of neonatal bacterial sepsis based on studies with blood culture confirmation of bacterial pathogens is estimated to be approximately 16/1,000 live births [23–25]. However, in the only population-based surveillance study of the burden and etiology of neonatal infections in a LMIC (Bangladesh), the incidence of culture-confirmed cases of bacterial sepsis was 3/1,000 live births [26], comparable with rates of EOD in the United States; 38% of cases were identified on days 0–3 [26]. A more recent systematic review of pSBI reported that in 2012 there were an estimated 6.9 million cases (uncertainty range 5.5 million–8.3 million) in neonates globally, with 3.5 million (2.8 million–4.2 million) in South Asia, 2.6 million (2.1 million–3.1 million) in sub-Saharan Africa, and 0.8 million (0.7 million–1.0 million) in Latin America [27]. In 2012, there were 0.68 million (0.46 million–0.92 million) neonatal deaths associated with pSBI.

Risk Factors and Pathogenesis

A neonate's susceptibility to infection is multifactorial. Unique to the neonatal host are deficiencies in various arms of the immune system and circumstances where exposure to a large number of organisms occurs. Susceptibility to infections in the neonate also arises when there are interruptions in the natural barriers of the body, such as the skin [28,29], which occur frequently in the birthing process.

Immunologic limitations have been documented in both innate immunity, including cellular defenses (e.g., eosinophils, neutrophils, platelets, and monocytes) and adaptive immunity, involving both cell-mediated immunity and humoral responses [30,31]. Antigen presentation by dendritic cells and the activity of natural killer cells have also been shown to be deficient in the neonate and in neonatal sepsis in particular [32]. In addition, the lack of opsonizing antibody to encapsulated bacteria confers a susceptibility to many of the bacteria in the maternal genital tract to which the neonate is exposed [33].

Table 30.1 Maternal Risk Factors Associated with Early-Onset Neonatal Sepsis in Term Infants for All Pathogens and Specific to Group B Streptococcal Disease

	Risk of proven sepsis
All neonatal pathogens	
Maternal fever ≥ 38°C (100.4°F)	↑ 1–4 times
Prolonged rupture of membranes > 18 hours	1%
Chorioamnionitis	3–20%
Vaginal examinations ≥ 6	↑ 3 times
Maternal urinary tract infection	Unknown
Group B *Streptococcus* (GBS)	
Maternal fever ≥ 38°C (100.4°F)	↑ 10 times
GBS bacteriuria	Unknown
Previous infant with invasive GBS disease	Additive with fever ↑ 5 times
Maternal colonization with GBS	1–2%

Source: Adapted from refs. [11,13,15,34,35].

Obstetric factors for the term infant can be used to determine risks for early-onset but not late-onset neonatal sepsis (Table 30.1). These risk factors have been studied most extensively for GBS and not for non-GBS sepsis, and differences do exist. In particular, 80% of GBS disease is seen in infants born at more than 37 weeks, whereas only 40% of non-GBS sepsis is reported under these circumstances. Thus preterm delivery is a strong risk factor for non-GBS neonatal sepsis [11,16].

An important obstetric risk factor for infection with a broad range of organisms is prolonged rupture of membranes (>18 hours) [34], with the longer time between rupture of membranes and delivery increasing the exposure of the fetus. Some organisms, such as *Listeria monocytogenes* and *Treponema pallidum*, can cause infection despite the barrier of the placenta and amniotic fluid, with inoculation occurring via maternal bacteremia [13].

Maternal fever is also associated with neonatal sepsis, with the degree of fever reflecting strongly on the risk to the infant [11,17]. Studies have shown that maternal fever alone predicts approximately 26% of term infants with proven EOD and who were asymptomatic at birth [36]. For GBS, EOD is 10-fold higher in the presence of maternal fever [37]. Additional risk factors for GBS infection include a pregnancy complicated by GBS bacteriuria, history of a previous infant with invasive GBS disease, young maternal age, African-American race, Hispanic ethnicity, and frequent vaginal examinations during labor [16,38,39].

Risk factors for LOD have been rarely reported. One recent study identified IAP exposure as being associated with nearly twofold higher risk for developing sepsis compared with control patients [40].

A number of underlying socioeconomic and cultural factors predispose newborns in developing countries to greater risk of infections or adverse outcomes from infections compared with newborns in high-income settings. These factors include poverty, illiteracy, and low social standing of women, including lack of agency, decision-making power, and access to resources [40a]. While skilled birth attendance rates are increasing globally, nearly half of births (45%, 21.3 million) in settings with high rates of neonatal mortality (≥30/1,000 live births) occur without a skilled attendant, typically in unhygienic home environments with unclean birth practices [41]. An additional 9.5 million births occur in similar conditions in countries with neonatal mortality rates (NMRs) ranging from 15 to 30/1,000 (31% of births in this mortality band). Common unhygienic practices during childbirth and the early postnatal period include lack of hand washing, delivery on a dirt floor (because the process of childbirth is considered polluting), umbilical cord cutting with unsterile instruments and rubbing substances such as cow dung on the cut cord, poor skin care such as vernix removal and rubbing the skin with substances that are potentially unclean and damaging to the skin barrier, and lack of immediate and exclusive breastfeeding, which is commonly associated with the feeding of other unclean substances such as sugared water [42–47]. Cultural beliefs regarding confinement of mother and baby at home, resulting in delays in care seeking; absence of sanitation and clean water supply; poor recognition of signs of illness; and lack of access to healthcare facilities and to skilled providers with the necessary equipment, supplies, and medication also contribute to risk of newborn mortality and morbidity from infections.

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Etiology

Overall, a small group of organisms accounts for the majority of neonatal sepsis, with a very large and varied group of organisms accounting for the minority of cases [4,17,48,49]. Before the introduction of antibiotics, the predominant organisms causing neonatal sepsis were gram positive, with group A β-hemolytic *Streptococcus* (*Streptococcus pyogenes*) the major etiologic entity. This was replaced by intestinal gram-negative bacilli, particularly *E. coli*, after the introduction of sulfonamides in the early 1940s [1]. *Staphylococcus aureus* was observed to be a major pathogen from 1950 to 1963 but for reasons that are not clear has diminished in importance since that time [1,5]. Recent reports of increasing rates of *S. aureus* infections in NICUs, with a particular focus on methicillin-resistant *S. aureus* (MRSA), have been almost exclusively in the preterm infant or resident of a NICU [50,51]. This is true also of the rising prevalence of commensal organisms as a cause of neonatal sepsis, such as coagulase-negative *S. aureus*, and thus neither will be covered further here [3].

Even in early reports, GBS held its place as a major contributor to neonatal sepsis and was a leader in early fulminant disease (Figure 30.1). Over time, GBS has risen in incidence to assume the lead in causing gram-positive septicemia in EOD since the 1970s, with a peak incidence in the 1990s before prevention methods were put into place [1–3,5,6,11,14,15,52,53]. GBS previously accounted for 25–35% of sepsis overall, with 80% occurring in the first 48 hours of life, resulting in 55% of EOD. Recent reports show a dramatic decline in overall numbers of EOD by about 80% secondary to decreases in GBS. Rates of EOD caused by GBS are still the highest but now more closely parallel infections caused by *E. coli*, which traditionally ranked second [49]. When stratifying by gestational age, GBS is predominant in causing EOD in term infants, and *E. coli* causes the majority of EOD in nonterm infants. *E. coli* causes 27% of sepsis overall and traditionally caused 13% of EOD but 31% of LOD [1–3,5]. Rates of *E. coli* infection have been reported to have declined, remained unchanged, or increased since the introduction of IAP depending on the study, but these changes do not appear to be dramatic [2,6,8]. *Klebsiella pneumoniae* and *Enterobacter cloacae* are seen in about 15% of cases of septicemia, with less frequent reports of other organisms, such as *Listeria monocytogenes, Haemophilus* spp., *Pseudomonas* spp., *S. pneumoniae, viridans streptococcus*, enterococcal group D *Streptococcus* (*Enterococcus*), and *Staphylococcus* spp. Some of the latter organisms have a strong association with prematurity or an underlying condition or procedure. The important individual organisms are discussed separately below.

In LMICs, most data on etiology of neonatal sepsis comes from hospital-based studies, which have limitations and potential biases due to poor care seeking, access to care, and quality assurance of laboratory methods. Moreover, capabilities for infection detection and diagnosis are particularly lacking in the poorest settings where the burden of infections is highest. Nevertheless, studies that have attempted to identify the etiology of community-acquired neonatal sepsis in LMICs indicate that about half of cases are caused by gram-positive pathogens (e.g., *S. aureus, S. pyogenes*, and *S. pneumoniae*) and about half are due to gram-negative pathogens (e.g., *Acinetobacter* spp., *E. coli*, and *Klebsiella* spp.) [54,55]. Some regional variation has been noted, with *S. aureus* and *S. pneumoniae* most prevalent in Africa and *Klebsiella* spp. most prevalent in Southeast Asia [55].

Clinical Presentation

The spectrum of clinical signs in neonates who develop sepsis is varied, and symptoms are nonspecific. During delivery, signs of fetal distress such as tachycardia and low Apgar scores have been associated with sepsis, but both lack specificity [56,57].

Subtle signs of infection include poor feeding and decreased responsiveness, with more prominent symptoms being temperature instability, apnea, respiratory distress, jaundice, lethargy, vomiting, and diarrhea [35]. Though a serious bacterial infection is rare in asymptomatic neonates [58], infants who are bacteremic may have no symptoms initially but deteriorate rapidly [18,59]. Due to the nonspecific and subtle presenting clinical signs of septic neonates, clinical symptoms alone cannot be used to identify high-risk infants.

Concerns regarding an increase in asymptomatic neonates who become septic have arisen with the institution of guidelines for the prevention of GBS sepsis and the rise of IAP in at-risk mothers. Ottolini et al. studied 20,554 newborns, including 1,665 asymptomatic at-risk infants [60], and found that 1.0% subsequently developed clinical signs of early-onset sepsis within 48 hours of delivery, but none had a positive blood culture, and complete blood count (CBC) parameters did not add value to clinical findings. All septic infants in this study were

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Table 30.2 Frequency of Signs of Sepsis in Neonates

Signs	Frequency (%)
Tachypnea	58.0
Cyanosis	25.0
Lethargy	20.0
Apnea/bradycardia	20.0
Hypoglycemia	8.4
Fever	7.0
Hypothermia	3.5

Source: Adapted from Ottolini et al. [60].

symptomatic within 48 hours of birth, with the majority symptomatic before then. Ninety-one percent of the septic infants had more than one sign or symptom of sepsis, and 71% had three or more, indicating that vigilance to clinical signs of sepsis within the first 48 hours is the most sensitive tool for determining septic newborns. The frequency of signs and symptoms of sepsis in this study is shown in Table 30.2. In a study of high-risk neonates who were born to mothers with chorioamnionitis, 13% of infants who later were diagnosed with sepsis were asymptomatic at 6 hours after birth, but all were symptomatic by 72 hours. The majority of the septic infants who initially were asymptomatic had GBS sepsis compared with symptomatic infants, who tended to be infected with *E. coli*. The use of intrapartum antibiotics did not differ between symptomatic and asymptomatic infants [61].

Focal infections such as meningitis are more commonly seen in LOD, and thus symptoms particular to the area of infection may be present [13].

In many LMIC settings, diagnostic testing for agents of neonatal sepsis is inaccessible, of poor quality, or unavailable to influence clinical care. Thus identification of newborns in need of antibiotic treatment rests largely on the use of clinical algorithms designed to identify young infants presenting to health facilities with clinical signs associated with poor outcomes. The World Health Organization (WHO) identified seven clinical signs singly or together (unable to feed since birth or stopped feeding well, convulsions, fast breathing [≥60 breaths/minute on two counts], severe chest in-drawing, fever [temperature ≥ 37.5°C], low body temperature [<35.5°C], and movement only when stimulated or no movement at all [62,63]) in young infants ages 0–6 days that are associated (sensitivity 85%, specificity 75%) with urgent need for hospitalization and initiation of empirical antibiotic therapy for pSBI [64]. These seven signs also performed well (sensitivity 74%, specificity 79%) in identifying 7- to 59-day-old infants needing antibiotic therapy.

Diagnosis

The optimal workup of a newborn with suspected sepsis is not well defined. Presenting clinical signs are often nonspecific, and thus, differentiating truly infected infants from infants symptomatic as a result of noninfectious causes is challenging. In addition, many septic infants will show rapid clinical deterioration relatively late, making clinical parameters less useful for identifying sepsis early. The importance of initiating prompt antimicrobial therapy to reduce the high mortality rate and for improving long-term outcomes makes it essential to identify the septic infant early. In addition, standard culturing procedures do not offer a timely method to differentiate septic neonates and may not prove helpful if IAP was used due to sterilization of the cultures.

Given the inherent difficulty in determining which infants are at risk for developing sepsis, infants with signs consistent with sepsis of any pattern historically have received therapy to reduce the potential morbidity and mortality. It is estimated that 11–23 infants are treated for every documented case of neonatal sepsis, accounting for the treatment of 4.4–10.5% of all infants born in the United States [65,66]. This overutilization of antibiotics results in most infants receiving antibiotics unnecessarily, putting these infants at risk for complications of therapy and contributing to the development of multiple drug-resistant bacteria.

Efforts have been made to develop rapid diagnostic methods for the early detection of infants who will progress to sepsis and for identifying infants who are symptomatic for noninfectious reasons. In the latter group, the goal is to safely allow for the discontinuation of antibiotics. Ideally, the development of a rapid test would aid in guiding the initiation of therapy on only infants in whom it is necessary [65]. Adjunctive tests have been evaluated, including markers such as C-reactive protein (CRP), interleukin 6 (IL-6), IL-8, procalcitonin (PCT), tumor necrosis factor α (TNF-α), neutrophil CD-11b, granulocyte colony-stimulating factor (G-CSF), neutrophil surface antigen CD64,

and hematologic abnormalities such as an elevated immature-to-mature neutrophil ratio.

Cultures are the "gold standard" for the definitive diagnosis of neonatal sepsis. All infants suspected of sepsis should have a blood culture drawn prior to the initiation of antibiotics. Venous puncture is the preferred method for obtaining blood for culture [67]. The optimal number of blood cultures is under debate. Some clinicians suggest obtaining blood from two sites in order to increase the yield of a positive result, especially when a small bacterial load is expected, as in the case of infants born to mothers who received IAP [68]. In addition, this may help to clarify when a contaminating organism is isolated. However, the density of bacteria may be higher in neonates and the bacteremia more continuous than in older patients, and thus a single blood culture may be adequate [69]. The volume of blood obtained is also important, and 1 mL is typically recommended [70].

Overall, approximately 92% of true pathogens are isolated from blood culture within 36 hours and 98% within 48 hours [71]. In one study of 451 positive blood cultures in a tertiary NICU, the negative predictive value (NPV) for infection with a definite bacterial pathogen in the presence of negative blood cultures was 99.7% at 36 hours and 99.8% at 48 hours [72], provided that the blood cultures were obtained before antibiotics were given. This high bacterial isolation rate would support the discontinuation of antibiotics in the asymptomatic term neonate who has negative blood cultures as part of a suspected sepsis rule-out. It will be important to determine whether this remains the case in the era of increased use of IAP.

The availability of rapid molecular techniques for identifying bacteria that may otherwise not grow in culture through 16S rRNA gene polymerase chain reaction (PCR) has been considered in the context of neonatal sepsis. The possibility that this modality may be more sensitive for isolating pathogens in neonates, especially when infants are born in the presence of IAP and may provide a more rapid result, warrants further investigation. PCR would allow for bacterial identification in hours versus days for cultures and uses small blood volumes. In one study of 706 suspected septic infants, the number of positive cultures and positive PCR results were 95 (13.5%) and 123 (17.4%), respectively. Compared with blood culture, the diagnosis of bacterial sepsis by PCR revealed 100.0% sensitivity, 95.4% specificity, 77.2% positive predictive value (PPV), and 100.0% NPV [73]. Therefore, this rapid method for bacterial identification is promising but is unlikely to replace culture given the lack of routine availability of the method and that methods for determining antibiotic susceptibility via PCR are early in development.

The added value of obtaining cultures of the cerebrospinal fluid (CSF) and urine has been debated. The necessity of doing a lumbar puncture in a neonate suspected of sepsis is covered in Chapter 31. Urine cultures have been shown to be important in LOD [74], but the data are variable for EOD. Given that neonatal urinary tract infections are thought to be a result of hematogenous spread of the organism and not direct inoculum into the urinary tract, the low yield of urine cultures in the evaluation of infants with suspected sepsis – only about 0.1–1% – warrants eliminating urine cultures from the workup in the first 24 hours of life [75]. There does not appear to be any additional useful information obtained from the culturing of nonsterile surface sites [76].

In an attempt to develop a rapid diagnostic test to distinguish between infants suspected of and infants with sepsis, many researchers have looked to blood test assays. One study evaluated multiple rapid tests and their utility in diagnosing neonatal bacteremia in cases of suspected sepsis [77]. The results showed the nonspecific nature of an elevated white blood cell (WBC) count because it was positive in 71% of culture-proven bacteremia but also 42% of infants with negative blood cultures. Immature-to-total neutrophil ratios were not elevated in the majority of infants with negative blood cultures, but they were also negative in 29% of infants with positive blood cultures.

CRP, an acute-phase reaction to inflammation or tissue necrosis, is thought to be a good predictor of bacterial sepsis in neonates [78], with its predictability peaking at 24–48 hours after presentation with infection [79]. The majority of the highest titers have been documented in response to bacterial illnesses, with moderate elevations tending to be more nonspecific. Levels decline rapidly once the ongoing process resolves, and thus serial titers are a helpful measure of disease activity [80]. The NPV of a negative CRP determination after 24 hours is approximately 85–99% predictive of not having a bacterial process, and thus a negative CRP may warrant the discontinuation of antibiotics [65,79]. Unfortunately, the PPV is not high enough right after delivery (~89–93%) in proven

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EOD, given that other processes, such as the stresses of delivery (prolonged rupture of membranes and low Apgar score), correlate with a nonspecific rise of CRP for approximately 3 days [79,81,82]. Thus CRP cannot be used to guide the initiation of therapy to only infants who are truly infected and in the early stages of sepsis but has value in discontinuing therapy in neonates undergoing a sepsis evaluation if levels remain low. Given the limitations of CRP, especially in the early stages of sepsis and right after birth, CRP has the best diagnostic accuracy when combined with other infection or inflammatory markers [83].

The poor PPV of CRP has led to evaluations of other cytokines, independently or in combination with CRP, to increase the sensitivity of rapid determination of infants at risk for sepsis because many of these cytokines may become abnormal prior to elevations in CRP. Many cytokines have been evaluated from multiple sources, and in many different settings, and thus the results vary depending on the study [82,84–87]. IL-6, the major inducer of CRP, has been one target of investigation [81,82]. While not performing better than CRP as a single marker of infection, IL-6 did have high NPV. In addition, the combination of IL-6 and CRP performed better than each parameter alone as a negative predictive guide, with a value of 90% even early in the first 24 hours after delivery. IL-8 has also been studied in combination with CRP because it is an early proinflammatory marker [88]. Franz et al. showed that using high thresholds for both IL-8 and CRP (>70 pg/mL and >10 mg/L, respectively) achieved a sensitivity of 96–100% but a PPV of only 65–77% for determining neonatal bacterial sepsis [88]. By restricting therapy to infants in this group only, there was a 60% reduction in antimicrobial use, and only 23% of infants were treated unnecessarily. Once again, there was a good NPV of having two negative tests 24 hours apart.

PCT and TNF-α have also been investigated as proinflammatory markers [85,87]. While some discrepancy in results exists, Kocabas et al. demonstrated that with high cutoff values, PCT and TNF-α had the best PPVs (97% and 96%) and NPVs (97% and 100%, respectively) compared with other markers studied, including CRP [85]. The levels of these cytokines declined over the first 7 days of treatment in neonates who recovered and stayed elevated in neonates who died, indicating the potential value of these markers for determining response to therapy. A recent small study showed the value of PCT in early sepsis with a significant rise in infected neonates. PCT performed better than PCR in this study in predicting infected infants, but larger studies are still needed before routine use of PCT is recommended because studies have shown conflicting findings [89,90].

Neutrophil CD11b, a surface marker activated early in a host's innate immune response to invading microbes, is elevated in infants with proven sepsis and remains low in infants with symptoms caused by noninfectious disorders [91,92]. Similar to other markers, if CD11b is determined to be helpful in the diagnosis of neonatal bacterial sepsis, it will most likely be in concert with other markers, especially CRP. Weirich et al. showed that while CD11b was elevated in infants with proven viral illnesses and symptoms indistinguishable from bacterial sepsis, the CRP never rose in these infants [92], and Nupponen et al. showed that used in combination with IL-8, most bacterial illnesses were determined very early in the workup of symptomatic neonates [91].

Both G-CSF and intercellular adhesion molecule 1 (ICAM-1) have been shown to have some promise for the early detection of neonatal sepsis. They lack reliable PPV and sensitivity but have good NPV [93,94].

Many of these assays are not readily accessible or results rapidly available to be useful clinically. Continuing the quest to determine the best diagnostic assay or profile has brought neutrophil surface antigen CD64 under investigation because levels have the potential to be rapidly determined using flow cytometry with very small blood volumes, and levels can be quantified precisely [84]. Studies have shown the high sensitivity of this marker (95–96%) in septic neonates and a good NPV of 93–97%, but again, it requires further evaluation for broader applicability [87].

None of the studied methods has improved on the PPV of using risk factors and clinical signs consistent with infection, low absolute neutrophil count, and immature-to-total neutrophil ratio of 0.25 or greater to identify infants with sepsis, even in the age of IAP, as revealed by a large outcome study of 2,785 infants [58]. In this study, the majority of infants who had either culture-proven or suspected sepsis were identified as "at risk for infection" using obstetric risk factors including maternal chorioamnionitis, prolonged rupture of membranes (>8 hours), maternal fever (>38°C), GBS carriage, foul-smelling amniotic fluid, and prematurity. The rest of the infants were

identified through screening, CBC, and clinical presentations. Eighty percent of these infants were symptomatic within 12 hours of birth. All the infants, including the 20% who were asymptomatic at the time of evaluation, had significantly lower absolute neutrophil counts than the infants without sepsis, and all received antibiotics by 12 hours of age. The infants whose mothers had received IAP were more likely to be asymptomatic, less likely to be critically ill or to be infected, and had better outcomes than infants whose mothers did not receive IAP.

Treatment

Empirical treatment with broad-spectrum antibiotics guided by the knowledge of etiologic organisms and their susceptibility patterns is the standard of care in neonatal sepsis. The goal of any antibiotic therapy is the elimination of the bacteria as quickly as possible, thus reducing the source for the host inflammatory process that is responsible for the clinical signs related to sepsis. In addition, it is important to avoid hematogenous dissemination of the infecting organism to secondary sites. Ampicillin is most commonly chosen for empirical use, given its coverage of GBS, group D nonenterococcal *Streptococcus, L. monocytogenes, Enterococcus*, and other anaerobes. In addition, an aminoglycoside is added for appropriate coverage of gram-negative organisms and for synergy with ampicillin for treatment of *Enterococcus*, GBS, and *L. monocytogenes* [95,96]. The choice of initial antibiotic therapy will require close monitoring in the age of growing IAP and the potential for emerging microbial resistance. A number of reports have tried to address the issue of changing patterns of antibiotic susceptibility in the era of IAP [2,7,10]. Most studies have not documented increased antibiotic resistance among organisms causing sepsis in term infants but have shown an increased incidence of resistant *E. coli* sepsis in preterm infants, particularly after prolonged antepartum exposures. Antibiotic treatment can be narrowed in culture-proven sepsis once susceptibility of the organism is known.

Despite appropriate antibiotic treatment, the mortality rate for neonates remains high. Therefore, there is interest in adjunctive therapy targeted at areas of immune immaturity in the neonate. Given the success of intravenous immunoglobulin (IVIG) in the prevention of bacterial infections in children with primary agammaglobulinemia, studies have been tried in neonatal sepsis. A meta-analysis reviewed three studies, all of which showed a sixfold decrease in acute mortality in the infants treated with one dose of 500–750 mg/kg of IVIG, but long-term mortality and morbidity and cost-effectiveness still must be evaluated [97].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been evaluated to target neonatal neutropenia, which is associated with increased morbidity and mortality when present during bacterial sepsis [98]. Studies have documented the safety of both G-CSF and GM-CSF in neonates, and a recent randomized, controlled trial showed a significant increase in neutrophil count in the GM-CSF-treated infants [99–101]. The mortality rate in this study was decreased by 20% in the infants receiving GM-CSF. Though promising for improving outcome of neonatal sepsis, there is concern about the long-term toxicity on the developing bone marrow of the neonate, and further efficacy studies in larger cohorts are still required before GM-CSF is used as standard adjunctive therapy for neonatal sepsis.

In LMICs, the empirical treatment recommended by WHO for suspected neonatal sepsis is similar to that described earlier: hospitalization and treatment for 7–10 days with two parenteral antibiotics, a penicillin such as ampicillin or benzyl penicillin and an aminoglycoside such as gentamicin [62]. For many families, however, this level of treatment is inaccessible, unaffordable, or unacceptable. To address this, a recent multicountry study in sub-Saharan Africa and South Asia enrolled newborns with pSBI whose families had refused referral to the hospital and randomized them to one of several simplified regimens administered at home or as clinic-based outpatient therapy. Treatment failure rate was similar across all study arms [102]. Thus the WHO provides the following guidelines for empirical treatment of suspected sepsis in situations where families do not accept or cannot access referral-level care:

- Neonates 0–6 days old with fast breathing as the only sign of illness should be referred to hospital after receiving a pre-referral treatment. Families should be counseled on the importance of referral. If the family does not accept or cannot access referral care, the infant should be treated with oral amoxicillin twice daily for 7 days by an appropriately trained health worker.
- Young infants 7–59 days old with fast breathing as the only sign of illness should be treated in an outpatient setting with oral amoxicillin twice daily

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for 7 days by an appropriately trained health worker.
- Young infants 0–59 days old with clinically severe infection should be referred to hospital with a pre-referral treatment. Families should be counseled on the importance of referral. If the family does not accept or cannot access referral care, the infant should be managed in an outpatient setting by an appropriately trained health worker according to one of two regimens.
  - Option 1: Oral amoxicillin twice daily for 7 days plus injectiable gentamicin once daily for 7 days
  - Option 2: Oral amoxicillin twice daily for 7 days plus injectable gentamicin once daily for 2 days
- Young infants 0–59 days old who have any sign of critical illness should be given pre-referral treatment and hospitalized.

Outcome

There is a clear association between sepsis and mortality, with a less well-defined causal relationship with long-term morbidity. Mortality from sepsis accounts for approximately 16% of neonatal deaths in the United States and about 15% globally [41]. Approximately 99% of global newborn deaths due to sepsis occur in LMICs. Case-fatality rates attributable to early-onset sepsis range from 15% to 50% [17,30]. Fatality rate due to sepsis is highest in the first few days after birth and does not depend on the causative agent. LOD carries a much lower case-fatality rate of approximately 17–22% and is more dependent on the etiologic organism, with *E. coli* carrying the highest rates of mortality, followed by *S. aureus* and GBS [17].

Over time, a dramatic decrease in mortality has been demonstrated, most closely associated with changes in mortality due to GBS sepsis. In the 1930s, case-fatality rates as high as 80% were documented, with a continued decline to present levels, which appear to have plateaued [30]. Case-fatality rates from GBS sepsis decreased dramatically from 47% in 1974 to a nadir of 18% in 1978. Mortality from other entities remained appreciably unchanged during the same period despite the use of appropriate antimicrobial therapy [1]. The cases of GBS reported in the later series also document a falling rate of fulminant disease. Using a National Hospital Discharge Survey, Lukacs et al. reported a decline in mortality rates for term infants with neonatal sepsis from 19/1,000 live births in 1990 to 14/1,000 live births in 2001, a decline of 23% [19]. The decline in neonatal mortality secondary to sepsis is multifactorial, related to prevention, early detection, advanced supportive care, and antimicrobial therapy [5].

With declining mortality rates and increasing numbers of survivors of neonatal sepsis, defining the morbidity in these survivors is becoming increasingly important. Most of the documented adverse outcomes, particularly neurologic deficits, are seen in neonates who had meningitis as part of their sepsis [103], and there are clear orthopedic deformities as a result of neonatal osteomyelitis [104]. These latter infants, however, are neurologically intact. Bennet et al. reviewed the outcomes of survivors of neonatal sepsis from 1969 to 1983, including premature and term neonates, and showed that approximately 8% of septic neonates who survived without meningitis or osteomyelitis had long-term sequelae [105]. These infants accounted for 40% of the infants who developed sequelae and 50% of those with severe developmental delay. Other complications were deafness, hydrocephalus, and mild developmental delay. The hearing impairment observed was associated with gram-negative sepsis, but it could not be determined if it was as a result of treatment with an aminoglycoside, sepsis alone, or both. All the infants who developed sequelae had obstetric and neonatal risk factors, and thus, identifying these infants and using preventive measures should have an impact not only on survival but also on long-term outcome. Alfven et al. studied 90 infants with neonatal sepsis and also reported that most survivors of sepsis without meningitis who developed long-term sequelae had other underlying conditions, such as prematurity, and maternal preconditions such as diabetes. Most other survivors were noted to have normal growth and development at the time of follow-up 2–6 years later [106].

The role of bacterial sepsis as an independent factor in the poor outcomes and long-term morbidity in infants with other neonatal complications, such as perinatal asphyxia, preterm labor, and prematurity, cannot be easily determined and has not been reported [107].

Investigators have also studied the role of intrauterine exposure to infection and inflammation, even in uninfected neonates, in long-term neurologic outcomes, particularly cerebral palsy (CP). While associations are strongest for preterm infants, there are some increased risks for term infants [108]. Changing epidemiology would be expected with the increased

use of intrapartum antibiotics, but this has not been addressed.

In LMICs, the estimated case-fatality rate for neonatal sepsis is 18% (95% CI 11–25%) and for neonatal meningitis is 36% (95% CI 30–42%) [22]. Due to scarcity of follow-up data on newborns with sepsis, the proportion who develop sequelae is unclear. Following meningitis, an estimated 23% (95% CI 19–26%) are moderately to severely impaired, and 12% (95% CI 5–19%) are mildly impaired; the incidence of hearing impairment is estimated to be 7% (95% CI 3–12%).

Prevention

Prevention measures have been targeted almost exclusively at GBS sepsis, and these are covered in more detail below. In theory, these strategies have the potential to also prevent non-GBS sepsis, but this has not been well studied. Schuchat et al. showed in a multicenter study that antibiotic prophylaxis for GBS was 63% effective in the prevention of non-GBS EOD [16]. Currently, the first-line agents for IAP are penicillin and ampicillin, which are less effective against the second leading cause of EOD, *E. coli*. Whether the impact would be greater on non-GBS EOD with different chemoprophylaxis is yet to be studied.

Globally, chlorhexidine cleansing of the cut umbilical cord with 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine, has been shown to reduce the incidence of umbilical cord infections by 27% to 56% and to reduce neonatal mortality among enrolled infants by 23% (RR 0.77, 95% CI 0.63–0.94) [109–111]. This formulation is now included in the WHO Model List of Essential Medicines [112], and treatment is being scaled up in several countries, especially where the proportion of births that occur at home and the neonatal mortality rate are high. Another promising approach to the prevention of neonatal sepsis in preterm infants is topical applications of emollients. Use of sunflower seed oil [113,114] or coconut oil [115] has been shown to reduce the incidence of bloodstream infections by about 50% (RR 0.50, 95% CI 0.36–0.71) and mortality by 27% (RR 0.73, 95% CI 0.56–0.94) and improved weight and weight gain among hospitalized preterm infants less than 33 weeks' gestational age [116]. Additional research on the impact of emollient therapy in newborns in community settings is underway in India and Nepal. Kangaroo Mother Care (KMC) has been shown to reduce mortality by 40% (95% CI 0.39–0.92) and nosocomial infection/sepsis by 55% (95% CI 0.27–0.76) among medically stable low-birth-weight (<2,000 g) infants [117]. Coverage rates for KMC remain low, although more concerted efforts are now being made to scale up this practice [118].

Specific Organisms

The major organisms associated with bacterial sepsis will be covered in more detail, but an exhaustive review of all etiologic agents of neonatal sepsis is beyond the scope of this chapter. Given the importance of GBS in neonatal sepsis and mortality, it will be discussed in more detail than other organisms, which will be reviewed for the qualities that are unique to them and deserve mention beyond the general discussion earlier.

Group B *Streptococcus*

The Organism

GBS emerged as a leading cause of neonatal infections and mortality in the 1970s and remains an important cause of disease in term and preterm infants [18,52,119]. The organism is a gram-positive coccus and is found as a colonizer of the female genital and rectal areas. The organism gains access to these secondary sites of colonization from the gastrointestinal tract, which serves as the most likely human reservoir [120]. Approximately 10–35% of women are asymptomatic carriers of GBS. The colonization rate of infants exposed to maternal sources of GBS is about 50%, but 98% of these infants are asymptomatic. Eighty percent of the remaining 1–2% of exposed infants will develop EOD presenting as sepsis, pneumonia, or meningitis. The majority of these infants are symptomatic within 2 days of birth, with the rest presenting within the first week [119,120].

Approximately nine serotypes of GBS have been identified, with serotype III causing approximately 36% of EOD, 90% of early-onset meningitis, and 71% of LOD (regardless of site of infection), despite a smaller representation in maternal colonization rates [18,121]. Recently, serotype V has been increasing as an important isolate in neonatal disease, accounting for about 14% of GBS EOD [122]. In EOD without meningitis, the non-III GBS serotypes are evenly distributed, with nontypable strains accounting for approximately 2–10% of disease [121].

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The capsular polysaccharide (CPS) antigens are major virulence factors of GBS, and immunity is due to type-specific anti-capsular antibody that promotes opsonization of homologous GBS strains in concert with the complement system. The concentration of CPS-specific antibody that is protective is not known and may depend on serotype and bacterial inoculum, as well as the functioning of the immune system [123]. The lack of passive antibodies at protective levels may partially explain the virulence of GBS serotype III in EOD disease with meningitis and in LOD.

Epidemiology

The exact incidence of GBS disease is hard to determine. Published reports are variable, reflecting reporting practices based on high-risk groups and single institutions, and may not correctly reflect disease incidence in a larger population. GBS was an infrequently reported pathogen in neonatal sepsis until the 1970s, when it became dominant in EOD, resulting in 7,500 cases and over 1,000 deaths annually in the United States [1]. Studies over a 10-year period from 1989 to 1999 in the United States reported an incidence of 1.4–3.2/1,000 births for EOD and 0.24–0.5/1,000 births for LOD [124]. After GBS incidence rose, prevention strategies were shown to be efficacious in preventing EOD by interrupting transmission vertically between mothers and their newborns [125]. Reports from the Centers for Disease Control and Prevention (CDC) showed a decline in the incidence of GBS EOD by 43% in some sites for the years 1993–95, but no changes were found at other locations [126]. In this evaluation, there were clear differences in rates when race was considered, with the highest rates among African Americans, and this was substantiated in other studies [127]. During the same period, the incidence for LOD remained unchanged. This trend, therefore, most likely represents practices that interrupt intrapartum transmission of GBS, including practice guidelines and enhanced detection techniques, rather than decreasing GBS carriage rates. This led to further attempts at prevention, and initial guidelines were issued in 1996, with revisions in 2002 and 2010 [128,129]. After implementation of these guidelines, studies showed 80% declines in incidence rates of GBS EOD, bringing the incidence from 1.7/1,000 live births in 1993 to 0.34/1,000 live births in 2004 (Figure 30.2) [130]. The greatest change was seen in the mid-1990s, but active surveillance by the CDC showed a continued

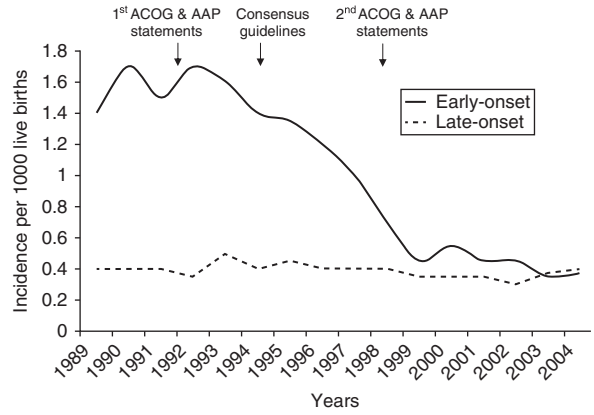


Figure 30.2 Incidence of early- and late-onset group B streptococcal disease and impact of preventive strategies from 1998 to 2004.

decline of 33% during 2003–5 for GBS EOD, whereas LOD rates were unchanged [131]. Annual cases for early-onset GBS disease were 131–202 over the study period, with an incidence of 0.33/1,000 live births and LOD accounting for 0.12/1,000 live births annually. The race discrepancy was again noted, with rates in African-American infants increasing by 70% over the study period. Based on data from the CDC's Active Bacterial Core surveillance (ABCs) system, a network of 10 sites across the United States that conduct active population-based surveillance, GBS has caused approximately 1,200 cases of early-onset invasive disease per year. In addition, from this surveillance data, the incidence among all black infants declined to 0.49/1,000 live births [132]. Recurrent disease occurs in only a small percentage (0.4–0.9%) of appropriately treated infants who survive their initial GBS infection [133]. Though GBS is strongly associated with disease in preterm infants, the majority of cases (between 70% and 82%) are still seen in term infants [38,134].

Pathogenesis

The pathogenesis of very early-onset GBS disease is hypothesized to occur through ascending spread of the organism into amniotic fluid, which the fetus aspirates [80]. This results in exposure to a larger inoculum of organisms than through other routes, for example, by GBS crossing intact membranes [135]. EOD is thought to represent acquisition of the organism at the time of delivery. LOD is less well understood, with only a portion of cases reflecting colonization at the time of delivery, because only 50% of infants with LOD are born to mothers with positive cultures for GBS. Nosocomial and

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community acquisition are thought to account for the remainder of cases [18,136,137].

Risk Factors

The major risk factors associated with GBS EOD are outlined above and in Table 30.1. The risk of disease is associated with infant exposure to a high inoculum of organisms and a relatively immunocompromised host. An infant will be at an increased risk for colonization with GBS if the mother is heavily colonized or if obstetric manipulations allow for bacterial replication [138]. African-American women have higher rates of heavy colonization with GBS, which may account for the higher rates of neonatal disease [139].

Clinical Presentation

The clinical presentations of GBS disease are nonspecific and include sepsis, meningitis, pneumonia, and less frequently cellulitis, omphalitis, osteomyelitis, and septic arthritis. Bacteremia with or without pneumonia accounts for 89% of disease in infants under 90 days, with meningitis complicating 10% of these cases [126]. Septicemia accounts for 25–40% of presentations and pneumonia for 35–55% [18].

Infants presenting with sepsis represent a wide spectrum of disease, including multiorgan failure, acidemia, and hypotension requiring full life-support measures as well as interventions to correct metabolic abnormalities. Respiratory findings are prominent in the majority of EOD (80%), but poor feeding, lethargy, hypothermia or fever, abdominal distension, pallor, tachycardia, and jaundice have all been described [18].

Severe pulmonary hypertension can adversely affect the clinical course and outcome of these infants and is thought to be secondary to cardiolipin and phosphatidylglycerol, which are components of the bacterial cell wall and may be over synthesized in the presence of antibiotic therapy [140]. Many of these infants require treatment with inhaled nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO), or both.

Diagnosis

The only definitive diagnostic test for GBS sepsis is a positive culture. Because culture results are not available at the time of presentation, all symptomatic neonates require a full septic evaluation and initiation of broad-spectrum antibiotics, usually with ampicillin and an aminoglycoside. These can be narrowed once culture results and sensitivities of the organism are determined (see below).

The evaluation and management of high-risk infants born to women with risk factors, particularly if they have received IAP, present particular difficulties and are controversial. This is particularly true if the infant is asymptomatic because some infants who are bacteremic may be asymptomatic at birth, and partial treatment afforded by antibiotics given to the mother may mask early signs [141]. However, several studies have found no significant difference in the clinical presentation of early-onset GBS disease between infants exposed to intrapartum antibiotics and those not exposed. Further, approximately 90% of cases of early-onset disease will manifest within the first 24 hours of life regardless of IAP [142–144]. Guidelines have been created in some institutions (Figure 30.3) that include obtaining a blood culture and CBC in infants who have one or more risk factors for sepsis. Empirical antibiotics are initiated if the total WBC count is below 5,000/mm^3 or an immature-to-total neutrophils ratio (I/T ratio) is above 0.2. Antibiotics are discontinued at 48 hours if blood cultures remain negative [71].

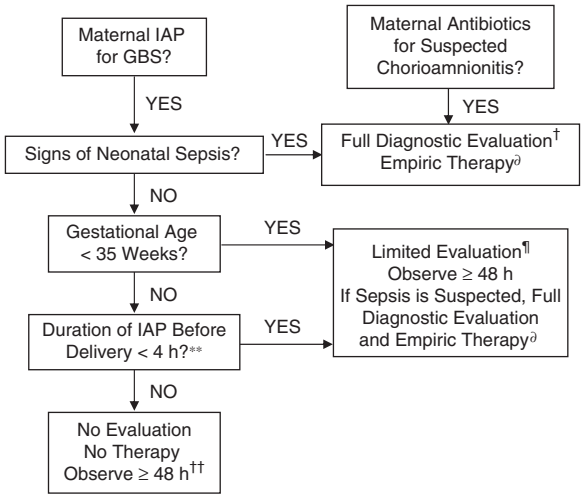
Treatment

Antibiotics are the hallmark of treatment for all forms of GBS sepsis, with the drug of choice being penicillin at 2 million units/kg per day. There have been no clinical isolates of GBS showing resistance to penicillin or ampicillin, though the latter has a slightly broader spectrum, and thus, when GBS has been confirmed, it is often recommended that penicillin be used when possible. These organisms are also sensitive to cephalosporins, vancomycin, and semisynthetic penicillins at variable activities. Erythromycin resistance is reported in 7–25% of isolates and resistance to clindamycin in 4–15%. There is evidence of synergy with an aminoglycoside. The duration of treatment of bacteremia without meningitis is 10–14 days [17,100]. Fear that GBS resistance would develop due to maternal IAP have been allayed by studies that have failed to show any change in susceptibility of GBS [7,145]. Therefore, no changes to treatment recommendations for GBS disease are needed at this time.

Outcome

Initial reports of GBS sepsis in the neonate documented mortality rates of approximately 50% [18], but this dropped quickly in the 1980s to 15% and further to present levels of about 4–6% [126]. Morbidity has

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* If no maternal intrapartum prophylaxis (IAP) for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy.

† Includes complete blood cell (CBC) count and differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed.

∂ Duration of therapy varies depending on results of blood culture, cerebrospinal fluid (CSF) findings, if obtained, and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 h.

¶ CBC with differential and blood culture.

** Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens.

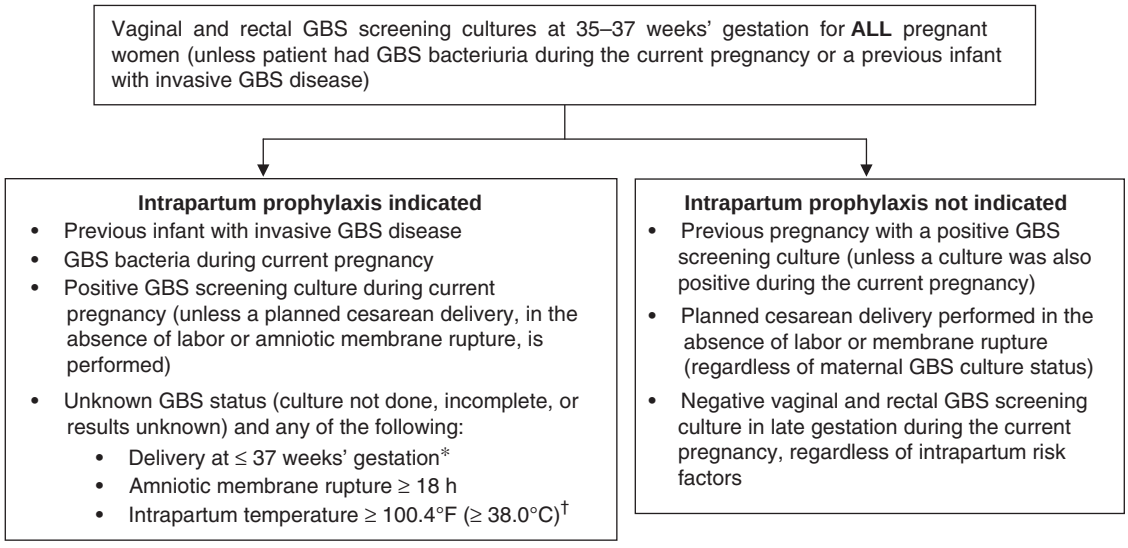
†† A healthy-appearing infant who was ≥ 38 weeks' gestation at delivery and whose mother received ≥ 4 h of IAP before delivery may be discharged home after 24 h if other discharge criteria have been met and a person able to comply fully with instructions for home observation will be present. If any one of these conditions is not met, the infant should be observed in the hospital for at least 48 h and until criteria for discharge are achieved.

Figure 30.3 Sample algorithm for management of a newborn whose mother received intrapartum antimicrobial agents for the prevention of early-onset group B streptococcal disease or suspected chorioamnionitis. This represents one approach only and is not definitive or the only algorithm that has been developed. (From Schrag et al. [128].)

been more difficult to define, but reports from the 1970s showed profound neurologic sequelae if meningitis was documented [18], and more recent reports of infants treated with ECMO have shown some long-term neurologic impairment [146]. Newer evaluations are needed for infants who survive GBS sepsis in the age of intensive supportive care.

Prevention

With the increase in GBS incidence and the decline in mortality, efforts have now turned to prevention. Strategies for the prevention of GBS transmission from mother to fetus have evolved over the past 25 years, but it was not until the CDC, the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) reached a consensus that prevention made sense and was economically affordable that practices started changing [129,147,148]. Because GBS disease in the neonate is rapidly progressive and often evident shortly after birth, and because antenatal antibiotics are effective in preventing the majority of EOD, the burden of prevention has fallen on those caring for pregnant women. Two strategic guidelines are in use to address this dilemma, with different efficacy and risk factors associated with each. The ACOG first published guidelines in 1992 and supported a risk-based strategy, whereas the AAP published a screening-based approach. Confusion persisted for a number of years as to the best strategy to use, and in 1996–7, all three bodies reissued consensus statements. After this time, all institutions that offered obstetric services had to either adapt a screening-based or a risk-based approach to GBS prevention, but it was not clear which was superior, if either. In 2002, a report comparing the rates of GBS EOD showed that the use of screening strategies prevented 50% more neonatal disease than risk-based protocols, calling into question the recommendation for endorsing both strategies as equivalent [37]. These findings led to the new prenatal GBS prevention guidelines put forth in 2002, which recommended antenatal screening of all pregnant women (Figure 30.4) [128]. These guidelines were updated in 2010 [52] and were endorsed by ACOG, the AAP, the American College of Nurse-Midwives, the American Academy of Family Physicians, and the American Society for Microbiology. The screening-based approach allows for the potential use of antibiotics early in delivery (as opposed to the alternative of waiting 18 hours after ruptured membranes or until a fever develops in the mother) and in mothers who may still colonize their infants despite the lack of symptoms. Reviews of maternal and infant records of infants with EOD show that 50–70% of these infants were born to mothers who lacked risk factors [38,149]. One of these studies reported that up to 79% of EOD could be prevented by the screening-based approach [149]. Consequently, the risk-based strategy has been abandoned and is now used only when screening has not been done. The new guidelines focus on challenges identified in the institution of the 2002 recommendations by expanding laboratory techniques for the



* If onset of labor or rupture of amniotic membranes occurs at < 37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided

† If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

Figure 30.4 Indications for intrapartum antibiotic prophylaxis to prevent group B streptococcal disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35–37 weeks' gestation from all pregnant women. (From Schrag et al. [128].)

identification of GBS, clarifying urine colony counts defining GBS bacteriuria, new recommendations for woman in preterm labor and with premature rupture of membranes, new treatment options for mothers, and a change to the treatment algorithm for neonates.

Despite the better performance of the screening strategies, methods for GBS detection are not sensitive enough to abandon the importance of intrapartum risk factors, and GBS EOD continues to occur in institutions relying on screening-based strategies [144].

Screening-based approaches provide IAP to all women with positive cultures for GBS performed late in gestation and all women without cultures who are delivering at less than 37 weeks' gestation. Risk-based approaches provide IAP to women with the following risk factors: delivery at less than 37 weeks' gestation, prolonged rupture of membranes of 18 hours or more, and intrapartum temperature of 38°C or higher. Both strategies provide IAP to women with GBS bacteriuria and to women who previously delivered an infant with GBS disease.

There is also evidence to suggest that at least 4 hours of intrapartum antibiotics is better than shorter courses: up to 40% of infants born to colonized mothers were still colonized if antibiotics were given within 1 hour of delivery, but only 1% of infants were colonized if the mothers received ampicillin more than 4 hours before delivery [150].

Others have advocated for more selective use of intrapartum chemoprophylaxis (SIC) [151,152]. By restricting intrapartum prophylaxis to GBS-colonized women with additional intrapartum risk factors, it was predicted that approximately 60% of the cases could be prevented while exposing fewer than 5% of women to antibiotics, with the remaining cases being of lesser severity because of the absence of risk factors.

Some of the issues raised earlier are addressed by combining this strategy with the use of intramuscular penicillin in neonates of colonized mothers without risk factors (selective neonatal chemoprophylaxis [SNC]). The use of penicillin in neonates has been shown to reduce the rate of EOD GBS without an increase in the incidence of LOD

[153]. Some authors advocate combining SIC with SNC [152]. In their proposal, all prenatal cultures would be obtained at 35 weeks' gestation and risk factors extended to include all women without prenatal care and delivering prematurely. In addition, any woman with a febrile course consistent with chorioamnionitis would receive full treatment with ampicillin and an aminoglycoside and not just prophylaxis. Further, all asymptomatic infants born to GBS-colonized women would be given penicillin. This approach would be expected to also protect infants born to colonized mothers who are Asymptomatic at the time of delivery. Infants more likely to be infected with GBS at the time of delivery are more likely to be born to colonized mothers without risk factors and therefore should be protected by SNC. This would be expected to decrease the incidence of GBS EOD by approximately 75–90% and limit the exposure to penicillin to less than 10%. There is still concern about the use of this strategy, particularly with the postpartum use of penicillin in neonates [154].

It is clear that the use of prevention strategies reduces the incidence of EOD. The CDC surveyed hospitals in eight states and reported that the proportion of hospitals with formal intrapartum GBS prevention policies increased to 59% in 1997 [126]. Even limited compliance with any prevention strategy that resulted in a reduction in EOD GBS was shown to be cost-effective [155]. It is important to note that despite best practices and the institution of appropriate IAP, GBS disease is not likely to be eliminated without the development of other strategies.

The impact of IAP on LOD has been evaluated in one study, which showed that in a small cohort of infants, cases of LOD were 14% more likely to occur in infants exposed to IAP than in unexposed infants. In addition, the bacterial isolates of the exposed infants were more likely to be resistant to ampicillin but not to other antibiotics [40]. Clearly, this is an area that deserves further study.

Chemoprophylaxis

Chemoprophylaxis during pregnancy, prior to onset of labor, has been studied as a way of preventing neonatal GBS disease. Most studies show that there is no impact on maternal carriage despite a reduction in the colonization of neonates and in invasive GBS disease [156]. The administration of antepartum chemoprophylaxis to all GBS carriers has potential for approximately 10 deaths annually from anaphylaxis [157] and for an additional proportion of women and fetuses to suffer less severe reactions [158]. In addition, the use of antepartum chemoprophylaxis challenges the pediatrician to understand how to treat the neonates born to mothers who have been treated with antibiotics [159].

Challenges for the use of IAP include adherence to the recommendation for administration of antibiotics at least 4 hours prior to delivery. As many as 50% of woman who are GBS carriers do not receive the antibiotics as recommended due to the rapidity of labor and delivery [160]. The use of intrapartum antibiotics is also plagued with the potential emergence of resistant microbes, including non-GBS organisms. Towers et al. showed that while the incidence of GBS in their institution declined over an 8-year study period as a result of increasing intrapartum ampicillin use, there was also a coincident rise in EOD caused by non-GBS organisms [158]. The majority of these cases were in infants whose mothers had been given intrapartum ampicillin, and 87% of the bacteria were ampicillin resistant. The conclusion was drawn that the use of penicillin, with its narrower spectrum, would be more prudent in this setting. These findings have not been supported by more recent studies that have sought to define the situation in more detail. In these early studies, the bulk of this disease was found in preterm rather than term infants [16].

The influence of IAP alone on these trends is not clear because bacterial resistance is seen as a general pattern outside of neonatal sepsis. Recent studies support no link between the increased use of IAP and emerging resistant GBS or non-GBS bacteria, except in preterm, low-weight neonates [7,10]. Further, there seems to be a trend toward decreasing non-GBS EOD by both gram-positive and in some studies gram-negative bacteria. It is probable that the phenomenon now highlighted is that the remaining cases of EOD reflect pathogens that are not susceptible to the current IAP, and thus these strains are causing a higher proportion of cases without an overall change in incidence [7].

In an attempt to define whether differences exist in neonatal bacterial colonization, Jaureguy et al. studied stool pathogens of 3-day-old neonates exposed to IAP compared with unexposed infants [161]. No differences were seen in colonization with resistant organisms, but infants receiving IAP had lower rates of anaerobic colonizers such as *Clostridium*.

Overall, surveillance studies have shown some changes to GBS susceptibility to antibiotics, peculiarly erythromycin and clindamycin, but not to the β-lactams [162,163], and have documented the relative safety of IAP. The clear impact of the strategy on GBS EOD prevention coupled with the lack of significant increases in resistance in neonates [7] supports the continued and expanded use of IAP.

Immunoprophylaxis

Despite the successes of prevention strategies on reduced incidence of GBS sepsis, there continue to be challenges in implementation of the guidelines and concerns related to adverse outcomes. In addition, the prevention strategies are not expected to prevent LOD, GBS-related stillbirths, or preterm birth, so recent developments are focusing on vaccines. Vaccines are expected to be effective by providing a boost in the maternal anti-capsular antibody titers so that higher levels are transferred transplacentally to the neonate. The hope is to overcome the neonatal susceptibility to GBS disease that is believed to arise from deficiencies in protective levels of maternal anti-capsular antibodies, particularly to serotype III [121].

Initial attempts at producing an effective vaccine concentrated on GBS serotype III, but it was not until the polysaccharide was conjugated to tetanus toxoid that promising results were observed [164]. In addition, the initial target populations for these vaccines were pregnant women in their second trimester, but this proved to be controversial. The focus for vaccine-induced immunity to GBS has shifted to women in the childbearing age prior to pregnancies and also to children. The immunity induced by a conjugate vaccine is expected to be lasting, and vaccinating the latter two populations would offer protection even to newborns born years after effective immunization.

One goal of GBS vaccination is to achieve decreases in mucosal colonization as well as protective antibody titers. Given the multitude of serotypes causing GBS disease, a multivalent vaccine will be the only viable strategy for achievement of disease elimination, although great accomplishments can be expected using vaccines targeted at GBS serotype III because it is the major cause of EOD associated with meningitis and LOD. Other GBS serotypes have been tested for immunogenicity, but a multivalent candidate vaccine has not yet been fully developed [165,166].

One approach focuses on the development of a recombinant vaccine that contains the pili that afford the bacteria abilities for enhanced colonization and infection. Animal studies have been successful, and a recent double-blind randomized trial of a conjugate vaccine against GBS serotype III among nonpregnant women of reproductive age found a significant delay in acquisition of colonization with the vaccine serotype among vaccine recipients [122,167–169].

Overall, while promising in early studies, all proposed vaccines in development face obstacles to starting phase III clinical trials. Among the challenges is the need for large-scale trials, and the use of intrapartum prophylaxis has created a need for immunologic correlates, which have not yet been identified. Most importantly are the issues regarding the use of vaccines in pregnant women. Nevertheless, progress toward development of an effective vaccine continues.

LMICs

In LMICs, the burden of GBS disease remains uncertain, although in several countries of southern Africa rates appear to be comparable with those of high-income countries [170]. Variation in colonization rates appears to be small across countries. In general, however, GBS is not a major developing-country pathogen. Therefore, immunoprophylaxis is not routinely recommended. Challenges remain in ascertaining the true disease burden, however, given that the disease is often rapidly fatal, and cases may be missed because of difficulties obtaining samples before babies die [26]. A failure to diagnose cases in the community, sick babies who then fail to reach healthcare facilities, inadequate culture methods, and widespread antibiotic usage may all lead to an underestimation of the GBS disease burden.

In a systematic review, Edmond et al. found only one study from a middle-income country (South Africa) that reported IAP use, and no low-income countries reported IAP use [171]. Only five low-income countries reported data on GBS disease incidence. The mean incidence (cases per 1,000 live births) of EOD was 0.43 (95% CI 0.37–0.49). Incidence was highest in studies from Africa (0.53, 95% CI 0.15–0.92), while studies from Southeast Asia reported the lowest incidence (0.11, 95% CI 0.012–0.220). The incidence of LOD was also highest in Africa (0.71, 95% CI 0.38–1.04). The case-fatality ratio was three times higher in low-income countries (12.6%, 95% CI 10.8–14.9) than in high-income countries (4.6%, 95% CI 2.1–9.1). The serotype distribution of GBS isolates is similar in Africa, western Pacific,

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Europe, the Americas, and eastern Mediterranean regions and has not changed over the past 30 years.

Escherichia coli

E. coli is the second most important pathogen in neonatal sepsis and the primary gram-negative coliform causing disease [1,17]. The antigenic structure of *E. coli* is very complex, and a great genetic diversity exists in the strains that colonize humans. Despite the large number of different colonizing strains, a strikingly small number of strains cause disease [172]. One of the capsular antigens of *E. coli*, the K1 antigen, is related to invasive disease and is uniquely associated with neonatal meningitis. Approximately 80% of *E. coli* meningitis in neonates is caused by K1 strains, and though this association is not as strong with bacteremia, K1 strains have been cultured from the blood of infants with sepsis without meningitis [173]. There is also a higher rate of morbidity and mortality associated with sepsis and meningitis caused by the K1 strains compared with disease caused by non-K1 strains. The increased morbidity and mortality are related to the concentration and persistence of the capsular polysaccharides of these K1 strains in blood and CSF [174].

Pili on the surface of *E. coli* K1 strains are important for mucosal colonization, but a shift to a nonpiliated form where the capsular protein becomes important is the form of the bacterium that is found in the bloodstream of animal models. Phase shifts in the *E. coli* K1 strain's ability to avoid immune recognition by the host defenses is considered an important virulence factor [175].

The pathogenesis of fetal colonization is similar to that of GBS and other organisms that are acquired from the maternal birth canal either prior to or at the time of delivery (see earlier). Though *E. coli* only causes approximately 13% of EOD, it is responsible for 31% of LOD, for reasons that are not clearly understood [1,5]. Sarff et al. and McCracken et al. showed high rates of carriage of K1 strains of *E. coli* in hospital personnel and subsequent acquisition of identical strains in the neonates they cared for [173,174]. In addition, there was acquisition of these strains in neonates born to mothers not colonized with these strains. Cook et al. examined other virulence factors of *E. coli* strains associated with neonatal sepsis, documenting unique adherence phenotypes that enhance the virulence of these strains [127]. These properties are related to those seen in other extraintestinal *E. coli* infections. In preterm infants, *E. coli* represents the majority of EOD [4,48].

E. coli sepsis is associated with higher rates of morbidity, longer hospital stays, and increased need for mechanical ventilation compared with GBS EOD. In addition, *E. coli* EOD carries higher mortality rates despite appropriate treatment [48,176]. Further, changing patterns of *E. coli* LOD will need to be monitored because one study documented an increase in both term and preterm *E. coli* LOD since 1997, the cause of which is yet unidentified [2]. In addition, multiple studies have identified prematurity as an increased risk for *E. coli* sepsis in any period after birth, whereas term *E. coli* EOD appears to be declining, and protection appears to be associated with longer exposure (≥4 hours) of IAP [21,48,177].

Treatment for *E. coli* bacteremia without meningitis is dictated by the susceptibility of the isolate to antibiotics. Treatment with ampicillin in susceptible strains alone or in combination with an aminoglycoside is appropriate therapy. The use of broader regimens, particularly cephalosporins, should be carefully considered and used only if deemed necessary because there is concern for the emergence of cephalosporin-resistant strains of *E. cloacae, Klebsiella*, and *Serratia* species in the institutions where these infants reside. However, the majority of *E. coli* strains causing neonatal disease have been shown to be ampicillin resistant, and therefore Gram stain and culture results are important tools for changes to empirical antibiotic regimens. Importantly, susceptibility patterns were not influenced by the use of IAP [49]. The duration of therapy for uncomplicated disease is usually 10–14 days.

Streptococcus pyogenes (Group A β-Hemolytic *Streptococcus*)

Streptococcus pyogenes has been a historically important cause of neonatal sepsis from the sixteenth century and was the predominant organism causing disease from 1930 to 1940 [1], but incidence dropped off markedly in the antibiotic era [178]. There has been a recent increase in group A β-hemolytic *Streptococcus* (GAS) disease rates in children and adults, and while still rare, increased reports of GAS disease in neonates from sporadic disease and associated with outbreaks have been published [179,180]. Surveillance will indicate whether this trend continues and the impact on neonatal disease, but given

the continued susceptibility of GAS to intrapartum penicillin and ampicillin, IAP is thought to represent a viable prevention strategy for this pathogen.

GAS has been cultured from the anuses and vaginas of pregnant women, the umbilical stumps of neonates, and the hands and nasopharynges of neonates, mothers, and nursery personnel. Transmission is thought to be at the time of delivery and postnatally. Most colonized infants are asymptomatic, but rare cases of invasive disease, such as sepsis and meningitis, have been documented. In the past, most disease presented as indolent omphalitis [178]. This is in contrast to more recent reports of neonates with a severe EOD associated with high mortality rates, pointing to the possibility of a resurgence of disease with a more aggressive course similar to GBS EOD [181,182]. If there appears to be a true increased incidence of such disease, then preventive measures such as those used to decrease the incidence of GBS may become increasingly important.

No strains of GAS have emerged that are resistant to penicillin, and this remains the drug of choice for treatment [183]. In the era of new, more invasive neonatal sepsis caused by GAS, adjunctive therapies with clindamycin and IVIG may be warranted, but studies in neonates are lacking at the present time [184,185].

Enterococcal Group D Streptococci

The incidence of enterococcal group D streptococci (*Enterococcus*) as a cause of neonatal sepsis rose in the 1980s and 1990s from approximately 0.12/1,000 live births to 0.8/1,000 live births in one study and threefold in another [186, 187]. Eliminating prematurity as a risk factor, EOD was not associated with obstetric complications, and very few term infants were noted to have LOD, and these were associated with complicated postnatal courses with invasive procedures. Further, the increased incidence was not a result of the use of broader-spectrum antibiotics, which were not in common use at the reporting institutions. Because the increased cases were late, occurring in hospitalized neonates, they were thought to reflect risks associated with longer survival of mostly preterm infants in NICUs [186,187].

The organism is a gram-positive organism that has been known as a human pathogen for approximately 100 years [188]. The two important species that cause disease in humans are *Enterococcus faecalis* and *E. faecium* [187].

The clinical signs again are often subtle and nonspecific. The major signs of enterococcal sepsis include respiratory distress and apnea, but chest x-rays are rarely positive. Temperature instability and hypothermia are also present in 15–60% of infants. Diarrhea was the second most frequent symptom encountered in EOD, and rarely does meningitis complicate EOD. About 40% of infants with EOD can be expected to be asymptomatic at birth, and they are often screened only because of maternal risk factors [186,187].

Enterococci are moderately resistant to ampicillin and penicillin and highly resistant to all cephalosporins. Optimal therapy includes both a penicillin and an aminoglycoside for synergy or vancomycin. There are concerns that neonatal enterococcal infections will continue to rise and be more difficult to treat given the appearance of strains that are vancomycin resistant in the United States. The hospital survival rates of infants with vancomycin-resistant *Enterococcus* (VRE) are significantly worse than those of infants with susceptible strains [186]. Outcomes for *Enteroccocus* sepsis appear to be good, with quick clinical improvements, but long-term studies are lacking. Case-fatality rates are low – approximately 5.5–10% – and appear to relate to underlying conditions [186,187].

Summary

The changing prevalence of organisms responsible for neonatal sepsis and the potential for emerging resistance in these organisms underscore the necessity for close vigilance and surveillance of this disease. Many advances have been made in the prevention and treatment of neonatal bacterial sepsis, but mortality and morbidity remain high. By adapting more stringent prevention guidelines and developing better diagnostic and treatment strategies, there is hope that dramatic improvement will occur in both the mortality rates and the incidence of morbidity in the survivors. Ideally, the future focus will be on the development of other prevention strategies such as vaccines and immunotherapies that could have broader and more dramatic influences on neonatal sepsis.

References

1. Freedman RM, Ingram DL, Gross I, et al. A half century of neonatal sepsis at Yale: 1928 to 1978. *Am J Dis Child* 1981; **135**: 140–4.

2. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics* 2008; **121**: 689–96.
3. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Pediatrics* 2005; **116**: 595–602.
4. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004–2013: the rise and fall of coagulase-negative staphylococci. *J Pediatr* 2015; **166**: 1193–9.
5. Gladstone IM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. *Pediatr Infect Dis J* 1990; **9**: 819–25.
6. Baltimore RS, Huie SM, Meek JI, et al. Early-onset neonatal sepsis in the era of group B streptococcal prevention. *Pediatrics* 2001; **108**: 1094–8.
7. Chen KT, Puopolo KM, Eichenwald EC, et al. No increase in rates of early-onset neonatal sepsis by antibiotic-resistant group B *Streptococcus* in the era of intrapartum antibiotic prophylaxis. *Am J Obstet Gynecol* 2005; **192**: 1167–71.
8. Daley AJ, Isaacs D. Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and *Escherichia coli* neonatal sepsis in Australasia. *Pediatr Infect Dis J* 2004; **23**: 630–4.
9. Edwards RK, Jamie WE, Sterner D, et al. Intrapartum antibiotic prophylaxis and early-onset neonatal sepsis patterns. *Infect Dis Obstet Gynecol* 2003; **11**: 221–6.
10. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. *Lancet Infect Dis* 2003; **3**: 201–13.
11. Schrag SJ, Stoll BJ. Early-onset neonatal sepsis in the era of widespread intrapartum chemoprophylaxis. *Pediatr Infect Dis J* 2006; **25**: 939–40.
12. Baker CJ, Halsey NA, Schuchat A. 1997 AAP guidelines for prevention of early-onset group B streptococcal disease. *Pediatrics* 1999; **103**: 701.
13. Eichenwald EC. Perinatally transmitted neonatal bacterial infections. *Infect Dis Clin North Am* 1997; **11**: 223–39.
14. Hyde TB, Hilger TM, Reingold A, et al. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. *Pediatrics* 2002; **110**: 690–5.
15. Schrag S, Schuchat A. Prevention of neonatal sepsis. *Clin Perinatol* 2005; **32**: 601–15.
16. Schuchat A, Zywicki SS, Dinsmoor MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics* 2000; **105**: 21–6.
17. Vesikari T, Janas M, Gronroos P, et al. Neonatal septicaemia. *Arch Dis Child* 1985; **60**: 542–6.
18. Edwards MS, Nizet V, Baker CJ. Group B streptococcal infections. In *Infectious Diseases of the Fetus and Newborn Infant*, 6th edn. Philadelphia: Saunders, 2006: 403–64.
19. Lukacs SL, Schoendorf KC. National estimates of newborn sepsis rates in the United States, 1990–2001. Presented at the Annual Meeting of the Society for Pediatric and Perinatal Epidemioloic Research, Salt Lake City, UT, 2004.
20. Lukacs SL, Schoendorf KC, Schuchat A. Trends in sepsis-related neonatal mortality in the United States, 1985–1998. *Pediatr Infect Dis J* 2004; **23**: 599–603.
21. Schrag SJ, Hadler JL, Arnold KE, et al. Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use. *Pediatrics* 2006; **118**: 570–6.
22. Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. *Pediatr Res* 2013; **74**: 73–85.
23. Ganatra HA, Zaidi AK. Neonatal infections in the developing world. In *Seminars in Perinatology*. New York: Elsevier, 2010: 416–25.
24. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatr Infect Dis* 2009; **28**: S3–9.
25. Zaidi AKM, Darmstadt GL, Stoll B. Neonatial infections: a global perspective. In *Infectious Disease of the Fetus and Newborn Infant*, 8th edn. Philadelphia: Saunders, 2014.
26. Darmstadt GL, Saha SK, Choi Y, et al. Population-based incidence and etiology of community-acquired neonatal bacteremia in Mirzapur, Bangladesh: an observational study. *J Infect Dis* 2009; **200**: 906–15.
27. Seale AC, Blencowe H, Manu AA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, South Asia, and Latin America for 2012: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14**: 731–41.
28. Darmstadt GL, Ahmed S, Ahmed ANU, Saha SK. Mechanism for prevention of infection in preterm neonates by topical emollients: a randomized, controlled clinical trial. *Pediatr Infect Dis J* 2014; **33**: 1124–7.

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.031

29. Darmstadt GL, Saha SK, Ahmed S, et al. Effect of topical emollient treatment of preterm neonates in Bangladesh on invasion of pathogens into the bloodstream. *Pediatr Res* 2007; **61**: 588–93.

30. Arachaisri T, Ballow M. Developmental immunology of the newborn. *Immunol Allergy Clin North Am* 1999; **19**: 253–79.

31. Lewis D, Wilson C. *Developmental Immunology and Role of the Host Defenses in Neonatal Susceptibility to Infection*, 4th edn. Philadelphia: Saunders, 1995.

32. Georgeson GD, Szony BJ, Streitman K, et al. Natural killer cell cytotoxicity is deficient in newborns with sepsis and recurrent infections. *Eur J Pediatr* 2001; **160**: 478–82.

33. Wilson DC, Edgar JD. Predictors of bacterial infection in neonates. *J Pediatr* 1997; **130**: 166.

34. Herbst A, Källén K. Time between membrane rupture and delivery and septicemia in term neonates. *Obstet Gynecol* 2007; **110**: 612–18.

35. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. *Pediatr Clin North Am* 2004; **51**: 939–59.

36. Chen KT, Ringer S, Cohen AP, Lieberman E. The role of intrapartum fever in identifying asymptomatic term neonates with early-onset neonatal sepsis. *J Perinatol* 2002; **22**: 653–7.

37. Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med* 2002; **347**: 233–9.

38. Towers CV, Suriano K, Asrat T. The capture rate of at-risk term newborns for early-onset group B streptococcal sepsis determined by a risk factor approach. *Am J Obstet Gynecol* 1999; **181**: 1243–9.

39. Yancey MK, Duff P, Kubilis P, et al. Risk factors for neonatal sepsis. *Obstet Gynecol* 1996; **87**: 188–94.

40. Glasgow TS, Young PC, Wallin J, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. *Pediatrics* 2005; **116**: 696–702.

40a. Taukobong HF, Kincaid MM, Levy JK, et al. Does addressing gender inequalities and empowering women and girls improve health and development programme outcomes? *Health Policy Plan* 2016; **10**: 1492–1514.

41. Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. *Lancet* 2014; **384**: 189–205.

42. Darmstadt GL, Syed U, Patel Z, Kabir N. Review of domiciliary newborn-care practices in Bangladesh. *J Health Popul Nutr* 2006; **24**: 380–93.

43. Kumar V, Kumar A, Ghosh AK, et al. Enculturating science: community-centric design of behavior change interactions for accelerating health impact. *Semin Perinatol* 2015; **39**: 393–415.

44. Kumar V, Mohanty S, Kumar A, et al. Effect of community-based behaviour change management on neonatal mortality in Shivgarh, Uttar Pradesh, India: a cluster-randomised controlled trial. *Lancet* 2008; **372**: 1151–62.

45. Mullany LC, Darmstadt GL, Katz J, et al. Risk factors for umbilical cord infection among newborns of southern Nepal. *Am J Epidemiol* 2007; **165**: 203–11.

46. Mullany LC, Katz J, Li YM, et al. Breast-feeding patterns, time to initiation, and mortality risk among newborns in southern Nepal. *J Nutrition* 2008; **138**: 599–603.

47. Winch PJ, Alam MA, Akther A, et al. Local understandings of vulnerability and protection during the neonatal period in Sylhet district, Bangladesh: a qualitative study. *Lancet* 2005; **366**: 478–85.

48. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. *Pediatr Infect Dis J* 2011; **30**: 937.

49. Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues. *Pediatrics* 2011; **127**:817–26.

50. Denniston S, Riordan FA. *Staphylococcus aureus* bacteraemia in children and neonates: a 10 year retrospective review. *J Infect* 2006; **53**: 387–93.

51. Hakim H, Mylotte JM, Faden H. Morbidity and mortality of staphylococcal bacteremia in children. *Am J Infect Control* 2007; **35**: 102–5.

52. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA, 2010.

53. Polin RA, Papile L-A, Baley JE, et al. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics* 2012; **129**: 1006–15.

54. Hamer DH, Darmstadt GL, Carlin JB, et al. Etiology of bacteremia in young infants in six countries. *Pediatr Infect Dis J* 2015; **34**: e1–8.

55. Waters D, Jawad I, Ahmad A, et al. Aetiology of community-acquired neonatal sepsis in low and middle income countries. *J Global Health* 2011; **1**: 154–70.

56. Schiano MA, Hauth JC, Gilstrap LC 3rd. Second-stage fetal tachycardia and neonatal infection. *Am J Obstet Gynecol* 1984; **148**: 779–81.

57. Soman M, Green B, Daling J. Risk factors for early neonatal sepsis. *Am J Epidemiol* 1985; **121**: 712–19.

58. Escobar GJ, Li DK, Armstrong MA, et al. Neonatal sepsis workups in infants weighing less than 2,000 grams at birth: a population-based study. *Pediatrics* 2000; **106**: 256–63.
59. Baker CJ. Group B streptococcal infections. *Clin Perinatol* 1997; **24**: 59–70.
60. Ottolini MC, Lundgren K, Mirkinson LJ, et al. Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. *Pediatr Infect Dis J* 2003; **22**: 430–4.
61. Wortham JM, Hansen NI, Schrag SJ, et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. *Pediatrics* 2016; **137**(1): e20152323.
62. World Health Organization (WHO). *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources*: Geneva: WHO, 2005.
63. UNICEF, Organization WH. *Caring for Newborns and Children in the Community: A Training Course for Community Health Workers. Caring for the Newborn at Home*. New York: United Nations, 2015.
64. Group YICSS. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. *Lancet* 2008; **371**: 135–42.
65. Bomela HN, Ballot DE, Cory BJ, Cooper PA. Use of C-reactive protein to guide duration of empiric antibiotic therapy in suspected early neonatal sepsis. *Pediatr Infect Dis J* 2000; **19**: 531–5.
66. Townsend TR, Shapiro M, Rosner B, Kass EH. Use of antimicrobial drugs in general hospitals. IV. Infants and children. *Pediatrics* 1979; **64**: 573–8.
67. Paerregaard A, Bruun B, Andersen GE, Witt J. No advantage of capillary blood compared with venous blood for culture in neonates. *Pediatr Infect Dis J* 1989; **8**: 659–60.
68. Wiswell TE, Hachey WE. Multiple site blood cultures in the initial evaluation for neonatal sepsis during the first week of life. *Pediatr Infect Dis J* 1991; **10**: 365–9.
69. Sarkar S, Bhagat I, DeCristofaro J, et al. A study of the role of multiple site blood cultures in the evaluation of neonatal sepsis. *J Perinatol* 2006; **26**: 18–22.
70. Yaacobi N, Bar-Meir M, Shchors I, Bromiker R. A prospective controlled trial of the optimal volume for neonatal blood cultures. *Pediatr Infect Dis J* 2015; **34**: 351–4.
71. Jardine L, Davies MW, Faoagali J. Incubation time required for neonatal blood cultures to become positive. *J Paediatr Child Health* 2006; **42**: 797–802.
72. Kumar Y, Qunibi M, Neal T, Yoxall C. Time to positivity of neonatal blood cultures. *Arch Dis Child Fetal Neonat Ed* 2001; **85**: F182–6.
73. Liu C, Ai H, Wang W, et al. Comparison of 16S rRNA gene PCR and blood culture for diagnosis of neonatal sepsis. *Arch Pediatr* 2014; **21**: 162–9.
74. Visser VE, Hall RT. Urine culture in the evaluation of suspected neonatal sepsis. *J Pediatr* 1979; **94**: 635–8.
75. DiGeronimo RJ. Lack of efficacy of the urine culture as part of the initial workup of suspected neonatal sepsis. *Pediatr Infect Dis J* 1992; **11**: 764–6.
76. Evans ME, Schaffner W, Federspiel CF, et al. Sensitivity, specificity, and predictive value of body surface cultures in a neonatal intensive care unit. *JAMA* 1988; **259**: 248–52.
77. Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteraemia. *Arch Dis Child* 1988; **63**: 639–43.
78. Schouten-Van Meeteren NY, Rietveld A, Moolenaar AJ, Van Bel F. Influence of perinatal conditions on C-reactive protein production. *J Pediatr* 1992; **120**: 621–4.
79. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. *Pediatrics* 1998; **102**: E41.
80. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J* 1997; **16**: 735–46; quiz 746–7.
81. Chiesa C, Signore F, Assumma M, et al. Serial measurements of C-reactive protein and interleukin-6 in the immediate postnatal period: reference intervals and analysis of maternal and perinatal confounders. *Clin Chem* 2001; **47**: 1016–22.
82. Laborada G, Rego M, Jain A, et al. Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis. *Am J Perinatol* 2003; **20**: 491–501.
83. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. *Neonatology* 2012; **102**: 25–36.
84. Bhandari V, Wang C, Rinder C, Rinder H. Hematologic profile of sepsis in neonates: neutrophil CD64 as a diagnostic marker. *Pediatrics* 2008; **121**: 129–34.
85. Kocabas E, Sarikcioglu A, Aksaray N, et al. Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. *Turk J Pediatr* 2007; **49**: 7–20.
86. Ng PC, Li G, Chui KM, et al. Neutrophil CD64 is a sensitive diagnostic marker for early-onset neonatal infection. *Pediatr Res* 2004; **56**: 796–803.

87. Santana Reyes C, Garcia-Munoz F, Reyes D, et al. Role of cytokines (interleukin-1β, 6, 8, tumour necrosis factor-α, and soluble receptor of interleukin-2) and C-reactive protein in the diagnosis of neonatal sepsis. *Acta Paediatr* 2003; **92**: 221–7.

88. Franz AR, Steinbach G, Kron M, Pohlandt F. Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infections. *Pediatrics* 1999; **104**: 447–53.

89. Mohsen AHA, Kamel BA. Predictive values for procalcitonin in the diagnosis of neonatal sepsis. *Electron Phys* 2015; **7**: 1190.

90. Sakha K, Husseini M, Seyyedsadri N. The role of the procalcitonin in diagnosis of neonatal sepsis and correlation between procalcitonin and C-reactive protein in these patients. *Pakistan J Biol Sci: PJBS* 2008; **11**: 1785–90.

91. Nupponen I, Andersson S, Jarvenpaa AL, et al. Neutrophil cd11b expression and circulating interleukin-8 as diagnostic markers for early-onset neonatal sepsis. *Pediatrics* 2001; **108**: E12.

92. Weirich E, Rabin RL, Maldonado Y, et al. Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. *J Pediatr* 1998; **132**: 445–1.

93. Edgar JD, Wilson DC, McMillan SA, et al. Predictive value of soluble immunological mediators in neonatal infection. *Clin Sci (Colch)* 1994; **87**: 165–71.

94. Kennon C, Overturf G, Bessman S, et al. Granulocyte colony-stimulating factor as a marker for bacterial infection in neonates. *J Pediatr* 1996; **128**: 765–9.

95. Backes RJ, Rouse MS, Henry NK, et al. Activity of penicillin combined with an aminoglycoside against group B streptococci in vitro and in experimental endocarditis. *J Antimicrob Chemother* 1986; **18**: 491–8.

96. Starr SE. Antimicrobial therapy of bacterial sepsis in the newborn infant. *J Pediatr* 1985; **106**: 1043–8.

97. Jenson HB, Pollock BH. Meta-analyses of the effectiveness of intravenous immune globulin for prevention and treatment of neonatal sepsis. *Pediatrics* 1997; **99**: E2.

98. Manroe BL, Rosenfeld CR, Weinberg AG, Browne R. The differential leukocyte count in the assessment and outcome of early-onset neonatal group B streptococcal disease. *J Pediatr* 1977; **91**: 632–7.

99. Bilgin K, Yaramis A, Haspolat K, et al. A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. *Pediatrics* 2001; **107**: 36–41.

100. Gillan ER, Christensen RD, Suen Y, et al. A randomized, placebo-controlled trial of recombinant human granulocyte colony-stimulating factor administration in newborn infants with presumed sepsis: significant induction of peripheral and bone marrow neutrophilia. *Blood* 1994; **84**: 1427–33.

101. Schibler KR, Osborne KA, Leung LY, et al. A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. *Pediatrics* 1998; **102**: 6–13.

102. Tshefu A, Lokangaka A, Ngaima S, et al. Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. *Lancet* 2015; **385**: 1767–76.

103. Bennet R, Eriksson M, Zetterstrom R. Neonatal septicemia: comparison of onset and risk factors during three consecutive 5-year periods. *Acta Paediatr Scand* 1987; **76**: 361–2.

104. Mok PM, Reilly BJ, Ash JM. Osteomyelitis in the neonate: clinical aspects and the role of radiography and scintigraphy in diagnosis and management. *Radiology* 1982; **145**: 677–82.

105. Bennet R, Bergdahl S, Eriksson M, Zetterstrom R. The outcome of neonatal septicemia during fifteen years. *Acta Paediatr Scand* 1989; **78**: 40–3.

106. Alfven G, Bergqvist G, Bolme P, Eriksson M. Longterm follow-up of neonatal septicemia. *Acta Paediatr Scand* 1978; **67**: 769–73.

107. Sehdev HM, Stamilio DM, Macones GA, et al. Predictive factors for neonatal morbidity in neonates with an umbilical arterial cord pH less than 7.00. *Am J Obstet Gynecol* 1997; **177**: 1030–4.

108. Wu YW. Systematic review of chorioamnionitis and cerebral palsy. *Ment Retard Dev Disabil Res Rev* 2002; **8**: 25–9.

109. Arifeen SE, Mullany LC, Shah R, et al. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial. *Lancet* 2012; **379**: 1022–8.

110. Imdad A, Mullany LC, Baqui AH, et al. The effect of umbilical cord cleansing with chlorhexidine on omphalitis and neonatal mortality in community settings in developing countries: a meta-analysis. *BMC Public Health* 2013; **13**: S15.

111. Mullany LC, Darmstadt GL, Khatry SK, et al. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial. *Lancet* 2006; **367**: 910–18.

112. World Health Organization (WHO). *WHO Model List of Essential Medicines*, 19th list (updated). Geneva: WHO, April 2015.

.031

113. Darmstadt GL, Badrawi N, Law PA, et al. Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in Egypt: a randomized, controlled clinical trial. *Pediatr Infect Dis J* 2004; **23**: 719–25.

114. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. *Lancet* 2005; **365**: 1039–45.

115. Salam RA, Darmstadt GL, Bhutta ZA. Effect of emollient therapy on clinical outcomes in preterm neonates in Pakistan: a randomised controlled trial. *Arch Dis Child Fetal Neonat Ed* 2015; **100**: F210–15.

116. Salam RA, Das JK, Darmstadt GL, Bhutta ZA. Emollient therapy for preterm newborn infants: evidence from the developing world. *BMC Public Health* 2013; **13**: 1–7.

117. Conde-Agudelo A, Díaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birth weight infants. *Cochrane Database Syst Rev* 2014; **4**: CD002771.

118. Engmann C, Wall S, Darmstadt G, et al. Consensus on kangaroo mother care acceleration. *Lancet* 2013; **382**: e26–7.

119. Schuchat A. Group B streptococcal disease: from trials and tribulations to triumph and trepidation. *Clin Infect Dis* 2001; **33**: 751–6.

120. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. *Clin Microbiol Rev* 1998; **11**: 497–513.

121. Davies HD, Adair C, McGeer A, et al. Antibodies to capsular polysaccharides of group B *Streptococcus* in pregnant Canadian women: relationship to colonization status and infection in the neonate. *J Infect Dis* 2001; **184**: 285–91.

122. Blumberg HM, Stephens DS, Modansky M, et al. Invasive group B streptococcal disease: the emergence of serotype V. *J Infect Dis* 1996; **173**: 365–73.

123. Klegerman ME, Boyer KM, Papierniak CK, Gotoff SP. Estimation of the protective level of human IgG antibody to the type-specific polysaccharide of group B *Streptococcus* type Ia. *J Infect Dis* 1983; **148**: 648–55.

124. Schuchat A, Deaver-Robinson K, Plikaytis BD, et al. Multistate case-control study of maternal risk factors for neonatal group B streptococcal disease. The Active Surveillance Study Group. *Pediatr Infect Dis J* 1994; **13**: 623–9.

125. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med* 1986; **314**: 1665–9.

126. CDC. Decreasing incidence of perinatal group B streptococcal disease – United States, 1993–1995. *MMWR Morb Mortal Wkly Rep* 1997; **46**: 473.

127. Whitney CG, Plikaytis BD, Gozansky WS, et al. Prevention practices for perinatal group B streptococcal disease: a multi-state surveillance analysis. Neonatal Group B Streptococcal Disease Study Group. *Obstet Gynecol* 1997; **89**: 28–32.

128. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. *MMWR Recomm Rep* 2002; **51**: 1–22.

129. Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 1996; **45**: 1–24.

130. CDC. Diminishing racial disparities in early-onset neonatal group B streptococcal disease – United States, 2000–2003. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 502.

131. CDC. Perinatal group B streptococcal disease after universal screening recommendations–United States, 2003–2005. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 701–5.

132. CDC. Active bacterial core surveillance report: Streptococcus *pneumoniae*, 2009.

133. Ekelund K, Konradsen H. Invasive group B streptococcal disease in infants: a 19-year nationwide study. Serotype distribution, incidence and recurrent infection. *Epidemiol Infect* 2004; **132**: 1083–90.

134. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA* 2008; **299**: 2056–65.

135. Katz V, Bowes WA Jr. Perinatal group B streptococcal infections across intact amniotic membranes. *J Reprod Med* 1988; **33**: 445–9.

136. Dillon HC Jr, Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. *J Pediatr* 1987; **110**: 31–6.

137. Trager JD, Martin JM, Barbadora K, et al. Probable community acquisition of group B *Streptococcus* in an infant with late-onset disease: demonstration using field inversion gel electrophoresis. *Arch Pediatr Adolesc Med* 1996; **150**: 766–8.

138. Ancona RJ, Ferrieri P, Williams PP. Maternal factors that enhance the acquisition of group-B streptococci by newborn infants. *J Med Microbiol* 1980; **13**: 273–80.

139. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections

and Prematurity Study Group. *Obstet Gynecol* 1991; **77**: 604–10.

140. Curtis J, Kim G, Wehr NB, Levine RL. Group B streptococcal phospholipid causes pulmonary hypertension. *Proc Natl Acad Sci USA* 2003; **100**: 5087–90.

141. CDC. Hospital-based policies for prevention perinatal group B streptococcal disease – United States, 1999. *MMWR Morbid Mortal Wkly Rep* 2000; **49**: 936–40.

142. Bromberger P, Lawrence JM, Braun D, et al. The influence of intrapartum antibiotics on the clinical spectrum of early-onset group B streptococcal infection in term infants. *Pediatrics* 2000; **106**: 244–50.

143. Pulver L, Hopfenbeck M, Young P, et al. Continued early onset group B streptococcal infections in the era of intrapartum prophylaxis. *J Perinatol* 2009; **29**: 20–5.

144. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics* 2005; **115**: 1240–6.

145. Maayan-Metzger A, Barzilai A, Keller N, Kuint J. Are the "good old" antibiotics still appropriate for early-onset neonatal sepsis? A 10 year survey. *Israel Med Assoc J* 2009; **11**: 138.

146. Glass P, Wagner AE, Papero PH, et al. Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation. *J Pediatr* 1995; **127**: 447–57.

147. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. *Pediatrics* 1997; **99**: 489–96.

148. American College of Obstetricians and Gynecologists. *Prevention of Early-Onset Group B Streptococcal Disease in Newborns [Opinion 173]*. Washington, DC: American College of Obstetricians and Gynecologists, 1996.

149. Rosenstein NE, Schuchat A. Opportunities for prevention of perinatal group B streptococcal disease: a multistate surveillance analysis. The Neonatal Group B Streptococcal Disease Study Group. *Obstet Gynecol* 1997; **90**: 901–6.

150. Cueto M, Sanchez M, Sanpedro A. Timing of intrapartum ampicillin and prevention of vertical transmission of group B streptococci. *Obstet Gynecol* 1998; **91**: 112–14.

151. Hall C, Easton J, Granoff D, et al. Guidelines for prevention of group B streptococcal (GBS) infection by chemoprophylaxis. *Pediatrics* 1992; **90**: 775–8.

152. Gotoff SP, Boyer KM. Prevention of early-onset neonatal group B streptococcal disease. *Pediatrics* 1997; **99**: 866–9.

153. Siegel JD, Cushion NB. Prevention of early-onset group B streptococcal disease: another look at single-dose penicillin at birth. *Obstet Gynecol* 1996; **87**: 692–8.

154. Benitz WE. The neonatal group B streptococcal debate. *Pediatrics* 1998; **101**: 494–6.

155. Lieu TA, Mohle-Boetani JC, Ray GT, et al. Neonatal group B streptococcal infection in a managed care population. Perinatal Group B Streptococcal Infection Study Group. *Obstet Gynecol* 1998; **92**: 21–7.

156. Yow MD, Mason EO, Leeds LJ, et al. Ampicillin prevents intrapartum transmission of group B *Streptococcus*. *JAMA* 1979; **241**: 1245–7.

157. Heim K, Alge A, Marth C. Anaphylactic reaction to ampicillin and severe complication in the fetus. *Lancet* 1991; **337**: 859–60.

158. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. *Am J Obstet Gynecol* 1998; **179**: 879–83.

159. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B *Streptococcus* colonization: management and outcome of newborns. *Pediatrics* 1994; **93**: 631–5.

160. Davis RL, Hasselquist MB, Cardenas V, et al. Introduction of the new Centers for Disease Control and Prevention group B streptococcal prevention guideline at a large West Coast health maintenance organization. *Am J Obstet Gynecol* 2001; **184**: 603–10.

161. Jaureguy F, Carton M, Panel P, et al. Effects of intrapartum penicillin prophylaxis on intestinal bacterial colonization in infants. *J Clin Microbiol* 2004; **42**: 5184–8.

162. Borchardt SM, DeBusscher JH, Tallman PA, et al. Frequency of antimicrobial resistance among invasive and colonizing group B streptococcal isolates. *BMC Infect Dis* 2006; **6**: 1.

163. Castor ML, Whitney CG, Como-Sabetti K, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. *Infect Dis Obstet Gynecol* 2008; **2008**: 727505.

164. Kasper DL, Paoletti LC, Wessels MR, et al. Immune response to type III group B streptococcal polysaccharide-tetanus toxoid conjugate vaccine. *J Clin Invest* 1996; **98**: 2308–14.

165. Baker CJ, Paoletti LC, Rench MA, et al. Immune response of healthy women to two different group B streptococcal type V capsular polysaccharide-protein conjugate vaccines. *J Infect Dis* 2004; **189**: 1103–12.

166. Guttormsen H-K, Liu Y, Paoletti LC. Functional activity of antisera to group B streptococcal conjugate vaccines measured with an opsonophagocytosis assay and HL-60 effector cells. *Human Vaccines* 2008; **4**: 370–4.

167. Buccato S, Maione D, Rinaudo CD, et al. Use of Lactococcus lactis expressing pili from group B Streptococcus as a broad-coverage vaccine against streptococcal disease. *J Infect Dis* 2006; **194**: 331–40.

168. Rosini R, Rinaudo CD, Soriani M, et al. Identification of novel genomic islands coding for antigenic pilus-like structures in *Streptococcus agalactiae*. *Mol Microbiol* 2006; **61**: 126–41.

169. Hillier S, Ferris D, Fine D, Ferrieri P. Women receiving group B *Streptococcus* serotype III tetanus toxoid (GBS III-TT) vaccine have reduced vaginal and rectal acquisition of GBS type III. Presented at the 47th Annual Meeting of the IDSA, 2009.

170. Le Doare K, Heath PT. An overview of global GBS epidemiology. *Vaccine* 2013; **31**(Suppl 4): D7–12.

171. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 2012; **379**: 547–56.

172. Bingen E, Picard B, Brahimi N, et al. Phylogenetic analysis of *Escherichia coli* strains causing neonatal meningitis suggests horizontal gene transfer from a predominant pool of highly virulent B2 group strains. *J Infect Dis* 1998; **177**: 642–50.

173. Sarff LD, McCracken GH, Schiffer MS, et al. Epidemiology of *Escherichia coli* K1 in healthy and diseased newborns. *Lancet* 1975; **1**: 1099–104.

174. McCracken GH Jr, Sarff LD, Glode MP, et al. Relation between *Escherichia coli* K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis. *Lancet* 1974; **2**: 246–50.

175. Guerina NG, Kessler TW, Guerina VJ, et al. The role of pili and capsule in the pathogenesis of neonatal infection with *Escherichia coli* K1. *J Infect Dis* 1983; **148**: 395–405.

176. Mayor-Lynn K, Gonzalez-Quintero VH, O'Sullivan MJ, et al. Comparison of early-onset neonatal sepsis caused by *Escherichia coli* and group B *Streptococcus*. *Am J Obstet Gynecol* 2005; **192**: 1437–9.

177. Alarcon A, Pena P, Salas S, et al. Neonatal early onset Escherichia coli sepsis: trends in incidence and antimicrobial resistance in the era of intrapartum antimicrobial prophylaxis. *Pediatr Infect Dis J* 2004; **23**: 295–9.

178. Charles D, Larsen B. Streptococcal puerperal sepsis and obstetric infections: a historical perspective. *Rev Infect Dis* 1986; **8**: 411–22.

179. Chuang I, Van Beneden C, Beall B, et al. Population-based surveillance for postpartum invasive group A *Streptococcus* infections, 1995–2000. *Clin Infect Dis* 2002; **35**: 665–70.

180. Miyairi I, Berlingieri D, Protic J, Belko J. Neonatal invasive group A streptococcal disease: case report and review of the literature. *Pediatr Infect Dis J* 2004; **23**: 161–5.

181. Greenberg D, Leibovitz E, Shinnwell ES, et al. Neonatal sepsis caused by *Streptococcus pyogenes*: resurgence of an old etiology? *Pediatr Infect Dis J* 1999; **18**: 479–81.

182. Macris MH, Hartman N, Murray B, et al. Studies of the continuing susceptibility of group A streptococcal strains to penicillin during eight decades. *Pediatr Infect Dis J* 1998; **17**: 377–81.

183. Kaplan EL, Johnson DR, Del Rosario MC, Horn DL. Susceptibility of group A beta-hemolytic streptococci to thirteen antibiotics: examination of 301 strains isolated in the United States between 1994 and 1997. *Pediatr Infect Dis J* 1999; **18**: 1069–72.

184. Norrby-Teglund A, Ihendyane N, Kansal R, et al. Relative neutralizing activity in polyspecific IgM, IgA, and IgG preparations against group A streptococcal superantigens. *Clin Infect Dis* 2000; **31**: 1175–82.

185. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J* 1999; **18**: 1096–100.

186. Dobson SR, Baker CJ. Enterococcal sepsis in neonates: features by age at onset and occurrence of focal infection. *Pediatrics* 1990; **85**: 165–71.

187. McNeeley DF, Saint-Louis F, Noel GJ. Neonatal enterococcal bacteremia: an increasingly frequent event with potentially untreatable pathogens. *Pediatr Infect Dis J* 1996; **15**: 800–5.

188. Murray BE. The life and times of the *Enterococcus*. *Clin Microbiol Rev* 1990; **3**: 46–65.

Chapter

31

Neonatal Bacterial Meningitis

Alistair G. S. Philip

Introduction

The term *meningitis* refers to inflammation of the leptomeninges covering the brain. Bacterial infection of the meninges usually produces a suppurative process or *purulent meningitis*. However, it is probably more correct in the newborn infant to consider the condition as bacterial *meningoencephalitis* because it is common to have involvement of the cerebral hemispheres as well as involvement of the meninges.

From the clinician's perspective, it has been traditional to think of neonatal sepsis (septicemia) and meningitis together because the clinical manifestations may be indistinguishable. For many years the proportion of cases of neonatal sepsis that also had documented meningitis was considered to be one-quarter to one-third. For instance, in 1986, it was estimated that one case of neonatal meningitis occurs for every four cases of sepsis [1]. Indeed, this was my personal experience in Vermont between 1975 and 1980, when 12 of 41 cases (29%) of neonatal sepsis in the first week after birth had associated meningitis [2]. However, in the early 1990s, the proportion of cases decreased to as low as 5% [3] and has remained low in the United States. This may be less true in other countries, with 32 of 229 cases (14%) noted in Israel, 107 of 577 (18.5%) in Panama, and 14 of 84 (17.8%) in Kenya [4–6]. It is also noteworthy that with meningitis due to group B *Streptococcus* (GBS), the proportion of cases may relate to the time of onset of the disease. For instance, if GBS sepsis was detected within 12 hours of birth, the proportion with meningitis was 6%, whereas it was 53% if over 7 days of age in a study from the Netherlands [7].

Incidence

The incidence of neonatal bacterial meningitis will vary from one center to the next, but national studies have shown the incidences to be quite similar (Table 31.1). In the Netherlands [8], the incidence in 1976–82 was 0.23/1,000 live births, and in England and Wales, the incidence in 1985–7 was 0.32/1,000 live births and did not change significantly when reevaluated in 1996–7 [9]. About 25 years ago the lowest incidence, 0.16–0.17/1,000 live births, was reported from Australia, where rates have since fallen to even lower levels [10–12]. We are now in an era of widespread intrapartum chemoprophylaxis to prevent GBS infection, and this seems to have resulted in a decrease in meningitis incidence in several countries [13]. In a review of early-onset infection from Australia and New Zealand (Australasia), the incidence of early-onset GBS meningitis fell from 0.24/1,000 in 1993 to 0.03/1,000 in 2002, whereas the incidence of meningitis due to *Escherichia coli* did not change [14]. However, data from the Netherlands documented a sharp reduction in early-onset GBS sepsis, from 0.54/1,000 in 1997–8 to 0.36/1,000 in 1999–2001, but GBS meningitis rates were 0.14 and 0.17/1,000 live births, respectively, for these two time periods [7]. Recent experience from the United Kingdom and the Republic of Ireland (2010–11) revealed an overall incidence of bacterial meningitis of 0.38/1,000 in infants aged less than 90 days, although the incidence in England and Wales was 0.21/1,000 [14a].

A further indication that the incidence may be falling is the fact that compared with the latter half of the twentieth century, there have been few reports concerning neonatal meningitis so far in the twenty-first century. A recent report of early-onset GBS sepsis/meningitis in Australia documented only one case of meningitis among 29 cases of sepsis [14b].The incidence of sepsis and meningitis is higher in neonates of low birth weight (<2,500 g) and especially very low-birth-weight infants (VLBW: <1,500 g) [14–17]. There is also a slight male preponderance in most reports.

Need for Lumbar Puncture

It is unusual to encounter meningitis in the first 24 hours after delivery, and because of this, many clinicians elect not to perform a lumbar puncture at that

Table 31.1 Incidence of Neonatal Bacterial Meningitis

Authors	Country	Years	Rate per 1000 live births
Mulder and Zanen 1984 [8]	Netherlands	1976–82	0.23
Tessin et al. 1990 [16]	Sweden	1975–86	0.40
De Louvois et al. 2005 [9]	England and Wales	1985–87	0.32
Francis and Gilbert 1992 [11]	Australia	1987–89	0.17
Greenberg et al. 1997 [4]	Southern Israel	1986–94	0.45
Isaacs et al. 1999 [10]	Australia	1991–97	0.16
De Louvois et al. 2005 [9]	England and Wales	1996–97	0.31
Gordon and Isaacs 2006 [12]	Australia and New Zealand	1992–2002	0.10

time, particularly when evaluation for sepsis/meningitis is being performed only for risk factors (e.g., prolonged rupture of membranes, maternal fever, etc.) [3].

This issue remains controversial, but in places with a higher incidence of neonatal meningitis, it would seem prudent to perform lumbar puncture whenever meningitis is suspected [18]. Where there is a low incidence of meningitis, there are differences of opinion about the best approach to adopt in the term infant, but there is also no uniformity of opinion regarding the VLBW infant. This is so because the procedure itself may cause disruption of normal physiology, may produce a "traumatic tap," or may be unsuccessful [19].

Some authors have documented an extremely low yield from cerebrospinal fluid (CSF) obtained very early, particularly when the procedure is performed for features of respiratory distress syndrome, and it may add little to blood culture alone. However, one study documented that 28% of infants (12/43) with meningitis had a negative blood culture, including seven of the eight infants whose mothers received prenatal antibiotics. With an increasing number of women receiving prenatal antibiotics to prevent GBS infection, this raises some concern, but there may be alternative strategies that can be adopted (see "Diagnosis" below). A 5-year analysis of neonatal bacterial sepsis also stressed the possible interference of intrapartum maternal antibiotics in obtaining positive blood cultures but recorded only five cases of bacterial meningitis and 209 cases of septicemia [20].

Johnson et al. (in 1997) looked at 24,452 term newborns from 1987 to 1993 [21]. Of the infants evaluated for infection based on risk factors, 3,423 (14%) were asymptomatic. Among this group, 17 (0.5%) were bacteremic, but none had meningitis. An additional 1,712 (7%) were evaluated for signs of sepsis, 55 of whom (3.2%) were bacteremic, with 11 cases of meningitis (10 of whom had positive blood cultures). The authors concluded that lumbar puncture is unnecessary in asymptomatic term newborns – a position affirmed by Pong and Bradley in their review [22].

I agree with this approach and, even in the presence of signs of sepsis, would recommend a selective policy on the first day, taking specific signs and markedly abnormal laboratory values into consideration (see "Diagnosis" below). After the first day, evaluation for sepsis/meningitis should include a lumbar puncture in most cases. Particularly when neonates with nonspecific illnesses are seen in an outpatient setting, the need to consider meningitis has been emphasized [23]. However, even in suspected cases of late-onset sepsis, a selective approach to lumbar puncture has been advocated. [23a].

It is also important to note that a lumbar puncture may be indicated even more in VLBW infants. In a large experience from the NICHD Neonatal Research Network, one-third of VLBW infants had meningitis in the absence of a positive blood culture [24].

Case-Fatality Rate

Despite a decrease in meningitis relative to sepsis, the case-fatality rate has remained extremely high until recently. The rate in England and Wales among 450 cases seen in 1985–7 was 20% [9]. Case-fatality rates are usually higher in neonates with gram-negative infections, with a rate of 32% in England and Wales and a threefold increase compared with gram-positive infections in another study [9,25].

However, a 21-year experience in Dallas, Texas, indicated a case-fatality rate with gram-negative bacillary meningitis of 17% for the years 1969–89 [26]. It should also be noted that 61% of the survivors in Dallas had long-term sequelae. Even with gram-positive meningitis the outcome frequently involves impairment. For instance, Edwards et al. evaluated 38 survivors of GBS meningitis at over 3 years of age [27]. Only 50% were functioning normally. In a more recent study from Toronto, Canada, the case-fatality rate was 13% in 101 infants with definitive bacterial meningitis born between 1979 and 1998, and an additional 17% had moderate or severe disability at 1 year of age [28]. The best outcome was reported from Greece for the years 1983–97, where 70 of 72 term infants with gram-negative bacterial meningitis survived to discharge, and survivors had a low incidence of neurologic sequelae [29]. Experience in England and Wales also suggests a marked decrease in the case-fatality rate in more recent years (8% in 1996–7) [30] but with continued high rates of disability [9]. The case-fatality rate was also markedly reduced (to 8%) in southern Taiwan in 1994–2001 compared with 17% in 1986–93 [31]. The most recent data from other countries (less well developed) continue to show high case-fatality rates of 30–40%, with a high incidence of neurologic sequelae in survivors [32,33,33a]. It has also been observed that case-fatality rates are higher in VLBW infants [13,24].

In a national report from France, the case-fatality rate (CFR) in term infants was 10%, whereas it was 26% in preterm infants. Infants born small for gestational age (SGA) had a CFR of 25% compared with 12% for appropriate for gestational age infants [33b]. The most recent information from the United States suggests a CFR of 11% in meningitis occurring in infants under 2 months of age [33c]. Similarly, in a recent study from the United Kingdom and Ireland, infants less than 90 days of age with bacterial meningitis had a CFR of 8% [14a].

Thus it is clear that neonatal meningitis remains an important cause of mortality and morbidity. Early diagnosis and treatment remain desirable goals, but prevention may be even more desirable. These areas will be discussed later.

Etiology

Prior to the mid-1970s, *Escherichia coli* was the leading cause of neonatal bacterial meningitis in most developed countries. Even in the period 1975–83, *E. coli* was the leading cause of neonatal meningitis in England and Wales [34], and the same was true in the Netherlands from 1976 to 1982. However, as long ago as the early 1970s, GBS accounted for 31% of 131 cases of neonatal meningitis and *E. coli* for 38% in the Neonatal Meningitis Cooperative Study. Since the late 1970s, GBS, also known as *Streptococcus agalactiae*, has assumed the dominant role in most countries reporting on the causative organisms of neonatal meningitis. However, gram-negative bacteria (*Klebsiella* spp. and *E. coli*) continue to predominate in some developing countries [4,5,15,35], although GBS may be increasing [4,33]. Experience from Dallas during 1987–94 indicated that GBS accounted for 52% and *E. coli* for only 9% of 74 cases of neonatal bacterial meningitis (Trujillo and McCracken, personal communication). However, in Toronto, Canada, between 1979 and 1998, GBS decreased from 59% to 42% and *E. coli* increased from 22% to 27% [28]. A further decrease in GBS meningitis, but not *E. coli* meningitis, has been seen in Australasia in recent years, presumably related to increased use of intrapartum antibiotics [14]. More recent data from France indicate that GBS remains prominent, accounting for 79% of cases of early-onset meningitis and 50% of cases of late-onset meningitis, with *E. coli* implicated in 18% and 33% of early- and late-onset cases respectively [33b].

Meningitis due to GBS is usually associated with late-onset infection, generally considered to be more than 5 days after birth, in contrast to the clinical picture of sepsis and pneumonia associated with early-onset GBS infection, although cases of early-onset meningitis certainly occur. In a report from Italy in 2007, among 30 infants with early-onset GBS infection, only 2 had culture-proven meningitis, whereas meningitis was documented in 12 of 26 with late-onset GBS disease [36]. Similarly, babies infected with *Listeria monocytogenes*, particularly serotype IVb, are more likely to have meningitis as the most frequent clinical manifestation with late-onset infection [37]. Although *L. monocytogenes* is not as prevalent in the United States, it has been an important organism in some countries and has been implicated in epidemics in North America [38]. In a report from Kuwait, *L. monocytogenes* was the most common organism isolated in 45 neonates with bacterial meningitis, accounting for 31% of the total, compared with 15% for GBS and 11% for *E. coli* [39]. A recent paper from the United Kingdom and Ireland reported on 364 cases of bacterial meningitis occurring in

infants less than 90 days of age. Of these, 50% were due to GBS, 14% due to *E. coli*, and 4% due to *L. monocytogenes* [14a].

Meningitis due to GBS is most frequently due to serotype III, even with early-onset meningitis. In contrast to a broad distribution of serotypes in neonatal early-onset sepsis, over 85% of early- ($n = 46$) and late-onset ($n = 121$) meningitis cases were reported due to serotype III by Baker in 1979 [40]. Rather similar findings were reported by Carstensen et al. when describing a national study from Denmark [41], in which 77% of early-onset ($n = 13$) and 100% of late-onset ($n = 18$) meningitis cases were type III infections. Experience from the Netherlands showed 57% of GBS meningitis to be due to type III [8]. A recent study from France documented that among 145 cases of late-onset GBS meningitis, 80% were due to type III [41a]. Recently, serotype V has been implicated more, and it has been shown that the biotype may be an important factor as a result of the loss of catabolic function [42]. Of 15 biotypes, types B1–B6 were 13 times more likely to invade the CNS of the neonate than types B7–B15. Among 42 GBS strains associated with neonatal meningitis, 86% were identified as types B1–B6 [42]. One possible mode of acquisition of late-onset GBS infection is via breast milk [42a].

Cases of neonatal meningitis attributed to *E. coli* are predominantly the result of those carrying the K1 capsular antigen. Most reports indicate that 75% of strains of *E. coli* causing neonatal meningitis are K1 strains, and Mulder et al. had 88% K1 strains [43]. *E. coli* meningitis was noted to be seven times more frequent in preterm infants than in term infants in a recent study from France, with most preterm infants seen at between 0 and 3 days of age, whereas term infants were most commonly detected at 11–15 days [43].

In at least one country (Serbia), comparatively recent experience (1991–2000) indicates that *Klebsiella* species account for more cases of neonatal meningitis than either *E. coli* or GBS [44]. Many other organisms have been implicated in neonatal meningitis, most of which are relatively uncommon (for extensive lists, with references, see Davies & Rudd [22] and Pong & Bradley [45]). It should be noted that the fourth most common organism in England and Wales was *Streptococcus pneumoniae* (or pneumococcus), which was almost as common as *L. monocytogenes* [34]. *Neisseria meningitidis*, which is a frequent etiologic agent in older infants and children, is an uncommon cause of neonatal meningitis, but cases continue to be reported [46]. *Haemophilus influenzae*, which used to be a common causative organism of meningitis in infancy, has also become an uncommon etiologic agent in neonates and is usually nontypable (not type b), even in years prior to the introduction of *H. influenzae* type b vaccine. In VLBW infants, the organisms noted earlier may still be implicated, but infection with coagulase-negative staphylococci (especially *S. epidermidis*) is more common [47].

Some organisms have a penchant for causing more difficulty than others. Important among them is *Citrobacter diversus*, which seems to predispose to the development of brain abscess (or abscesses) [48] for reasons that are not completely clear.

Pathophysiology and Pathology

Bacteremia and Susceptibility

Although some cases of neonatal meningitis are encountered without accompanying bacteremia, the most likely route of spread is via bloodstream infection. Indeed, it has been suggested that the magnitude of bacteremia is associated with the occurrence of gram-negative meningitis. Thus factors that predispose to neonatal sepsis (septicemia) may also be considered risk factors for meningitis.

Infection may be acquired from the mother or may be acquired after birth. Bacteria may also possibly gain access to the meninges by direct spread from the oropharynx. Prenatal risk factors include prolonged rupture of the fetal membranes, particularly if there is evidence of chorioamnionitis, and preterm labor without apparent explanation. Much research has linked amniotic fluid infection to preterm labor [49]. Male infants seem to be more susceptible to infection than females, with a higher incidence in almost every series. VLBW infants are at particularly high risk (see "Introduction" above), and an increased risk for GBS infection has been reported in twins [50], although this may be related to the higher incidence of preterm delivery with multiple births. An additional high-risk group is infants with galactosemia, who are particularly susceptible to infection with *E. coli* [51].

The characteristics of some bacteria seem to be associated with an increased propensity to cause neonatal meningitis [52]. The capsular polysaccharide of GBS type III, *E. coli* K1, and *L. monocytogenes* serotype IVb all contain sialic acid in high concentration.

All these organisms have been closely linked to meningitis. The ability of bacteria to interact with neutrophils may also affect virulence. It has been shown that impaired interaction with neutrophils is characteristic of virulent clones of *E. coli* more likely to produce invasive infection [53].

The hospital environment can be particularly hostile for VLBW infants, who may require prolonged intubation with endotracheal tubes or prolonged catheterization of major blood vessels. Central venous catheters in particular seem to predispose to bacteremia, with the possibility of meningitis as a consequence.

Anatomic Pathology

Because meningitis is now relatively infrequent, it is necessary to rely on older information for a description of the morphological inflammatory response [54]. Initially (during the first week), polymorphonuclear leukocytes (PMNs) aggregate in a meshwork of fibrin over the outer part of the arachnoid membrane. This exudate may occur over the cerebral hemispheres but is also found at the base of the brain. Later (second and third week), PMNs decrease, while histiocytes and macrophages increase [54].

Pathologically, changes in blood vessels are very common, with inflammatory infiltrates leading to thromboses of arachnoidal or subependymal veins. There may be severe congestion or hemorrhagic encephalopathy of the brain substance. This may lead to necrosis of nerve cells and leukomalacia. Additional findings that may help to explain the sequelae among survivors of bacterial meningitis are segmental arteritis of meningeal and perforating branches of the carotid artery, compression or collapse of surface veins by purulent meningeal exudate and cerebral edema, and phlebitis of cortical veins [55]. The major neuropathologic features of neonatal bacterial meningitis are summarized in Table 31.2.

Table 31.2 Neuropathologic Features of Neonatal Bacterial Meningitis

Acute[a]	Chronic
Arachnoiditis	Cerebral cortical atrophy
Cerebral edema	Developmental defects
Cerebral abscess	Hydrocephalus
Encephalopathy	Multicystic encephalomalacia
Infarction	Organizational defects
Vasculitis	Subdural effusion
Ventriculitis	White matter atrophy

[a] May be visible on ultrasonography [74].

Cytokines and Chemokines

In recent years, there has been an increased awareness that outcome may be related to circulating humoral factors as well as direct bacterial invasion of the meninges [56]. These humoral factors are called *cytokines* and *chemokines*. Levels of the proinflammatory cytokines interleukin 1β and tumor necrosis factor α (cachectin) were detected in the CSF of most neonates with gram-negative bacterial meningitis, and peak concentrations of interleukin-1β correlated with outcome. While some cytokines may produce adverse effects, others have been shown to have beneficial effects (e.g., interleukin 10, which is an anti-inflammatory cytokine) and could prove useful as adjunctive therapy [56].

Blood-Brain Barrier

Another factor that normally plays a role in protection against the spread of bacterial infection is the blood-brain barrier. The permeability of the blood-brain barrier has been shown to increase in stressed neonates and those with bacterial meningitis compared with "healthy" infants or neonates with aseptic meningitis [57]. The brain is normally protected from undesirable fluctuations of humoral factors by the blood-CSF-brain barrier, which primarily exists at the arachnoid membranes, the choroid plexus, and the endothelial cells of brain capillaries. The endothelial cells produce continuous tight junctions in the walls of capillaries, which act as the barrier but can be disrupted by hyperosmotic solutions.

The ability of lipopolysaccharide derived from *E. coli* O111 B4 to disrupt the blood-brain barrier has been shown in newborn piglets during experimental neonatal meningitis [58]. Disruption was demonstrated by leakage of sodium fluorescein from blood vessels within about 1 hour of intracisternal injection of lipopolysaccharide. *E. coli* was chosen because this organism remains a frequent cause of meningitis in human newborns. The authors postulated that "the products of Gram-negative organisms could adhere to the adventitial surface of cerebral capillaries, resulting directly in separation of the tight junctions between endothelial cells and a marked increase in pinocytotic

activity within the endothelium" [58]. This model could prove useful for studying both pathogenesis of neonatal meningitis and its therapy.

Disruption of the blood-brain barrier with exudation of albumin across the leaky junctions may lead to cerebral edema, with increased intracranial pressure and altered cerebral blood flow. These, in turn, can produce cranial nerve injury, seizures, and hypoxic-ischemic injury.

There is also evidence to suggest that genetic factors may contribute to bacterial penetration of the blood-brain barrier. This transcellular penetration (transcytosis) has been demonstrated for GBS, *E. coli* K1, *L. monocytogenes, C. freundii*, and *S. pneumoniae* [59].

Diagnosis

Clinical Features

Bell and McGuinness have noted that there were only occasional publications on neonatal bacterial meningitis in the first half of the twentieth century [55], with authors stressing the rareness of the condition and the difficulty of clinical diagnosis until the advanced stages were reached. However, during the second half of the twentieth century, many cases were encountered and diagnosed, probably as a result of increased awareness, and there was a voluminous literature on the subject. Now, in the twenty-first century, the condition is becoming relatively rare again, but the clinical features that initiate investigation for sepsis continue to be those that should also raise the possibility of meningitis. These clinical manifestations include lethargy, abdominal distension, respiratory distress, temperature instability, irritability, apnea, and cyanotic spells [26,60]. When these features cannot be explained by other diagnoses, it is important to evaluate the baby for infection, including a lumbar puncture to obtain CSF.

Late signs of bacterial meningitis are a bulging anterior fontanel and seizures, although in some reports seizures were surprisingly common [26,28,29]. Nuchal rigidity is almost never seen in neonates [29]. If investigation for meningitis is not performed until these late signs are seen, serious mortality and morbidity are likely to result [30]. Unfortunately, in many cases of later onset, this is the situation that prevails.

Cerebrospinal Fluid

In contrast to older infants and children, CSF obtained early in the course of meningitis may not demonstrate specific cellular changes in neonates. The interpretation of CSF changes is compounded by the presence of up to 25–30 white blood cells per cubic millimeter (WBCs/mm^3) in neonates without infection (Table 31.3) and by the difficulties in obtaining CSF uncontaminated with blood. In one study, 21 samples from 39 neonates with meningitis on CSF culture could be evaluated with cell counts. Only 12 of 21 had more than 25 WBCs/mm^3, illustrating the importance of sending the fluid for culture in every case where lumbar puncture is performed. It also illustrates that when infection is suspected, antibiotics should be initiated promptly after specimens for culture have been sent. Decisions about discontinuing antibiotics can be made 48–72 hours later.

Table 31.3 Findings in the CSF of Noninfected Term Neonates

Features	Bonadio et al. [123]	Ahmed et al. [124]
Number of infants	35	108
Age at evaluation	0–4 weeks	0–30 days
White blood cells		
Mean	11/mm^3 (11 × 10^6/L)	7.3/mm^3 (7.3 × 10^6/L)
Range	0–35/mm^3 (0–35 × 10^6/L)	0–130/mm^3 (0–130 × 10^6/L) (only 3 with > 20/mm^3)
Protein, mean	84 mg/dL (0.84 g/L)	64 mg/dL (0.64 g/L)
Glucose, mean	47 mg/dL (2.6 mmol/L)	51 mg/dL (2.8 mmol/L)

Culture of CSF remains the "gold standard" as far as diagnosis of bacterial meningitis in the neonate is concerned. Higher WBC counts may be seen with gram-negative rods than with gram-positive cocci, although CSF protein and glucose usually are not different [61]. As just mentioned, it is possible to have a lack of pleocytosis but to have a positive culture (presumably early in the course of the illness). One study showed that 10% of infants with meningitis had less than 4 WBCs/mm^3 in the CSF, leading to the suggestion that no single value in the CSF can reliably exclude the presence of meningitis in the neonate [62]. For this reason, CSF should always be sent for culture. A case has also been made for

repeating lumbar punctures when bacteremia is documented because pleocytosis developed in several infants whose CSF was initially normal [63]. In cases of meningitis that grow gram-negative organisms, it is common for the CSF to remain culture positive for several days [26]. This seems to be less true with gram-positive organisms, but whenever persistently positive cultures occur, ventriculitis may be present.

The technique of performing a lumbar puncture (or spinal tap) is important. Care needs to be taken to avoid excessive flexion of the trunk or neck because this may produce hypoxemia. Although intuitively local anesthesia might seem to lessen physiologic instability, this was not observed in a controlled trial [64]. However, it seems important to use needles with stylets because needles without stylets carry the risk of introducing epithelial cells into the spinal canal, with subsequent development of epidermoid tumors [65]. Short needles for this purpose are available, and they allow considerable stability during manipulation.

Examination of CSF microscopically may reveal a specific organism more rapidly than waiting for culture. In one large cooperative study, smear with Gram's stain correctly identified 80% of organisms prior to culture results [66].

Although it was suggested in older children that CSF C-reactive protein (CRP) levels might help to make a rapid diagnosis of bacterial meningitis, CRP in CSF was not shown to be helpful in neonates [67].

It is also possible to detect bacterial antigen in CSF using either countercurrent immunoelectrophoresis or latex particle agglutination (LPA). The latter is quicker and simpler and has proved quite useful in type III GBS meningitis. Although there is an LPA test for *E. coli* K1 antigen, which cross-reacts with *Neisseria meningitidis* group B, this has not been shown to be particularly reliable or useful.

Other Laboratory Evaluations

One possible approach to diagnosis is to evaluate pregnant mothers who are at potential risk for infection. Rather than relying on bacterial culture results, which may take 24–48 hours to return, rapid evaluation for both GBS and *E. coli* has been documented using polymerase chain reaction (PCR) to screen for maternal colonization. Sensitivity was 97% for GBS and 71% for *E. coli* K1 antigen [67a].

Additional help in evaluating infants with suspected sepsis and/or meningitis comes from blood leukocyte counts and CRP measurements. As with any severe infection, total leukocyte counts are frequently low (below 5.0×10^9/L), with increased ratios of immature to total neutrophils [68]. Important observations on the usefulness of serum CRP determinations in bacterial meningitis were published over 40 years ago [69]. The most uniform pattern of high serum CRP values in neonates was seen with cases of *E. coli* meningitis. Marked increases in serum CRP were noted in four cases of neonatal meningitis reported by Sabel and Wadsworth, with three cases seen on the first day after delivery [70]. Although serum CRP may not always be elevated at the initial evaluation for suspected sepsis/meningitis [68,71], it increases reliably in cases of meningitis, sometimes to very high levels, within 24–48 hours [68,72]. Pourcyrous et al. documented increased levels of CRP in 11 of 13 (85%) neonates with meningitis at initial evaluation [71]. By 12 hours later, all 13 had elevated levels. Consequently, CRP determinations may be particularly helpful if a decision has been made to defer performing a lumbar puncture in an unstable infant. If the serum CRP remains normal, meningitis is virtually eliminated, but if it increases substantially (above 4 mg/dL), lumbar puncture should be performed. This number proved useful in infants over 2 months of age who had been ill for more than 12 hours and had fever [73]. When CRP was less than 2 mg/dL, all had confirmed or probable viral infection, whereas above 4 mg/dL, 79% had bacterial infection [73].

Imaging Studies

The most useful technique for imaging the brain in cases of bacterial meningitis is probably ultrasonography. This is so because it can be accomplished at the bedside (through the anterior fontanel), and considerable experience has accumulated with this technique in the last 30 years [74,75]. In recent years, magnetic resonance imaging (MRI) has proved valuable. In particular, diffusion tensor imaging (DTI) has documented meningeal inflammation by revealing increased fractional anisotropy in cases of neonatal bacterial meningitis, which decreased with antibiotic treatment [76]. Computed tomography may also provide better delineation than ultrasonography [22]. Most recently, MRI has documented cerebrovascular complications in late-onset GBS meningitis in the form of either arterial ischemic stroke or cerebral vasculopathy [76a].

In a series of infants from Toronto, a constellation of abnormalities was documented by ultrasonography

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in the great majority (25/34) with pyogenic meningitis [74]. Abnormalities included ventriculomegaly, echogenic sulci, subdural effusion, ventriculitis, infarction, cerebritis, cerebral edema, and porencephalic cysts [74].

As noted earlier, brain abscess (or abscesses) may be seen more commonly in association with meningitis due to *C. diversus*, and imaging studies are particularly valuable in this context [48].

Antibody to Common Bacteria

Susceptibility to infection is related to the presence (or absence) of antibody. This has been most strikingly demonstrated with regard to GBS infection. Vogel et al. documented the lack of serospecific antibody in neonates who acquired GBS infection [77]. The increased susceptibility of VLBW infants is probably related (in part) to decreased transfer of antibody from mother to baby because transfer of immunoglobulin G (IgG) occurs predominantly after 32 weeks' gestation [78]. Only IgG usually traverses the placenta. Transfer of IgG seems to be by an active rather than passive process.

Because meningitis is a serious infection, it would be suspected that survivors would have a significant antibody response. It is therefore interesting to learn that the patterns of response in survivors of type III GBS meningitis were quite variable [79]. In 5 of 10 infants, specific immunoglobulin M antibody failed to develop at a mean of 3.8 weeks after diagnosis, increased after another 4–8 weeks, and declined to baseline again another 2–4 months later. This inability to sustain an antibody response is akin to the comparatively low response of mothers to unconjugated GBS vaccine [80].

The prominence of *E. coli* in neonatal infection has been attributed to the fact that antibody to this and other gram-negative organisms is predominantly found in the immunoglobulin M fraction, which does not cross the placenta. However, it has been documented that selective transport of anti–*E. coli* antibody in the IgG fraction can provide some protection, even in very preterm infants [81].

Complications

Several acute complications have been reported in association with bacterial meningitis in neonates. The most frequently reported are ventriculitis, hydrocephalus, and cerebral abscess, but more recently, cerebral infarction has been noted in infants with meningitis [82]. Although frequently recognized in older infants, very few cases of inappropriate secretion of antidiuretic hormone have been documented in neonates. Diabetes insipidus has been associated with GBS sepsis/meningitis and was presumed to be related to brain edema, inflammation, and vasculitis leading to infarction [83]. In a few instances, the inflammatory process and ischemic change may lead to liquefaction of the brain. The author has encountered three such cases, one with GBS and one each with *S. pneumoniae* and *E. coli* (unpublished) [68].

Because ventriculitis was so commonly encountered with gram-negative organisms, the first Neonatal Meningitis Cooperative Study Group used intrathecal antibiotics and the second used intraventricular gentamicin [66,84]. The results of these interventions were no better (and possibly worse) than intravenous antibiotics alone, so intrathecal or intraventricular therapy is not considered necessary or particularly beneficial. It may be possible to detect ventriculitis using cephalic ultrasound [75].

Hydrocephalus seems to be the result of outflow obstruction secondary to high CSF protein levels. Earlier treatment may possibly minimize this problem, but when it develops (possibly in one-third), it usually requires ventriculoperitoneal shunt repair.

As noted earlier, cerebral abscesses seem to be particularly common in association with neonatal meningitis caused by *C. diversus* [48]. The diagnosis has become easier to make because of newer imaging techniques. Cranial ultrasonography in particular allows the imaging to be performed at the bedside, although MRI may provide better images. Other organisms that have been associated with neonatal brain abscesses are *Proteus* and *Enterobacter* spp. In one series, among 30 cases of brain abscess, 27 were caused by *Proteus* spp. infections [85]. Many of them were enormous and easily detected with ultrasonography or computed tomographic scans. In only 20 cases did meningitis precede the brain abscess. *Enterobacter sakazakii* also has been reported to produce brain abscess because it seems to have neurotropic qualities [86].

Ment et al. performed cranial computed tomographic scans on all eight neonates with bacterial meningitis admitted during a 36-month period [82]. Six had large areas of infarction related to major arterial vascular distributions. The authors suggested that computed tomographic scans be done on all neonates with bacterial meningitis, although MRI

may now be considered. Long-term complications (such as deafness) are discussed in the subsection on neurologic sequelae in the "Outcome" section below.

Treatment and Management

Although antibiotic therapy is often referred to as *specific treatment*, it should be remembered that antibiotics are used to suppress bacterial growth so that the baby's defense mechanisms have time to respond. There are many instances where appropriate antibiotic therapy is used with a sensitive organism, but the baby with sepsis and/or meningitis has been overwhelmed by the infection and died. Nevertheless, the judicious use of antibiotics may minimize the emergence of resistant organisms [87].

In addition, as mentioned earlier, there may be other humoral factors (e.g., cytokines) that produce undesirable effects. With gram-negative enteric organisms there is frequently release of endotoxin, and with GBS, "endotoxin-like effects" have been described [56]. The presence of endotoxin was found in the CSF of all infants with gram-negative bacterial meningitis who died but was also frequently found in those with an abnormal or normal outcome [88].

Thus, although antibiotic therapy is very important for the eradication of bacteria, other adjunctive measures may be almost as important in determining survival and in minimizing the long-term sequelae. The two major supportive measures that are used are assisted ventilation (for infants who develop respiratory failure) and cardiovascular support. It is common with severe infections to have shock, and the use of volume (colloid or crystalloid) replacement, as well as pressor agents (e.g., dopamine) to support blood pressure may be lifesaving. It is also important to recognize (and aggressively treat) seizure activity. In this situation, assisted ventilation may be particularly valuable, and there may be benefits from moderate hyperventilation, which may decrease increased intracranial pressure. Extreme hypocarbia (PCO_2 < 20 mmHg) may substantially decrease cerebral blood flow and probably should be avoided.

Choice of Antibiotics

The recommendations made by an American Academy of Pediatrics Task Force regarding antibiotic therapy for neonatal meningitis still seem to be valid [1]. Initial antibiotic therapy in the first week after birth seems to be fairly well agreed on in most developed countries and consists of ampicillin and an aminoglycoside (usually gentamicin). This combination has stood the test of time (somewhat remarkably) and seems to be effective for the most common etiologic bacteria [88a], although this may be changing, and the combination of ampicillin and cefotaxime has been suggested [88,89]. In a retrospective review from Sweden covering the years 1975–86, of the 365 pathogens isolated from blood and/or CSF, 91% were sensitive to either ampicillin or aminoglycosides or both [90]. Treatment failed in 6 of 34 patients with neonatal meningitis, but the failure was not related to ampicillin or aminoglycoside resistance [90]. Ampicillin resistance occurred most frequently with late-onset infections in VLBW and low-birthweight infants. Currently, initial antibiotic therapy after the first week usually includes antistaphylococcal coverage in such infants.

It is often stated that aminoglycosides do not penetrate well into CSF, but in the presence of inflamed meninges, the penetration may be better. Certainly intrathecal administration combined with intravenous gentamicin seemed to offer no advantage over intravenous therapy alone [66]. Nevertheless, one disadvantage of aminoglycosides is that levels may need to be monitored to avoid toxicity, although data about nephrotoxicity and ototoxicity in neonates are limited. Much of what is written concerns potentially toxic concentrations rather than documented permanent sequelae [91].

While there seems to be reasonable unanimity of opinion about ampicillin-aminoglycoside in the first week after birth, this is not the case beyond that age. Another Swedish study has documented (in infants up to 1 year of age) that ampicillin plus gentamicin is inadequate empirical therapy for meningitis [92]. The combination of ampicillin and ceftazidime has proved superior, and cefotaxime has also shown more effective coverage [89]. However, when cefotaxime is incorporated into empirical therapy, it has been shown to increase bacterial resistance [93].

In older infants and children, both cefuroxime and ceftriaxone proved efficacious, with ceftriaxone perhaps superior [94]. However, the prolonged excretion time for ceftriaxone makes it difficult to know what should be its dosing frequency in the neonate.

Prior to the introduction of the cephalosporins, another antibiotic that was deemed to be of considerable value was chloramphenicol. In contrast to the cephalosporins, use of chloramphenicol necessitates the determination of levels to accomplish therapeutic but nontoxic effect [95]. This is certainly a disadvantage but does not

Table 31.4 Antibiotics Commonly Used in Neonatal Meningitis and Their Dosage[a]

Antibiotic	<1 week	>1 week	Frequency
Penicillin G	100,000 units	200,000 units	b.i.d./q.i.d.
Ampicillin	200 mg	300 mg	b.i.d./q.i.d.
Gentamicin[b]	4-mg load, then	3 mg	Daily
Cefotaxime	100 mg	150 mg	b.i.d./t.i.d.
Vancomycin[b]	30 mg	45 mg	b.i.d./t.i.d.
Chloramphenicol[b]	25 mg	50 mg	Daily/b.i.d.
Nafcillin	50 mg	100 mg	b.i.d./q.i.d.

[a] All as per kilogram per day.
[b] Serum levels need to be monitored.

exclude chloramphenicol from the therapeutic armamentarium, if sensitivities suggest that it may be the antibiotic of choice. In addition, chloramphenicol is comparatively inexpensive, especially when compared with the cephalosporins. Although frequently used in England and Wales in the mid-1980s, chloramphenicol use there decreased from 50% to less than 5% in the late 1990s [30]. The cost factor may make chloramphenicol particularly valuable in developing countries.

With late-onset infection in VLBW infants, there is the strong possibility of staphylococcal infection. There are now many methicillin-resistant strains of *S. aureus*, and most hospital-acquired strains of *S. epidermidis* are resistant to the penicillins. With these organisms, it may be possible to use nafcillin or oxacillin [88], but it is frequently necessary to use vancomycin, and in sick infants beyond the first week it is probably wise to initiate antibiotic treatment with vancomycin and a cephalosporin, although few data are available concerning their use in neonatal meningitis [96]. Vancomycin levels need to be monitored.

Because there is considerable variation from one country to another (and even within countries), it is important to keep track locally of the most frequent organisms causing sepsis and meningitis and to know local antibiotic sensitivities. The more frequently used antibiotics are displayed in Table 31.4. Successful treatment of gram-negative bacterial meningitis in term neonates was reported quite recently using cefotaxime and amikacin [29].

Special mention was made earlier of *C. diversus* and its propensity to lead to brain abscesses. One report describes the poor response to third-generation cephalosporins, aminoglycosides, and trimethoprim-sulfamethoxazole but the successful treatment of *C. diversus* meningitis complicated by brain abscesses using imipenem-cilastatin [97]. However, a favorable outcome has been reported with protracted courses of more traditional antibiotics [98].

Duration of Antibiotics

Since there is reasonable consensus regarding which antibiotics to use in the first week, one might imagine that duration of therapy would also be agreed on. Unfortunately, although many authors have firm opinions about duration of therapy for neonatal bacterial meningitis, there are very few data on which to base those opinions. In older infants and children, there has been a reevaluation of the duration of therapy for sepsis/meningitis. In particular, the "7–10–14-day rule" has been called in question [99]. To quote Radetsky, "The numerology of infectious disease has never been investigated. Even in the absence of specific data certain numbers have an unaccountable power to satisfy and reassure, and they are the numbers that are preferentially chosen. For the duration of antimicrobial therapy 7, 10, 14 and 21 days have consistently appeared . . . The numbers 7, 10 and 14 are enshrined in the treatment recommendations for meningitis in all current textbooks" [99].

In older infants and children, serum CRP levels have been shown to be helpful in following the course of illness. Peltola et al. in Finland documented that in uncomplicated cases of bacterial meningitis, CRP levels returned to normal within 7 days. Secondary elevations of CRP may indicate complications such as subdural

effusion [100]. Further experience from Peltola's group documented the value of CRP in helping to determine the duration of antibiotic therapy. Although the mean duration was 10 days, it varied from 5.5 to 34 days, and antibiotic therapy was not discontinued unless CRP values had normalized [100].

The ability of serum CRP to distinguish complicated cases from uncomplicated cases of bacterial meningitis in infants and children was also reported from France [101]. The authors were able to shorten the duration of antibiotic therapy in the majority of these children to 4–5 days for 21 of 24 with meningococcal meningitis and to 7 days for 16 of 22 with *H. influenzae* meningitis and 4 of 6 with pneumococcal meningitis without an increase in neurologic sequelae.

Data in neonates are quite limited, but in the early experience of Sabel and Hanson, relapse of meningitis was only encountered (in three cases) when the CRP remained elevated at the time of discontinuance of antibiotics [69]. In my reported experience and unpublished observations, serum CRP was elevated in neonatal meningitis for a minimum of 5 days and not infrequently for more than 10 days [67]. It therefore seems reasonable to discontinue antibiotics within 2–3 days of the CRP level returning to normal (<1.0 mg/dL or 10 mg/L). Saez-Llorens and McCracken have supported this position [88]. While acknowledging traditional and commonly recommended durations of therapy (quite prolonged), their recommendation was that "duration of antibiotics should be individualized, on the basis of clinical, laboratory and bacteriologic responses. Normalization of the acute-phase reaction (i.e. ESR [erythrocyte sedimentation rate] and CRP) can be considered one index for when antimicrobial therapy could be safely stopped" [88]. It is interesting to note that a recent randomized, controlled trial showed that a 10-day course of antibiotics was as effective as a 14-day course in treating neonatal bacterial meningitis [101a].

Peak levels of CRP with neonatal meningitis are frequently in excess of 10 mg/dL (100 mg/L) and almost always greater than 7.0 mg/dL [68–70]. It is not completely clear whether extremely high levels of CRP (e.g., >20 mg/dL) can predict an adverse neurologic outcome, although limited experience suggests this [68].

Corticosteroids

The role of corticosteroids in the management of neonatal meningitis is not well defined. Even in infants and children, the benefits of dexamethasone are debated. The arguments for and against have been summarized by Prober [102]. It seems reasonably clear that dexamethasone administered before antibiotics are given is beneficial in meningitis due to *H. influenzae* type b, but the picture is not clear with other organisms, particularly when dexamethasone is given after antibiotics have been started. The rationale for use of corticosteroids is to decrease meningeal inflammation and swelling and to decrease concentrations of potentially harmful cytokines. To date, there is limited experience in neonates. Daoud et al. in Jordan performed a randomized, controlled trial of dexamethasone use in 52 cases of neonatal bacterial meningitis, the majority being due to *Klebsiella pneumoniae*, and showed no benefit [103]. Of 27 in the dexamethasone group, 6 died and 6 had permanent neurologic deficit. The control group had 25 neonates, with 7 deaths and 7 neurologically impaired [103]. Further analysis of the subject, in a Cochrane systematic review, indicates that corticosteroids *may* reduce deaths and hearing loss, although the data may be of "low quality" [103a].

Other Anti-inflammatory Therapy

While there are limited data concerning corticosteroids in neonates, even less is known about most other anti-inflammatory agents that could be used in human bacterial meningitis. Various animal studies have dealt with indomethacin, anti-cytokine antibodies or inhibitors, anti-endothelium leukocyte adhesion agents, and so on [88].

Outcome

Case-Fatality Rate

It was mentioned in the Introduction that case-fatality (mortality) rates are high in almost every series dealing with neonatal bacterial meningitis, although recent experience provides a more optimistic view [28–30]. The national studies from the Netherlands, England and Wales in the 1980s, and Australia had case-fatality rates of 27%, 20%, and 26%, respectively, and more recent experience from Dallas documented a case-fatality rate of 17% [8,9,11,26]. My own limited experience in Maine in the late 1980s and early 1990s, with 18 cases, was associated with a case-fatality rate of 25% within 1 week of diagnosis and 28% if one late death (5 months later, following cerebral infarction) was included [3]. Age at diagnosis may also be

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important, with higher case-fatality rates at younger ages. Mulder et al. documented case-fatality rates of 77% at 0–2 days, 28% at 3–6 days, and 15% at 7–27 days in cases of neonatal meningitis caused by *E. coli* [43]. Different rates may also be seen with different strains of *E. coli*. The *E. coli* K1 strains produced a 31% case-fatality rate in one study versus 0% with non-K1 strains [104]. In addition, case-fatality rates are usually higher in VLBW infants and those with a high CSF protein level [13,24,27].

More recently, data from England and Wales documented a case-fatality rate in 1996–7 of only 8% [9,30], which was duplicated in the United Kingdom and Ireland for the years 2010–11 [14a]. Experience in Toronto, Canada, 1979–98 revealed a case-fatality rate of 13%, and in Athens, Greece, the rate was only 3% for gram-negative bacterial meningitis in term infants during the period 1983–97 [28,29]. These data are summarized in Table 31.5.

Neurologic Sequelae

The high percentage of major neurologic sequelae in survivors was emphasized in a series of papers in the mid-1980s dealing with GBS meningitis [27]. With case-fatality rates varying between 26% and 38%, major neurologic sequelae were found in 15–29% of the survivors (Table 31.6). Edwards et al. summarized the long-term sequelae of several groups reporting on GBS meningitis [27]. Of a total of 218, the case-fatality rate was 26%, and of the 152 survivors, 17% had major neurodevelopmental sequelae, 16% had mild/moderate sequelae, and 67% were considered normal. More recent experience is quite similar [9,28]. The most recent results, from the twenty-first century, indicate a case-fatality rate of 5.7% but major neurologic sequelae in 22% of 50 survivors of GBS meningitis at hospital discharge [104a]. This percentage may have increased on later follow-up.

In their review in 1982, Bell and McGuinness noted that sequelae had been reported in 31–56% of survivors in different reports [55]. Almost identical figures were reported from Stockholm, Sweden, for 5-year periods from 1969 to 1983, with sequelae from neonatal meningitis noted in 31–53% of survivors and case-fatality rates of 23–35% [105]. The highest rate of sequelae accompanied the lowest case-fatality rate. Data from England and Wales documented a decrease in acute mortality to 6.6% in 1996–7, but serious disability remained at 23% [9].

The most common severe sequelae include "hydrocephalus, seizures, mental retardation, hyperactivity and cranial nerve or long tract signs. Localized deficits include hearing loss, optic atrophy and hypothalamic injury manifested by endocrine deficiencies, diabetes insipidus, precocious puberty or abnormalities of temperature regulation" [55]. In addition, spastic paresis (hemiplegia or quadriplegia) is frequently mentioned [27,106].

In the large experience with gram-negative enteric bacillary meningitis reported by Unhanand et al., hydrocephalus, seizure disorder, cerebral palsy, developmental delay, and hearing loss were seen in 28%, 28%, 19%, 25%, and 16%, respectively, in 32 term infants and 36%, 36%, 45%, 55%, and 18%, respectively, in 11 preterm infants who survived [26]. However, more recently, Dellagrammaticas et al. reported in term babies both a high survival rate and a low incidence of sequelae, with persisting seizures, spastic paralysis, developmental delay, and hearing deficit in 4%, 3%, 4%, and 6%, respectively [29]. Delay in achieving sterile CSF may increase the frequency of sequelae [29].

Table 31.7 shows the factors that are associated with poor outcome in bacterial meningitis. Clinical manifestations on admission that were predictive of a poor outcome (death or severe impairment) in the study of Edwards et al. were presence of coma or semicoma, decreased perfusion, total peripheral WBC count $< 5.0 \times 10^9$/L, absolute neutrophil count $< 1.0 + 10^9$/L, or CSF protein > 3 g/L [27]. The study by Klinger et al. showed that the best predictors of an adverse outcome were quite similar [28]. Both at 12 hours and at 96 hours after admission, seizures, coma, use of inotropes to maintain blood pressure, and leukopenia ($<5.0 \times 10^9$/L) were predictive of a poor outcome. Of 101 infants (born in the years 1979–98) with bacterial meningitis, 13 died, and 17 others had moderate to severe disability at 1 year of age [23]. Among 50 infants with GBS meningitis, 15 (30%) had an adverse outcome.

Although not routinely obtained in neonatal meningitis, an additional predictor of outcome is the neonatal electroencephalogram (EEG). When interpretation is normal or only mildly abnormal, the outcome is usually good. An adverse outcome has been associated with moderate to marked abnormality. Repeating the EEG may improve the accuracy of prediction [107].

Klein et al. suggested that a cautiously optimistic note be struck with parents when discussing the long-term complications of meningitis because "there is a

Table 31.5 Outcome in Neonatal Bacterial Meningitis

Authors	Country	Year	Number	Case- fatality rate (%)	Neurologic sequelae (%)[a]	Predominant bacteria
Mulder and Zanen 1984 [8]	Netherlands	1976–82	380	27	N/A	*E. coli*
Bennet et al. 1989 [105]	Sweden (Stockholm)	1969–83	60	28	40	*S. aureus*[b]
DeLouvois et al. 2005 [9]	England and Wales	1985–7	280	25	20	GBS, *E. coli*
Francis and Gilbert 1992 [11]	Australia	1987–9	116	26	23	GBS, *E. coli*
Unhanand et al. 1993 [26]	United States (Dallas)	1969–89	98	17	61	*E. coli*
Daoud et al. 1996 [32]	Jordan	1992–4	53	32	39	*K. pneumoniae*
Klinger et al. 2000 [28]	Canada (Toronto)	1979–98	101	13	26	GBS
Dellagrammaticas et al. 2000 [29]	Greece (Athens)	1983–97	72	3	8	*E. coli*
De Louvois et al. 2005 [9]	England and Wales	1996–7	166	7	23	GBS

Note: N/A, not available; GBS, group B β-hemolytic *Streptococcus*.

[a] Percent of survivors.

[b] Cases of sepsis, N/A for meningitis.

Table 31.6 Outcome in Infants with Group B β-Hemolytic *Streptococcus* (GBS) Meningitis

Authors	Age at diagnosis	Case-fatality rate (%)	Number of survivors	Major neurologic sequelae[a]	Age at follow-up
Edwards et al. [27]	0–3 months	38	38	11 (29%)	3.3–9.0 years
Harvey et al. [30]	0–28 days	25	65	12 (18%)	5 years
Klinger et al. [28]	1–28 days	13[b]	50	15 (30%)	1–19 years
Levent et al. [104a]	0–28 days	5.7	50	11 (22%)	Hospital discharge

[a] Percentages of survivors.

[b] Based on all cases, not just GBS.

Table 31.7 Factors Associated with Poor Outcome in Neonatal Bacterial Meningitis

Very low birth weight (<1,500 g)
Coma (or semicoma)
Decreased perfusion
Need for inotropes to maintain blood pressure
Seizures (>12 hours' duration)
Peripheral WBC count < 5,000/mm^3 (<5.0 × 10^9/L)
Absolute neutrophil count < 1,000/mm^3 (<1.0 + 10^9/L)
CSF protein > 300 mg/dL (>3 g/L)
Delay in achieving sterile CSF
Abnormal EEG reading (moderate to severe)

tendency for even major neurologic defects to resolve unpredictably with time" [1].

Prevention

Before discussing the potential for preventing specific kinds of meningitis, it should be remembered that general infection control measures (especially careful hand washing) may be particularly important in preventing the spread of infection. Attempts to prevent neonatal bacterial meningitis have largely dealt with those organisms that are frequently implicated. Two major strategies have been employed. The first is chemoprophylaxis, and the second is immunoprophylaxis. Both strategies have been used to prevent neonatal sepsis and meningitis rather than specifically preventing meningitis. In keeping with the important role it plays in many countries, GBS infection has received the most attention.

Neonatal Approach

Both chemo- and immunoprophylaxis have been evaluated from the maternal or neonatal approach. While there has been some success using the maternal approach, using only the neonatal approach has been contradictory or disappointing. For instance, prophylactic administration of penicillin to neonates seemed to be beneficial in reducing GBS infection in some centers but not in others [108,109]. There was also the possibility that one problem (early-onset GBS infection) might be exchanged for another (late-onset GBS or gram-negative bacterial infection). Similarly, the use of prophylactic intravenous immunoglobulin in VLBW infants seemed beneficial in one large (n = 588) study but not in an even larger (n = 2,416) study [110,111]. Different preparations were used in the two studies, which may explain the differences. Another large study (n = 753) using the same preparation as that of Fanaroff et al. also failed to find a protective effect in early- or late-onset infection [111,112]. It has been documented that considerable variability of availability of specific antibody to the common pathogens occurs within different lots of immunoglobulin [113]. Greater success seems likely if preparations with species-specific antibody can be administered.

Maternal Approach

The use of maternal chemoprophylaxis has proved to be much more striking. In the study by Boyer and Gotoff, bacteremia was seen in none of 85 babies born to ampicillin-treated women versus 5 of 79 babies born to untreated mothers [114]. Although this strategy does not prevent transmission of infection in all

cases, in the early 1990s a consensus developed that women at high risk (rupture of membranes > 18 hours, preterm labor, or maternal fever possibly caused by choriamnionitis) should be screened and treated [115].

This led to the publication by the Centers for Disease Control and Prevention (CDC) in 1996 of new guidelines for the prevention of GBS infection, which resulted in a substantial change in obstetric practice in North America, with approximately 25% of women receiving intrapartum antibiotics (penicillin or ampicillin) [116]. This resulted in a marked decrease in the incidence of early-onset GBS infection, with a 65% decrease from 1.7/1,000 live births in 1993 to 0.6/1,000 live births in 1998. Only 6% with early-onset GBS infection had meningitis [117]. This contrasts with a study from Finland, where 17% had meningitis in 1985–94 [118]. After changing the strategy in the United States to concentrate on routine maternal screening (the "era of widespread intrapartum chemoprophylaxis" mentioned earlier) [13], there has been a further reduction to 0.37/1,000 live births [119]. Other countries have also adopted a more aggressive approach to prevention of GBS infection. Using a risk-based strategy in the Netherlands, early-onset GBS sepsis declined, but the incidence of GBS meningitis did not [7]. To date, this increased use of intrapartum antibiotics has not changed antibiotic sensitivity patterns substantially, although it has created some difficulty in deciding which neonates should be treated after delivery [120].

With regard to maternal immunoprophylaxis, there is variable enthusiasm. While intuitively it would seem that this might be the most effective strategy, there are several possible drawbacks. One significant disadvantage is that because transfer of antibody from mother to infant occurs primarily after 32 weeks' gestation, the group of infants at greatest risk might not be protected. Another disadvantage (to date) is that the response of women to a polysaccharide vaccine of GBS has been disappointing [80]. Of 35 women with low or unprotected antibody levels before immunization, only 20 (57%) responded to the vaccine in a study published in 1988 [80]. This study used type III capsular polysaccharide vaccine. While it is true that this serotype accounts for the majority of cases of neonatal meningitis, it would be preferable to have a polyvalent vaccine with increased immunogenicity. The many problems in finding and distributing a suitable vaccine have been discussed [121]. One approach that has shown promise is to increase the immunogenicity of vaccines by conjugating (coupling) them to tetanus toxoid or other agents. Polyvalent conjugate vaccines for GBS infection have been tested, show promise with several different strains, and may soon be available commercially [122]. The protective effect of maternal antibody has been further demonstrated by Baker et al. [122a]. For GBS types Ia and III, maternal antibody concentrations over 0.5 μg/mL produced a risk reduction of 90% and risk reduction of 70% with type V [122a]. The authors previously showed a response to two different types of type V glycoconjugate of 6.5 and 8.9 μg/mL 4 weks after immunization and even higher responses with GBS types Ia and III glycoconjugate vaccines [122a]. For other organisms, particularly *E. coli*, the ability to provide protection by maternal immunization seems a daunting prospect.

Conclusion

Despite the fact that the incidence of neonatal bacterial meningitis may be falling, there is little room for complacency. This is a disease with high case-fatality rates, although these have fallen in some recent reports, and very high morbidity rates. The neurologic sequelae can be quite devastating in some cases, and a completely normal outcome can be anticipated in only half the survivors. It is therefore important to consider the possibility of sepsis/meningitis in any sick neonate so that treatment can be initiated as early as possible. However, prevention is even more desirable, and continued efforts in this direction must remain a high priority.

References

1. Klein JO, Feigin RD, McCracken GH. Report on the task force on diagnosis and management of meningitis. *Pediatrics* 1986; **78**: 959–82.
2. Philip AGS. *Neonatal Sepsis and Meningitis*. Boston: G. K. Hall, 1985: Appendix.
3. Philip AGS. The changing face of neonatal infection: experience at a regional medical center. *Pediatr Infect Dis J* 1994; **13**: 1098–102.
4. Greenberg D, Shinwell ES, Yagupsky P, et al. A prospective study of neonatal sepsis and meningitis in southern Israel. *Pediatr Infect Dis J* 1997; **16**: 768–73.

5. Moreno MT, Vargas S, Poveda R, et al. Neonatal sepsis and meningitis in a developing Latin American country. *Pediatr Infect Dis J* 1994; **13**: 516–20.
6. Laving AM, Musoke RN, Wasunno AO, et al. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. *East Afr Med J* 2003; **80**: 456–62.
7. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jonge PC, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. *Arch Dis Child Fetal Neonatal Ed* 2007; **92**: F271–6.
8. Mulder CJJ, Zanen HC. A study of 280 cases of neonatal meningitis in the Netherlands. *J Infect* 1984; **9**: 177–84.
9. De Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. *Eur J Pediatr* 2005; **164**: 730–4.
10. Isaacs D, Royle JA. Intrapartum antibiotics and early onset neonatal sepsis caused by group B *Streptococcus* and by other organisms in Australia. Australasian Study Group for Neonatal Infections. *Pediatr Infect Dis J* 1999; **18**: 524–8.
11. Francis BM, Gilbert GL. Survey of neonatal meningitis in Australia:1987–1989. *Med J Aust* 1992; **156**: 240–3.
12. Gordon A, Isaacs D. Late onset neonatal gram-negative bacillary infection in Australia and New Zealand, 1992–2002. *Pediatr Infect Dis J* 2006; **25**: 25–9.
13. Schrag SJ, Stoll BJ. Early-onset neonatal sepsis in the era of widespread intrapartum chemoprophylaxis. *Pediatr Infect Dis J* 2006; **25**: 939–40.
14. May M, Daley AJ, Donarth S, et al. Early onset neonatal meningitis in Australia and New Zealand, 1992–2002. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F324–7.

14a. Okike IO, Johnson AP, Henderson KL, et al. Incidence, etiology and outcome of bacterial meningitis in infants aged <90 days in the United Kingdom and the Republic of Ireland: prospective, enhanced national population-based surveillance. *Clin Infect Dis* 2014; **59**: e150–7.

14b. Darlow BA, Voss L, Lennon DR, Grimwood K. Early-onset neonatal group B *Streptococcus* sepsis following national risk-based prevention guidelines. *Austr NZ Obstet Gynaecol* 2016; **56**: 60–74.

15. Longe AC, Omene JA, Okolo AA. Neonatal meningitis in Nigerian infants. *Acta Paediatr Scand* 1984; **73**: 477–81.
16. Tessin I, Trollfors B, Thiringer K. Incidence and etiology of neonatal septicemia and meningitis in western Sweden 1975–1986. *Acta Paediatr Scand* 1990; **79**: 1023–30.
17. Hristeva L, Booy R, Bowler I, et al. Prospective surveillance of neonatal meningitis. *Arch Dis Child* 1993; **69**: 14–18.
18. Shiva F, Mosaffa N, Khabbaz R, et al. Lumbar puncture in neonates under and over 72 hours of age. *J Coll Phys Surg Pak* 2006; **16**: 525–8.
19. Weiss MG, Ionides SP, Anderson CL. Meningitis in premature infants with respiratory distress: role of admission lumbar puncture. *J Pediatr* 1991; **119**: 973–5.
20. Sanghvi KP, Tudehope DI. Neonatal bacterial sepsis in a neonatal intensive care unit: a 5 year analysis. *J Paediatr Child Health* 1996; **32**: 333–8.
21. Johnson CE, Whitwell JK, Pethe K, et al. Term newborns who are at risk for sepsis: are lumbar punctures necessary? *Pediatrics* 1997; **99**: E10.
22. Pong A, Bradley JS. Bacterial meningitis and the newborn infant. *Infect Dis Clin North Am* 1999; **13**: 711–33.
23. Albanyan EA, Baker CJ. Is lumbar puncture necessary to exclude meningitis in neonates and young infants: lessons from the group B *Streptococcus* cellulitis-adenitis syndrome. *Pediatrics* 1998; **102**: 985–6.

23a. Flidel-Rimon O, Leibovitz E, Eventor Friedman S, et al: Is lumbar puncture (LP) required in every work-up for suspected late-onset sepsis in neonates? *Acta Paediatr* 2011; **100**: 303–4.

24. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap:high likelihood of meningitis without sepsis among very low birth weight infants. *Pediatrics* 2004; **113**: 1181–6.
25. Franco SM, Cornelius VE, Andrews BF. Long-term outcome of neonatal meningitis. *Am J Dis Child* 1992; **146**: 567–71.
26. Unhanand M, Mustafa MM, McCracken GH Jr, et al. Gram-negative enteric bacillary meningitis: a twenty-one-year experience. *J Pediatr* 1993; **122**: 15–21.
27. Edwards MS, Rench MA, Haffar AAM, et al. Long-term sequelae of group B streptococcal meningitis in infants. *J Pediatr* 1985; **106**: 717–22.
28. Klinger G, Chin CN, Beyene J, et al. Predicting the outcome of neonatal bacterial meningitis. *Pediatrics* 2000; **106**: 477–82.
29. Dellagrammaticas HD, Christodoulou C, Megaloyanni E, et al. Treatment of gram-negative bacterial meningitis in term neonates with third generation cephalosporins plus amikacin. *Biol Neonate* 2000; **77**: 139–46.
30. Harvey D, Holt DE, Bedford H. Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. *Semin Perinatol* 1999; **23**: 218–25.

31. Chang CJ, Chang WN, Huang LT, et al. Neonatal bacterial meningitis in southern Taiwan. *Pediatr Neurol* 2003; **29**: 288–94.

32. Daoud AS, al-Sheyyab M, Abu-Ekteish F, et al. Neonatal meningitis in northern Jordan. *J Trop Pediatr* 1996; **42**: 267–70.

33. Molyneux E, Walsh A, Phiri A, et al. Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996–97. *Trop Med Int Health* 1998; **3**: 610–18.

33a. Kamoun F, Dowlut MB, Ameur SB, et al. Neonatal purulent meningitis in southern Tunisia: Epidemiology, bacteriology, risk factors and prognosis. *Fetal Pediatr Pathol* 2015; **34**: 233–40.

33b. Gaschignard J, Levy O, Olivier R, et al. Neonatal bacterial meningitis: 444 cases in 7 years. *Pediatr Infect Dis J* 2011; **30**: 212–17.

33c. Thigpen MC, Whitney CG, Massonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011; **364**: 2016–25.

34. Synnott MB, Morse DL, Hall SM. Neonatal meningitis in England and Wales: a review of routine national data. *Arch Dis Child* 1994; **71**: F75–80.

35. Gebremariam A. Neonatal meningitis in Addis Ababa: a 10 year review. *Ann Trop Paediatr* 1998; **18**: 279–83.

36. Berardi A, Lugli L, Baronciani D, et al. Group B streptococcal infections in a northern region of Italy. *Pediatrics* 2007; **120**: e487–93.

37. Mulder CJJ, Zanen HC. *Listeria monocytogenes* neonatal meningitis in the Netherlands. *Eur J Pediatr* 1986; **145**: 60–2.

38. Linnan MJ, Mascola L, Lou XD, et al. Epidemic listeriosis associated with Mexican-style cheese. *N Engl J Med* 1988; **319**: 823–8.

39. Zaki M, Daoud AS, al Saleh Q, et al. Bacterial meningitis in the newborn: a Kuwaiti experience. *J Trop Pediatr* 1990; **36**: 62–5.

40. Baker CJ. Group B streptococcal infections in neonates. *Pediatr Rev* 1979; **1**: 5–15.

41. Carstensen H, Henrichsen J, Jepsen OB. A national survey of severe group B streptococcal infections in neonates and young infants in Denmark, 1978–83. *Acta Paediatr Scand* 1985; **74**: 934–41.

41a. Joubrel C, Tazi A. Six A, et al. Group B *Streptococcus* neonatal invasive infections, France 2007–2012. *Clin Microbiol Infect* 2015; **21**: 910–16.

42. Domelier AS, van der Mee-Marquet N, Grandet A, et al. Loss of catabolic function in *Streptococcus agalactiae* strains and its association with neonatal meningitis. *J Clin Microbiol* 2006; **44**: 3245–50.

42a. Brandolini M, Corbella M, Cambieri P, et al. Late-onset neonatal group B streptococcal disease associated with breast-milk transmission: molecular typing using RAPD-PCR. *Early Hum Dev* 2014; **90**(Suppl 1): S84–6.

43. Mulder CJJ, van Alphen L, Zanen HC. Neonatal meningitis caused by *Escherichia coli* in the Netherlands. *J Infect Dis* 1984; **150**: 935–40.

43a. Basmaci R, Bonacorsi S, Bidot P, et al. *Escherichia coli* meningitis features in 325 children from 2001 to 2013 in France. *Clin Infect Dis* 2015; **61**: 779–86.

44. Ignjatovic M. Bacterial causes of meningitis in newborns [in Serbian]. *Srp Arh Calok Lek* 2001; **129**: 36–41.

45. Davies PA, Rudd PT. *Neonatal Meningitis* (Clinics in Developmental Medicine 132). London: MacKeith Press, 1994.

46. Arango CA, Rathore MH. Neonatal meningococcal meningitis: case reports and review of literature. *Pediatr Infect Dis J* 1996; **15**: 1134–6.

47. Doctor BA, Newman N, Minich NM, et al. Clinical outcomes of neonatal meningitis in very low-birth-weight infants. *Clin Pediatr* 2001; **40**: 473–80.

48. Tse G, Silver M, Whyte H, et al. Neonatal meningitis and multiple brain abscesses due to *Citrobacter diversus*. *Pediatr Pathol Lab Med* 1997; **17**: 977–82.

49. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med* 2000; **342**: 1500–7.

50. Edwards MS, Jackson CV, Baker CJ. Increased risk of group B streptococcal disease in twins. *JAMA* 1981; **245**: 2044–6.

51. Levy HL, Sepe SJ, Shih VE, et al. Sepsis due to *Escherichia coli* in neonates with galactosemia. *N Engl J Med* 1977; **297**: 823–5.

52. Bingen E, Bonacorsi S, Brahimi N, et al. Virulence patterns of *Escherichia coli* K1 strains associated with neonatal meningitis. *J Clin Microbiol* 1997; **35**: 2981–2.

53. Öhman L, Tullus K, Katouli M, et al. Correlation between susceptibility of infants to infection and interaction with neurotrophils of *Escherichia coli* strains, causing neonatal and infantile septicemia. *J Infect Dis* 1995; **171**: 128–33.

54. Berman P, Banker B. Neonatal meningitis:a clinical and pathological study of 29 cases. *Pediatrics* 1966; **38**: 6–24.

55. Bell WE, McGuinness GA. Suppurative central nervous system infections in the neonate. *Semin Perinatol* 1982; **6**: 1–24.

56. Polin RA, Harris MC. Neonatal bacterial meningitis. *Semin Neonatol* 2001; **6**: 157–72.

57. Anagnostakis D, Messaritakis J, Damianos D, et al. Blood-brain barrier permeability in "healthy," infected and stressed neonates. *J Pediatr* 1992; **121**: 291–4.

58. Temesvari P, Abraham CS, Speer CP, et al. *Escherichia coli* O111 B4 lipopolysaccharide given intracisternally induces blood-brain barrier opening during experimental neonatal meningitis in piglets. *Pediatr Res* 1993; **34**: 182–6.

59. Huang S, Stins MF, Kim KS. Bacterial penetration across the blood-brain barrier during the development of neonatal meningitis. *Microbes Infect* 2000; **2**: 1237–44.

60. Chang Chien HY, Chiu NC, Li WC, et al. Characteristics of neonatal bacterial meningitis in a teaching hospital in Taiwan from 1984–1997. *J Microbiol Immunol Infect* 2000; **33**: 100–4.

61. Smith PB, Cotton CM, Garges HP, et al. A comparison of neonatal gram-negative rod and gram-positive cocci meningitis. *J Perinatol* 2006; **26**: 111–14.

62. Garges HP, Moody MA, Cotten CM, et al. Neonatal meningitis:what is the correlation among cerebrospinal fluid cultures, blood cultures and cerebrospinal fluid parameters? *Pediatrics* 2006; **117**: 1094–100.

63. Sarman G, Moise AA, Edwards MS. Meningeal inflammation in neonatal gram-negative bacteremia. *Pediatr Infect Dis J* 1995; **14**: 701–4.

64. Porter FL, Miller JP, Cole FS, et al. A controlled clinical trial of local anesthesia for lumbar puncture in newborns. *Pediatrics* 1991; **88**: 663–9.

65. Halcrow SJ, Crawford PJ, Craft AW. Epidermoid spinal cord tumour after lumbar puncture. *Arch Dis Child* 1985; **60**: 978–9.

66. McCracken GH, Mize SG. A controlled study of intrathecal antibiotic therapy in gram-negative enteric meningitis of infancy: report of the Neonatal Meningitis Co-operative Study Group. *J Pediatr* 1976; **89**: 66–72.

67. Philip AGS, Baker CJ. Cerebrospinal fluid C-reactive protein in neonatal meningitis. *J Pediatr* 1983; **102**: 715–17.

67a. Martinez de Tejada B, Stan CM, Boulvain M, et al: Development of rapid PCR assay for screening maternal colonization by group B *Streptococcus* and neonatal invasive *Escherichia coli* during labor. *Gynecol Obstet Invest* 2010; **70**: 250–5.

68. Philip AGS. Response of C-reactive protein in neonatal group B streptococcal infection. *Pediatr Infect Dis J* 1985; **4**: 145–8.

69. Sabel KG, Hanson LA. The clinical usefulness of C-reactive protein (CRP) determinations in bacterial meningitis and septicemia in infancy. *Acta Paediatr Scand* 1974; **63**: 381–8.

70. Sabel KG, Wadsworth C. C-reactive protein (CRP) in early diagnosis of neonatal septicemia. *Acta Paediatr Scand* 1979; **68**: 825–31.

71. Pourcyrous M, Bada HS, Korones SB, et al. Significance of serial C-reactive protein responses in neonatal infection and other disorders. *Pediatrics* 1993; **92**: 431–5.

72. Andersen J, Christensen R, Hartel J. Clinical features and epidemiology of septicemia and meningitis in neonates due to *Streptococcus agalactiae* in Copenhagen County, Denmark: a 10 year survey from 1992 to 2001. *Acta Paediatr* 2004; **93**: 1334–9.

73. Putto A, Ruuskanen O, Meurman O, et al. C-reactive protein in the evaluation of febrile illness. *Arch Dis Child* 1986; **61**: 24–9.

74. Raju VSN, Rao MN, Rao VSRM. Cranial sonography in pyogenic meningitis in neonates and infants. *J Trop Pediatr* 1995; **41**: 68–73.

75. Hill A, Shackelford GD, Volpe JJ. Ventriculitis with neonatal bacterial meningitis: identification by real-time ultrasound. *J Pediatr* 1981; **99**: 133–6.

76. Trivedi R, Malik GK, Gupta RK, et al. Increased anisotropy in neonatal meningitis: an indicator of meningeal inflammation. *Neuroradiology* 2007; **49**: 767–75.

76a. Tibussek D. Sinclair A. Yau I, et al: Late-onset group B streptococcal meningitis has cerebrovascular complications. *J Pediatr* 2015; **166**: 1187–92.

77. Vogel LC, Boyer KM, Gadzala CA, et al. Prevalence of type-specific group B streptococcal antibody in pregnant women. *J Pediatr* 1980; **96**: 1047–51.

78. Sidiropoulos D, Hermann U, Morell A, et al. Transplacental passage of intravenous immunoglobulin in the last trimester of pregnancy. *J Pediatr* 1986; **109**: 505–8.

79. Edwards MS, Hall MA, Rench MA, et al. Patterns of immune response among survivors of group B streptococcal meningitis. *J Infect Dis* 1990; **161**: 65–70.

80. Baker CJ, Rench MA, Edwards MS, et al. Immunization of pregnant women with a polysaccharide vaccine of group B *Streptococcus*. *N Engl J Med* 1988; **319**: 1180–5.

81. Sennhauser FH, Balloch A, MacDonald RA, et al. Materno-fetal transfer of IgG anti-*Escherichia coli* antibodies with enhanced avidity and opsonic activity in very premature neonates. *Pediatr Res* 1990; **27**: 365–71.

82. Ment LR, Ehrenkranz RA, Duncan CC. Bacterial meningitis as an etiology of perinatal cerebral infarction. *Pediatr Neurol* 1986; **2**: 276–9.

83. Cohen C, Rice EN, Thomas DE, et al. Diabetes insipidus as a hallmark neuroendocrine complication of neonatal meningitis. *Curr Opin Pediatr* 1998; **10**: 449–52.

84. McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy: report of the Second Neonatal Meningitis Co-operative Study Group. *Lancet* 1980; **i**: 787–91.

85. Renier D, Flandin C, Hirsch E, et al. Brain abscesses in neonates: a study of 30 cases. *J Neurosurg* 1988; **69**: 877–82.

86. Burdette JH, Santos C. *Enterobacter sakazakii* brain abscess in the neonate: the importance of neuroradiologic imaging. *Pediatr Radiol* 2000; **30**: 33–4.

87. Isaacs D. Unnatural selection: reducing antibiotic resistance in neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2006; **91**: F72–4.

88. Saez-Llorens X, McCracken GH. Antimicrobial and anti-inflammatory treatment of bacterial meningitis. *Infect Dis Clin North Am* 1999; **13**: 619–36.

88a. Puopolo K. Eichenwald EC: No change in incidence of ampicillin-resistant neonatal early-onset sepsis over 18 years. *Pediatrics* 2010; **125**: e1031–8.

89. Heath PT, Nik Yussoff NK, Baker CJ. Neonatal meningitis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**: F137–8.

90. Tessin I, Trollfors B, Thiringer K, et al. Ampicillin-aminoglycoside combination as initial treatment for neonatal septicaemia or meningitis: a retrospective evaluation of 12 years experience. *Acta Paediatr Scand* 1991; **80**: 911–16.

91. Adelman RD, Wirth F, Rubio T. A controlled study of the nephrotoxicity of mezlocillin and gentamicin plus ampicillin in the neonate. *J Pediatr* 1987; **111**: 888–93.

92. Tullus K, Olsson-Liljequist B, Lundstrom G, et al. Antibiotic susceptibility of 629 bacterial blood and CSF isolates from Swedish infants and the therapeutic implications. *Acta Paediatr Scand* 1991; **80**: 205–12.

93. Quinn JP, Rodvold KA. Antibiotic policies in neonatal intensive-care units. *Lancet* 2000; **355**: 946–7.

94. Lebel MH, Hoy MJ, McCracken GH. Comparative efficacy of ceftriaxone and cefuroxime for treatment of bacterial meningitis. *J Pediatr* 1989; **114**: 1049–54.

95. Black SB, Levine P, Shinefield HR. The necessity for monitoring chloramphenicol levels when treating neonatal meningitis. *J Pediatr* 1978; **92**: 235–6.

96. Ahmed A. A critical evaluation of vancomycin for treatment of bacterial meningitis. *Pediatr Infect Dis J* 1997; **16**: 895–3.

97. Haimi-Cohen Y, Amir J, Weinstock A, et al. The use of imipenem-cilastatin in neonatal meningitis caused by *Citrobacter diversus*. *Acta Paediatr Int J Paediatr* 1993; **82**: 530–2.

98. Leggiadro RJ. Favorable outcome possible in *Citrobacter* brain abscess. *Pediatr Infect Dis J* 1996; **15**: 557.

99. Radetsky M. Duration of treatment in bacterial meningitis: a historical inquiry. *Pediatr Infect Dis J* 1990; **9**: 2–9.

100. Peltola H, Luhtala K, Valmari P. C-reactive protein as a detector of organic complications during recovery from childhood purulent meningitis. *J Pediatr* 1984; **104**: 869–72.

101. Astruc J, Taillebois L, Rodière F, et al. Raccourcissement du traitment antibiotiques des méningites bactériennes de l'enfant:interêt de la surveillance de la C-réactive protéine. *Arch Franc Pédiatr* 1990; **47**: 637–40.

101a. Mathur NB Kharod P, Kumar S: Evaluation of duration of antibiotic therapy in neonatal bacterial meningitis: a randomized, controlled trial. *J Trop Pediatr* 2015; **61**: 119–25.

102. Prober CG. The role of steroids in the management of children with bacterial meningitis. *Pediatrics* 1995; **95**: 29–31.

103. Daoud AS, Batieha A, Al-Sheyyab M, et al. Lack of effectiveness of dexamethasone in neonatal bacterial meningitis. *Eur J Pediatr* 1999; **158**: 230–3.

103a. Ogunlesi TA. Odigwe CC, Oladpo OT. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. *Cochrane Database Syst Rev* 2015; **11**: CD010435.

104. McCracken GH, Sarff LD, Glode MP, et al. Relation between *Escherichia coli* K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis. *Lancet* 1974; **ii**: 246–50.

104a. Levent F, Baker CJ, Rench MA, Edwards MS. Early outcomes of group B streptococcal meningitis in the 21st century. *Pediatr Infect Dis J* 2010; **29**: 1009–12.

105. Bennet R, Bergdahl S, Eriksson M, et al. The outcome of neonatal septicemia during fifteen years. *Acta Paediatr Scand* 1989; **78**: 40–3.

106. Moffett KS, Berkowitz FE. Quadriplegia complicating *Escherichia coli* meningitis in a newborn infant: case report and review of 22 cases of spinal cord dysfunction in patients with acute bacterial meningitis. *Clin Infect Dis* 1997; **25**: 211–14.

107. Klinger G, Chin CN, Otsobu H, et al. Prognostic value of EEG in neonatal bacterial meningitis. *Pediatr Neurol* 2001; **24**: 28–31.

108. Siegel JD, McCracken GH, Threlkeld N, et al. Single-dose penicillin prophylaxis of neonatal group B streptococcal disease: conclusion of a 41 month controlled trial. *Lancet* 1982; **i**: 1426–30.

109. Pyati SP, Pildes RS, Jacobs NM, et al. Penicillin in infants weighing two kilograms or less with early-onset group B streptococcal disease. *N Engl J Med* 1983; **308**: 1383–9.

110. Baker CJ, Melish ME, Hall RT, et al. Intravenous immune globulin for the prevention of nosocomial infection in low-birth-weight neonates. *N Engl J Med* 1992; **327**: 213–19.

111. Fanaroff AA, Korones SB, Wright LL, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med* 1994; **330**: 1107–13.

112. Weisman LE, Stoll BJ, Kueser TJ, et al. Intravenous immune globulin prophylaxis of late-onset sepsis in premature neonates. *J Pediatr* 1994; **125**: 922–30.

113. Weisman LE, Cruess DF, Fischer GW. Opsonic activity of commercially available standard intravenous immunoglobulin preparations. *Pediatr Infect Dis J* 1994; **13**: 1122–5.

114. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med* 1986; **314**: 1665–9.

115. Ascher DP, Becker JA, Yoder BA, et al. Failure of intrapartum antibiotics to prevent culture-proved neonatal group B streptococcal sepsis. *J Perinatol* 1992; **13**: 212–16.

116. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective. *MMWR Recomm Rep* 1996; **45**: 1–24.

117. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000; **342**: 15–20.

118. Kalliola S, Vuopio-Varkilla J, Takala AK, et al. Neonatal group B streptococcal disease in Finland:a ten-year nationwide study. *Pediatr Infect Dis J* 1999; **18**: 806–10.

119. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics* 2005; **115**: 1240–6.

120. Philip AGS, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. *Pediatrics* 2000; **106**: e4.

121. Paoletti LC, Madoff LC. Vaccines to prevent neonatal GBS infection. *Semin Neonatol* 2002; **7**: 315–23.

122. Baker CJ, Paoletti LC, Rench MA, et al. Immune response of healthy women to two different group B streptococcal type V capsular polysaccharide-protein conjugate vaccines. *J Infect Dis* 2004; **189**: 1103–12.

122a. Baker CJ, Carrey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early-onset streptococcal disease. *J Infect Dis* 2014; **209**: 781–8.

123. Bonadio WA, Stanco L, Bruce R, et al. Reference values of normal cerebrospinal fluid composition in infants ages 0 to 8 weeks. *Pediatr Infect Dis J* 1992; **11**: 589–91.

124. Ahmed A, Hickey SM, Ehrett S, et al. Cerebrospinal fluid values in the term neonate. *Pediatr Infect Dis J* 1996; **15**: 298–303.

Chapter

32 Neurologic Sequelae of Congenital and Perinatal Infections

Scott H. James, Kathleen Gutierrez, and David W. Kimberlin*

Introduction

Maternal infections contracted during pregnancy may be without fetal consequence, or they may have serious adverse effects on the fetus. These adverse effects may include fetal death, stillbirth, intrauterine growth restriction, and congenital infection. Congenitally infected neonates may be symptomatic or asymptomatic at birth. Those who are symptomatic at birth are at risk for significant long-term sequelae. Those who are asymptomatic at birth may never manifest evidence of damage, or they may develop clinically evident sequelae later in life.

This chapter discusses the neurologic consequences of congenital and perinatal infections. The infectious agents that will be discussed include *Toxoplasma gondii*, varicella-zoster virus (VZV), *Treponema pallidum* (syphilis), rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV). These infectious etiologies of congenital and perinatal disease have often been grouped together under the acronym *TORCH*. With the exception of HSV, the major clinical impact of these agents results from exposure in utero. Morbidity and mortality attributable to neonatal HSV infection usually result from infection contracted at delivery. Human immunodeficiency virus (HIV) can also be a cause of congenital or perinatal infection and is considered separately in Chapter 33.

Cytomegalovirus

CMV is the most common cause of congenital infection worldwide, with estimated incidences ranging from 0.5% to 2% of all live births [1,2]. Congenital CMV infection may result from maternal primary infection, reactivation of a prior latent infection, or reinfection with a new CMV strain. More than 90% of neonates with congenital CMV infection are asymptomatic at birth [3]. Approximately 10–15% of these asymptomatic infants develop late-onset sequelae, including sensorineural hearing loss (SNHL), microcephaly, motor defects, chorioretinitis, and learning and behavioral abnormalities [3–7]. In contrast, most congenitally infected neonates who are symptomatic at birth manifest SNHL, severe developmental deficits, and intellectual disability [5,8,9]. Most cases of symptomatic congenital CMV infection result from a primary maternal infection, although symptomatic infection can also follow maternal reinfection with a different CMV strain [10,11]. Similarly, primary infections early in pregnancy (before the twenty-seventh week of gestation) are more likely to be associated with a poor outcome than those occurring later in gestation [12].

Outcome in Infants with Asymptomatic Congenital CMV Infection

Most neonates with congenital CMV infections are asymptomatic at birth. These infants are likely to be detected only if routine viral cultures or polymerase chain reaction (PCR) assays are performed within the first few weeks of life. Several prospective studies assessing the possible long-term effects of asymptomatic congenital CMV infections have been conducted [6,13–16]. The most common sequelae of asymptomatic congenital CMV infection are SNHL, which may not be present or detected at birth, and possible intellectual impairment. The incidence of SNHL in older children with asymptomatic congenital CMV ranges from 7% to 15% [6,7,16]. Chorioretinitis may develop later in life in up to 2% of children with asymptomatic congenital CMV infection [7].

Congenital CMV infection is the leading nongenetic cause of SNHL, estimated to be responsible for one-third of all cases in children [6,17]. A large prospective study of 307 asymptomatic congenitally infected children and 277 controls found a 7%

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incidence of SNHL in infected children and no hearing loss in the matched controls [6]. Of those children with SNHL, 50% had bilateral disease; 23% suffered from profound bilateral hearing loss. In this study, none of the children with SNHL had other risk factors for hearing impairment. Because CMV hearing impairment often presents after the newborn period, is progressive, and can fluctuate, a significant portion of SNHL from asymptomatic congenital CMV infection may be initially missed by universal newborn hearing screens. The addition of universal newborn CMV screening would serve to improve the identification of all those at risk for hearing impairment in childhood. Investigation into potential predictors of sequelae in infants with asymptomatic CMV infection has demonstrated an association between CMV virus burden and hearing loss. Children with asymptomatic congenital CMV infection who developed hearing loss have been shown to have increased amounts of CMV DNA detected in urine and blood at birth compared with children who did not develop hearing loss [18,19]. Breakpoints that would allow these data to be used in clinical management have yet to be identified, though.

The impact of hearing impairment on intellectual development has confounded the evaluation of intellectual function in congenitally infected infants. Several studies have attempted to evaluate the possible intellectual consequences of asymptomatic congenital CMV infection. Interpretation of the results of some of the studies is hampered by relatively short periods of follow-up, lack of appropriately matched controls, and failure to control for hearing loss. One well-designed study evaluated the intellectual development of 18 prospectively followed school-aged children with asymptomatic congenital CMV infection and normal hearing [15]. The results of testing these children were compared with the results from 18 controls matched for age, sex, race, school grade, and socioeconomic status. All children were evaluated at between 6.5 and 12.5 years of age using the Wechsler Intelligence Scale for Children – Revised, the Kaufman Assessment Battery for Children, and the Wide Range Achievement Test. No differences between the infected and uninfected children on intelligence scores or subscales, achievement scores, or incidence of learning disabilities were observed. These researchers concluded that children with asymptomatic CMV infection and normal hearing have normal intellectual development. However, the small sample size of this study prohibits a definite conclusion regarding the independent effects of congenital CMV infection on intellectual impairment.

Expression of adverse consequences of asymptomatic CMV infections appears to be influenced by socioeconomic conditions. One study predicted increased school failure rate in infected children of lower socioeconomic class but not in infected children from middle and higher socioeconomic classes [14]. Future studies must attempt to control for other relevant factors contributing to intellectual development.

Table 32.1 Clinical Manifestations of Symptomatic Congenital CMV Infection

Petechiae	++++[a]
Thrombocytopenia	++++
Hepatosplenomegaly with elevated ALT	+++[b]
Jaundice with direct hyperbilirubinemia	+++
Microcephaly	+++
Small for gestational age	++[c]
Prematurity	++
Inguinal hernia	++
Chorioretinitis	+[d]

Note: ALT, alanine aminotransferase.
[a]75–100% incidence.
[b]50–75% incidence.
[c]25–50% incidence.
[d]0–25% incidence.

Outcome in Infants with Symptomatic Congenital CMV Infection

Most neonates with symptomatic congenital CMV disease have been infected as a result of a primary maternal gestational infection [10,20]. The clinical abnormalities found most frequently in neonates with symptomatic congenital CMV are listed in Table 32.1 [5,21]. Cerebral abnormalities reported in association with congenital CMV infection include microcephaly, microgyria, periventricular calcifications, migrational abnormalities, disturbed myelination, spongiosus of the brain, encephalomalacia, calcification of the cerebral arteries, parietal lobe cysts, cerebral cortical immaturity, cerebellar

hypoplasia, paraventricular cysts, intraventricular strands, and dolichocephaly [5,8,9,22–25]. CMV has been isolated from CSF by PCR in patients with symptomatic congenital infection, and follow-up studies have shown this to be associated with long-term neurodevelopmental sequelae [26]. Postmortem examination of brains from infants who have died with severe congenital CMV infection have noted decreased brain weight, subependymal cysts, deformed cerebellum, irregular gyri, thickened leptomeninges, cortical and cerebellar neuronal migration abnormalities, and paraventricular bands of necrosis and calcification [23].

Fortunately, fewer than 10% of neonates congenitally infected with CMV manifest overt signs of disease at birth. The long-term prognosis of symptomatic infants is usually poor [7]. CNS sequelae include microcephaly, intellectual disability and developmental delays, learning and behavioral disorders, seizures, and neuromuscular disorders, including facial asymmetry, spasticity, quadriparesis, diplegia, hemiatrophy, and hemiparesis [27]. Defects in hearing and vision are also common after symptomatic congenital CMV infection.

One of the earlier prospective studies of symptomatic neonates was published in 1980 [8]. In that study, 34 patients who had clinically evident disease at birth were followed for a mean duration of 4 years. Twenty-nine percent of the patients died, and more than 90% of the survivors developed CNS or auditory impairment, 70% had microcephaly, 61% had intellectual disability, 35% had neuromuscular disorders, 30% had hearing loss, and 22% had chorioretinitis or optic atrophy. Although the extent of disease apparent at birth was not entirely predictive of CNS sequelae, all children with an IQ of less than 50 or neuromuscular disorders showed signs of impairment by 1 year of age. Other studies have documented similarly poor outcomes. In a long-term follow-up of 17 children with symptomatic congenital CMV followed for a mean of 5.5 years, 75% met criteria for intellectual disability [28]. In this study, three children with normal hearing and IQ scores still exhibited deficits in expressive language. The Houston CMV longitudinal study followed 41 children with symptomatic congenital CMV infection; the median age at follow-up was 5.7 years [27]. Microcephaly at birth (present in 19.5% of the study population) was the most specific predictor of intellectual disability and major motor disability.

Another long-term prospective follow-up study evaluated the predictors of hearing loss in children with symptomatic congenital CMV infection [29]. Hearing outcome was followed in 180 children, and 48% of the children had hearing loss on follow-up. Of these children, 70% had hearing loss at birth or in the neonatal period. The presence of disseminated disease at birth was predictive for the development of hearing loss, but microcephaly and other neurologic findings were not.

Recommendations

Congenital CMV infection should be considered in any newborn with unexplained prematurity, growth restriction, hepatomegaly, splenomegaly, jaundice, microcephaly, chorioretinitis, or petechiae. The diagnosis can be confirmed by isolating CMV in viral culture or detection of CMV DNA by PCR from urine or saliva during the first 3 weeks of life. CMV identified after the first few weeks of life with a documented negative culture in the neonatal period may represent postnatal CMV infection.

Neuroimaging by computed tomography (CT) scan or magnetic resonance imaging (MRI) has been shown to be useful in identifying infants at risk for CNS sequelae of congenital CMV infection. In a study of 56 infants with symptomatic congenital CMV, 70% had CT abnormalities [9]. Of those with CT abnormalities, 60% had IQ scores of less than 70; half the IQ scores were below 50. In contrast, none of the 17 symptomatic infants with normal CT scans had severe intellectual disability. In this study, clinical and laboratory data were not able to predict the neurologic sequelae. Microcephaly, seizures, lethargy, and poor suck did not predict CT scan abnormality. Intracranial calcification was the most common abnormality found in 77% of abnormal scans. White matter abnormalities were also identified in a small number of patients, with MRI more sensitive than CT at detecting these changes.

The effectiveness of antiviral therapy has been established for the treatment of infants with symptomatic congenital CMV disease. The Collaborative Antiviral Study Group (CASG) conducted a phase III randomized, controlled study evaluating the effect of intravenous ganciclovir therapy on hearing in newborns with symptomatic congenital CMV infection involving the CNS [30]. Ganciclovir treatment, at a dose of 6 mg/kg intravenously every 12 hours for 6

weeks, prevented hearing deterioration at 6 months in the treated group compared with the placebo group, but nearly two-thirds of the ganciclovir-treated infants developed significant neutropenia during therapy.

Further studies evaluating valganciclovir, the orally bioavailable prodrug of ganciclovir, in infants with symptomatic congenital CMV infection have demonstrated that 6 months of antiviral therapy improved hearing and neurodevelopmental outcomes beyond that which was seen with the 6-week course [31]. Neutropenia was seen in approximately 20% of subjects receiving 6 months of valganciclovir, but this was not significantly different from the amount of neutropenia detected in the placebo group.

The decision to treat newborns with symptomatic congenital CMV infection must be individualized, involving counseling and discussion with the parents regarding the potential risks and benefits of prolonged antiviral therapy. At this time, it is not recommended that infants with asymptomatic congenital CMV infection receive antiviral therapy. Regardless of whether or not treatment is initiated, it is important to identify all infants with congenital CMV infection so that appropriate long-term follow-up, including frequent audiologic and developmental examinations over the first several years of the child's life, may be arranged. In order to maximize a child's full potential, defects, including those in hearing and language, should be identified and addressed with appropriate therapeutic interventions as soon as possible.

Toxoplasmosis

The etiologic agent of toxoplasmosis, the parasite *Toxoplasma gondii*, was first demonstrated in the brain of a newborn infant with encephalomyelitis in 1939 [32]. The overall incidence of congenital toxoplasmosis in the United States is estimated to range from 1/1,000 to 1/10,000 live births [33–35]. *Toxoplasma* infection in pregnancy is usually asymptomatic, but occasionally women develop nonspecific symptoms and signs of malaise, fever, myalgias, and lymphadenopathy. Among immunocompetent women, transmission to the fetus is limited almost solely to those who contract primary infection during gestation. Case reports indicate that it is possible for toxoplasmosis to be transmitted to infants from immunocompetent women who acquired an acute *T. gondii* infection up to 2–3 months prior to conception [36]. Vertical transmission can also result from maternal acquisition of a new *T. gondii* strain or reactivation of previous maternal infection, with the latter scenario most commonly occurring in women with immunodeficiency from acquired immune deficiency syndrome (AIDS), neoplasm, or autoimmune disease [37].

The risk of fetal infection increases as pregnancy progresses. Increasing placental blood flow with advancing gestation may explain the increased transplacental transmission [34]. The transmission rate may be as low as 5% if maternal infection occurs before 16 weeks' gestation and as high as 75–80% if maternal infection occurs near term. Fortunately, the severity of neonatal disease decreases with advancing gestational age [33]. Thus, although transmission of toxoplasmosis to the fetus is greatest late in pregnancy, manifestations resulting from infection at this stage are uncommon.

Several studies suggest that the incidence and severity of neonatal infection may be reduced if mothers who acquire toxoplasmosis during pregnancy receive antiparasitic therapy [38]. In one study of 1,270 women with proven toxoplasmosis during pregnancy, fetal transmission was reduced to 7%. Most (81%) of the infected newborns had subclinical disease if mothers were treated with spiramycin or pyrimethamine/sulfadiazine/folinic acid during pregnancy. Thus treatment appeared to decrease both the incidence and the severity of congenital toxoplasmosis. Although a second study failed to demonstrate a decrease in transplacental transmission of *T. gondii* by prenatal treatment, it did confirm that the severity of neonatal illness was significantly decreased by prenatal treatment [39]. The Systematic Review on Congenital Toxoplasmosis (SYROCOT) Study Group published a meta-analysis using individual patients' data from 26 cohorts. They found that treatment started within 3 weeks of maternal seroconversion decreased the odds of mother-to-child transmission by 52% compared with treatment started after more than 8 weeks [40]. Several other observational studies have further confirmed the benefits of antenatal treatment for the overall prevention of mother-to-child transmission and the prevention of symptomatic disease in particular [41–44].

The clinical spectrum of congenital toxoplasmosis is broad. Although the majority of infants infected in utero with *T. gondii* are asymptomatic at birth, approximately 90% of infected infants will manifest sequelae at a later age, particularly ophthalmologic and intellectual impairment [39,45].

Outcome in Infants Asymptomatic at Birth

Congenital toxoplasmosis is not as prevalent as congenital CMV, but it is potentially more dangerous for the individual. Although a majority of infants with congenital toxoplasmosis appear normal based on routine clinical examination at birth, subclinical infection with *T. gondii* is more frequently associated with impaired intellectual performance and chorioretinitis than subclinical infection with CMV [46,47]. Nearly all children with subclinical congenital toxoplasma infection who remain undiagnosed and untreated during their first year of life will develop adverse sequelae later in life. An estimated 85% of untreated infants with congenital toxoplasmosis will suffer at least one episode of chorioretinitis, developmental delay will be evident in 20–75%, and hearing loss will occur in 10–30% [34,46,47]. These sequelae of congenital infection may not become clinically apparent until 6–18 years of age [45].

Outcome in Infants Symptomatic at Birth

One large study showed that only 4% of neonates congenitally infected with *T. gondii* were symptomatic at birth based on initial clinical examination. However, more detailed examination after positive serologic screening revealed either CNS or ophthalmologic abnormalities in 40% of the infants [48]. Congenital toxoplasmosis is rarely fulminant but is often severe. Symptoms and signs of generalized infection are prominent, and signs of CNS involvement are invariably present [33]. The "classic triad" in these symptomatic neonates is hydrocephalus, chorioretinitis, and diffuse intracranial calcifications. The most frequent extraneural signs associated with symptomatic congenital toxoplasmosis include hepatosplenomegaly, thrombocytopenia, anemia, and jaundice. The mortality rate of symptomatic infants is estimated to be 5% [49]. Approximately 85% of untreated survivors develop intellectual disability; 75% develop convulsions, spasticity, and palsies; and 50% develop severe visual impairment [50]. Deafness, a prominent sequela of congenital viral infections (e.g., CMV and rubella), occurs less frequently after congenital toxoplasmosis. The approximate incidence of hearing loss can be as high as 30% [51]. Microcephaly, also commonly seen in other congenital infections, is less common in congenital toxoplasmosis, the highest reported incidence being less than 25% [51]. When microcephaly does occur, it is a predictor of poor outcome. Other factors associated with poor prognosis in congenital toxoplasmosis include neonatal hypothermia, apnea, bradycardia, prolonged hypoxemia, CSF protein > 1 g/dL, delayed treatment, and brain atrophy on CT scan that persists for months after ventriculoperitoneal shunt placement.

Good outcomes have occurred in children with significant CNS involvement at birth treated with antiparasitic drugs for 1 year. The US National Collaborative Chicago-based, Congenital Toxoplasmosis Treatment Trial Study (NCCCTS) is a prospective longitudinal study evaluating long-term outcomes of infants with congenital toxoplasmosis treated for 1 year with pyrimethamine, sulfadiazine, and the folinic acid analogue leucovorin [51,52]. The study, conducted between 1981 and 2004, included 120 infants who were routinely evaluated at diagnosis (near the time of birth) and at frequent intervals thereafter (at 1, 3.5, 5, 7.5, 10, 15, and 20 years). Treatment of infants who had moderate to severe neurologic disease at birth resulted in normal neurologic and/or cognitive outcomes in more than 72% (28% had an IQ < 70 when evaluated at ≥3.5 years of age). None of the patients had sensorineural hearing loss. Ninety percent of infants without substantial neurologic disease and 64% of those with moderate to severe disease at birth did not develop new eye lesions. Almost all the outcomes in the NCCCTS were better and more favorable than outcomes reported for children who were untreated or treated only for 1 month in earlier decades. Infants presenting with hydrocephalus at birth, however, are at increased risk for poor neurodevelopmental outcome [53].

Disseminated calcifications at birth do not necessarily reflect poor prognosis; following treatment, normal development can occur despite these findings. Intracranial calcifications may diminish or completely resolve with 1 year of therapy. In one study, intracranial calcifications were demonstrated in 40 of 56 newborns with congenital toxoplasmosis [54]. Following 1 year of therapy with pyrimethamine, sulfadiazine, and leucovorin, 75% had decreased or undetectable calcifications.

Screening and Prenatal Diagnosis

Because the majority of infants with subclinical congenital toxoplasmosis ultimately develop sequelae, identification and treatment of all infected newborns should decrease long-term morbidity. Massachusetts and New Hampshire have screened newborns for congenital toxoplasmosis since 1986 and 1988, respectively. The New England Regional Toxoplasma

Working Group previously reported that of 50 neonates with congenital toxoplasmosis identified by screening, nearly all had normal newborn examinations [48]. However, on the basis of detailed perinatal evaluations conducted shortly after serologic diagnosis, 19% had ocular disease at birth (4% active chorioretinitis, 15% uninflamed retinal scars) and 29% had CNS disease (20% had intracranial calcifications found on CT scan, 25% had increased protein in the CSF, and 2% had ventriculomegaly). All infants were treated for 1 year with pyrimethamine, sulfadiazine, and folinic acid. Only 1 of 46 infants had persistent neurologic deficits. None of 9 infants with macular lesions at birth had progressive ocular disease. However, 10% developed new ocular lesions during ophthalmologic follow-up at more than 1 year of age.

The NCCCTS demonstrated that treatment during the first year of life with pyrimethamine and sulfadiazine results in better outcomes in general than no treatment or short-term treatment [51]. Thus prolonged treatment with pyrimethamine, sulfadiazine, and supplemental folinic acid seems to benefit both symptomatic and asymptomatic neonates with congenital toxoplasmosis.

In order to maximize the benefits of prenatal and postnatal therapy, infected neonates must be identified. In France, where the rate of *T. gondii*–seronegative women of childbearing age is low, monthly serologic screening is performed for all seronegative pregnant women. If seroconversion is documented, amniotic fluid *T. gondii* PCR is done, and prompt therapy is given to the mother during pregnancy. Neonates born to those mothers receive a complete clinical and laboratory evaluation. If the diagnosis of congenital toxoplasmosis is established, treatment is initiated in consultation with an expert in pediatric infectious disease to determine optimal drug regimen, duration of therapy and risk factors for side effects.

In the United States, there has been much debate over systematic universal screening for toxoplasmosis in pregnant women. However, a recent cost analysis by Stillwaggon et al. demonstrated a cost-effective model for universal screening of pregnant women in the United States. Their model followed the French protocol of monthly prenatal screening and treatment followed accordingly by postnatal evaluation and treatment if congenital infection is confirmed [49]. The prevalence of seronegative pregnant women in the United States is much higher than in Europe; thus more US women would need routine monthly screening throughout pregnancy. In addition, the sensitivity, specificity, and positive and negative predictive values vary with each serologic test and are less reliable if run outside of reference laboratories [55]. Further validation of the diagnostic performance of potential point-of-care tests would be necessary before the introduction of universal screening.

An alternative to screening pregnant women is to screen neonates at birth for serologic evidence of congenital infection. Due to limitations in the immunoglobulin (IgM) assays, newborn screens employing these assays only diagnose 70–80% of congenital infections. The 20–30% false-negative rate of neonatal screens may be unacceptably high. In a European study of various prenatal and postnatal screening tests, the sensitivity of IgM testing of neonatal blood was 43%; IgA testing of neonatal blood was 66% sensitive [55]. Sensitivity increased to 70% if results of IgM and IgA testing on neonatal blood were combined. Moreover, maternal prenatal treatment with antiparasitic drugs significantly decreased the incidence of positive serologic diagnosis. The 85% positive rate for specific IgM in neonatal blood dropped to 25% in neonates whose mothers were treated prenatally. The lack of accuracy of neonatal IgM and IgA tests to diagnose congenital toxoplasmosis has also been demonstrated in other studies, although another study showed the combination of IgA and IgM testing in neonates to be 93% sensitive for the diagnosis of congenital toxoplasmosis [56,57]. Fetal infection may be detected through amniocentesis or cordocentesis [58]. PCR on amniotic fluid is superior to cordocentesis with fetal blood serologic evaluation. PCR of amniotic fluid has a sensitivity of 80–90% and a specificity of 96–100% [59].

Recommendations

Infants with congenital *T. gondii* infection must be recognized as being at high risk for the development of ophthalmologic and intellectual impairment. Serial ophthalmologic and neurodevelopmental assessments must be performed until the child is at least 18 years of age because onset of sequelae can be delayed.

Normal developmental and neurologic outcomes have been observed in up to 70% of treated infants despite the presence of systemic disease, hydrocephalus, microcephaly, multiple intracranial calcifications, and extensive macular involvement evident at birth [34,51]. Since delays in diagnosis and therapy are associated

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with worse outcomes, prompt diagnosis and treatment are important.

Prevention of congenital toxoplasmosis is possible. Primary prevention to decrease infection of susceptible pregnant women should focus on hygiene: avoiding consumption of raw meat, avoiding potentially *T. gondii*–contaminated material (e.g., cat feces, litter boxes, soil when gardening), and washing fruits and vegetables before consumption. Secondary prevention involves prenatal screening for the identification of acute seroconversions in pregnant women and instituting prenatal therapy to reduce mother-to-child transmission and decrease the severity of infection in the fetus. Tertiary prevention includes neonatal evaluation, antiparasitic treatment, and long-term follow-up of congenitally infected infants. Evaluations should include general physical and neurologic, audiologic (auditory brainstem evoked response), ophthalmologic, and developmental examinations, as well as head CT scan, serologic tests, complete blood counts, liver function tests, cerebrospinal evaluation, PCR in CSF, blood, or urine, and close monitoring for drug toxicity while on therapy. Serologic tests should be performed in a reference laboratory with expertise in *Toxoplasma* assays and should include *T. gondii* IgG, *T. gondii* IgM immunosorbent agglutination assay (ISAGA) and *T. gondii* IgA enzyme immunoassay (EIA) or ISAGA. Neonatal serologies should always be tested in parallel with maternal serologies. Serial ophthalmologic examinations, ideally by a retinal specialist, should occur every 3–4 months during the first several years of life.

Rubella

Rubella is an RNA virus, classified as a togavirus, unrelated to any other human viral pathogen. Before the introduction of childhood immunization for rubella in the late 1960s, rubella virus caused major epidemics once or twice every decade in the United States. During these rubella epidemics, many infected individuals were asymptomatic, whereas others had classic infection with diffuse exanthem, low-grade fevers, lymphadenopathy, and arthritis/arthralgia [60]. Because most children in the United States are now immunized at 12 months and 4–6 years of life, widespread epidemics of rubella have disappeared. However, outbreaks of rubella and congenital rubella syndrome have occurred in the United States in the late 1980s and early 1990s. Most outbreaks have been attributed to a failure to vaccinate susceptible individuals in colleges, prisons, and religious communities [61,62]. In October 2004, the CDC convened an independent panel of internationally recognized authorities on public health, infectious disease, and immunization that concluded that rubella and congenital rubella syndrome are no longer endemic in the United States [63]. During 2004–12, six cases of congenital rubella syndrome were reported in the United States, with five of these involving mothers who traveled to the United States from regions in which rubella remains endemic [64]. In many developing countries, congenital rubella syndrome continues to be a problem, with an estimate of more than 100,000 new cases of congenital rubella syndrome annually [65]. Even in countries with established rubella control programs, unvaccinated cohorts can lead to epidemics such as the one seen in Japan in 2012–14, during which over 40 infants with congenital rubella syndrome were reported [66].

Transmission of Rubella to the Fetus

Rubella produces viremia in susceptible hosts during primary infection. In pregnant women, this viremic phase often results in placental infection with or without subsequent infection of the fetus [65]. The risk of fetal infection depends on gestational age at the time of maternal infection. The risk of fetal infection is highest in the first trimester, declines during the second trimester, and then increases again during the end of the third trimester [67]. Specifically, the risk of fetal infection is 80–90% during the first 12 weeks of gestation, drops to 25% by 23–26 weeks, and then increases to 60–100% near term.

Clinical Manifestations of Intrauterine Rubella Infection and the Risk of Neurologic Sequelae

Isolation of virus by culture or PCR from the saliva of infants with suspected intrauterine rubella is the most reliable method of proving congenital infection [68]. Infants with congenital rubella shed virus from this site for 6 months or longer after birth. The virus can also be found in the stool, urine, and CSF [68]. Although efforts have been made to develop a rubella-specific IgM antibody assay for the diagnosis of congenital rubella infection, many infants with infection proven by culture do not have detectable rubella-specific IgM antibodies using optimal serologic methodology [69]. The lack of detectable

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antibodies in infants with congenital rubella syndrome may reflect infection at a time of fetal immune system immaturity in early gestation. The finding of persistent or increasing rubella-specific IgG titers during the first year of life can also aid in the diagnosis of congenital rubella syndrome. Avidity testing of IgG can also help to identify acute infection in a newborn [65]. Using reverse-transcriptase PCR to detect rubella virus RNA in amniotic fluid, chorionic villus samples, and fetal blood also appears to offer a reliable method of diagnosis [70].

The likelihood of clinical manifestations of intrauterine rubella infection is inversely related to fetal age at the time of maternal infection [71]. The estimated risk of defects is 85% following maternal rubella infection at 8 weeks, 52% at 9–12 weeks, and 16% at 13–20 weeks' gestation [72]. Maternal infection after 20 weeks' gestation can cause fetal infection, but these infants are typically asymptomatic in the newborn period, and the risk of late-onset sequelae is low. Infants infected with rubella virus at the earliest stages of development are more likely to have cardiac defects (e.g., patent ductus arteriosus and pulmonary artery stenosis) in addition to the hearing and ocular abnormalities that are characteristic of later in utero infection.

Neurologic manifestations of congenital rubella syndrome include meningoencephalitis, microcephaly, intellectual disability, motor impairment, behavioral difficulties, psychiatric disorders, SNHL, and, rarely, late-onset progressive rubella panencephalitis [73,74]. Meningoencephalitis occurs in 10–20% of infected neonates who are symptomatic at birth. In these cases, CSF analysis reveals elevated protein concentrations with or without a pleocytosis. Extensive meningoencephalitis is one cause of early postnatal death from congenital rubella [73].

The risk of microcephaly depends on the gestational age at infection. Microcephaly occurs in 60% of fetuses infected before 13 weeks' gestation. In contrast, less than 10% of infants infected after 20 weeks' gestation are microcephalic [67]. Infants with congenital rubella who are microcephalic can be expected to have additional neurologic impairment [75]. Acquired microcephaly has also been documented in congenital rubella syndrome. Chang et al. described five infants with confirmed congenital rubella syndrome who, despite having normal head size at birth, developed microcephaly and global neurodevelopmental impairment by 27 months of age. Of note, head ultrasonography revealed linear and punctate hyperechogenicities and occasional subependymal cysts early in the course of disease [76]. In another study, white matter hyperintensities were noted on MRI scans performed on 11 adults with a history of congenital rubella syndrome and schizophrenia-like symptoms [77]. These hyperintensities were not found in any of 19 controls with schizophrenia who had no evidence of congenital infection.

A few children with congenital rubella developed a syndrome of progressive rubella panencephalitis similar to subacute sclerosing panencephalitis caused by the measles virus [74]. These children manifest progressive neurologic deterioration after 10 years of age. Neurologic manifestations included progressive intellectual disability, motor incoordination, and cerebellar signs, including nystagmus, ataxia, and choreoathetoid movements. Elevated rubella-specific IgG was demonstrated in the CSF, and rubella virus was recovered from brain biopsy in one case. Autopsies revealed diffuse white matter involvement, microglial nodules, panencephalitis, reactive gliosis, ventricular enlargement, and brain atrophy [78].

Neurologic sequelae of congenital rubella are often subtle and include hearing deficits, language delays, psychomotor retardation, and behavioral/psychiatric disturbances. The progressive nature of intrauterine rubella infection was demonstrated in a group of children with congenital rubella infection without significant neurodevelopmental impairment at baseline who were followed for 9–12 years [79]. With increasing age, an increase was observed in the percentage of the population with hearing loss, motor incoordination, and behavioral disturbances. At last follow-up, 86% of the children had hearing deficits, 52% had learning problems, 48% had behavioral problems, and 61% had poor balance and/or muscle weakness. A 50-year cohort follow-up from a congenital rubella epidemic in Australia has been reported, demonstrating that in 40 individuals, 100% had hearing deficits, most of which were profound, and 50% had visual deficits. Over 50% of these individuals were able to maintain employment [80].

Behavioral and psychiatric disorders are often found at later ages in children with congenital rubella syndrome. Chess et al. described the psychiatric and behavioral consequences of congenital rubella among 243 preschoolers examined at 2.5–5 years of age; 205 children of this cohort were reexamined at 8–9 years of age [81]. Between 25% and 40% of the children had significant cognitive impairment, 15–20% had

diagnoses of reactive or other behavior disorders, and approximately 6% were autistic. In another psychiatric outcome study, the Diagnostic Interview Schedule for Children was administered to 70 young adults with a history of congenital rubella syndrome and 164 controls [82]. Those with congenital rubella syndrome were 5–16 times more likely than age-matched controls to have nonaffective psychiatric disorders defined as delusions and/or hallucinations. Conclusions from these studies are tentative because the impacts of multiple deficits in hearing, visual, and other neurologic domains have not been clearly separated from the direct impact of viral infection on behavior and psychiatric well-being.

Recommendations

The evaluation of a pregnancy potentially complicated by rubella remains a difficult diagnostic problem. The interval required to isolate the virus limits the utility of tissue culture as a diagnostic method. If the pregnant woman has not had a previous rubella titer, it is often impossible to determine whether seroconversion has occurred because rubella antibodies are present within a few days of onset of infection. The detection of rubella-specific IgM antibodies can be helpful, but the method can yield false-positive results, and the absence of an IgM response does not exclude recent rubella infection [65]. A high titer of rubella antibodies in a single maternal serum sample does not establish a diagnosis of recent infection because many individuals maintain persistently high rubella titers. PCR has been performed on amniotic fluid, chorionic villi samples, and fetal blood for detection of in utero rubella infection, and use of PCR as a diagnostic tool appears very promising [83].

If a pregnant woman is exposed to rubella and her immune status is not known, she should be tested for rubella antibodies immediately. A positive rubella titer at the time of exposure eliminates any concern. If the titer is negative, it should be repeated at 2 and 6 weeks after exposure to be certain that subclinical infection has not occurred. Transplacental transmission of the virus is possible if seroconversion is demonstrated, whether or not the pregnant woman has had symptoms.

The risk of congenital rubella can be eliminated by an effective vaccination program. In the last three decades, the US rubella vaccination program has halted the endemic transmission of rubella [84,85]. Similar to other vaccine-preventable disease, localized rubella outbreaks continue to occur when vaccine uptake is low. Cases of congenital rubella infection that do occur in the United States are usually either imported from an endemic region outside the Americas or are attributable to multiple missed opportunities to vaccinate susceptible women of childbearing age [85]. Immunization coverage rates of 80–90% are needed to prevent rubella transmission in a community. Nonimmune young women should be encouraged to receive rubella vaccine. Pregnancy is a contraindication to rubella immunization. If a pregnant woman is found to be rubella nonimmune, she should wait until the completion of her pregnancy before receiving the vaccine. Of note, rubella vaccination has inadvertently been given during pregnancy and has not been associated with congenital rubella syndrome or other birth defects [86]. Infants with congenital rubella infection require long-term medical, neurologic, psychiatric, ophthalmologic, audiologic, and developmental evaluations.

Congenital Syphilis

In the United States, the late 1980s and early 1990s were marked by a resurgence in the number of congenital infections caused by the spirochete *Treponema pallidum*, the etiologic agent of syphilis [87]. Factors believed to contribute to this increased frequency of infection include patterns of substance abuse, HIV infection, and changing patterns of sexual activity. In addition, modification of the CDC case definition of congenital syphilis facilitated the identification and reporting of cases [88]. Though the overall incidence of primary and secondary syphilis continues to rise, the rate of congenital syphilis in the United States has declined steadily since 1992, with a total of 322 cases reported in 2012 [89].

The risk of syphilis transmission to the fetus varies with the stage of maternal illness [90]. In early, untreated primary maternal infection, transmission rates range from 70% to 100%. In early latent infection (infection of less than 1 year's duration), the risk of fetal infection is 40%. Once a mother has late latent infection, fetal transmission rates drop to 10% due in part to low levels of spirochetemia and treponemal proliferation.

There are substantial problems in the diagnosis of congenital syphilis and the evaluation of neurosyphilis in infants. *T. pallidum* cannot be cultured from clinical specimens except by inoculation into rabbits,

a process that is time-consuming, impractical, and only done in a research setting [89,91]. In addition, *T. pallidum* is often present in low numbers in clinical specimens. Thus the value of histologic documentation of infection by dark-field microscopy or antigen detection is limited. Because of these difficulties in directly identifying the pathogen, most cases of congenital syphilis are not established by definitive diagnosis but rather by presumptive diagnosis based on various clinical and laboratory evaluations. Unfortunately, there is no "gold standard" for diagnosis. Diagnosis relies on a combination of screening with nontreponemal antibody tests such as the rapid plasma reagin (RPR) card test or the Venereal Disease Research Laboratory (VDRL) titers and making a presumptive diagnosis with treponemal tests such as *T. pallidum* particle agglutination (TP-PA), fluorescent treponemal antibody absorption (FTA-ABS), and *T. pallidum* enzyme immunoassay (TP-EIA) [92]. However, transplacentally acquired maternal antibodies complicate the serologic evaluation of exposed infants. Moreover, an infected infant may have a titer four times higher than his or her mother, a lower titer than his or her mother, or a negative titer despite active infection.

Clinical diagnosis of congenital syphilis is also challenging because approximately two-thirds of infants are asymptomatic at birth [93]. Sequelae from these asymptomatic infections frequently develop at later ages. When symptoms appear within the first 2 years of life, they are designated *early congenital syphilis*; those developing thereafter are designated *late congenital syphilis*. Manifestations of syphilitic infections may include stillbirth, prematurity, intrauterine growth restriction, hepatosplenomegaly, generalized lymphadenopathy, rhinitis ("snuffles"), dermatologic abnormalities, renal disease, hyperbilirubinemia, and CNS abnormalities [89,90]. In order to prevent morbidity from congenital syphilis, it is important to identify and treat both asymptomatic and symptomatic newborns.

Neurologic Sequelae of Congenital Syphilis

Older literature suggested that more than 60% of neonates with congenital syphilis had abnormal findings on CSF examinations. However, this high rate of abnormality was based on considering CSF abnormal if it contained 5 or more white blood cells (WBCs)/mm^3 and had a protein content greater than 45 mg/dL. These definitions of abnormal CSF may not be appropriate for newborn infants [94]. One study of 78 newborn infants born to mothers with serologic evidence of syphilis found only one neonate with a positive CSF VDRL titer, though other infants had as many as 32 WBCs/mm^3 and CSF protein concentrations as high as 170 mg/dL [95]. Another study evaluated the CSF of 19 infants born to mothers with untreated early syphilis using the rabbit infectivity test, PCR, and immunoblot IgM assays in addition to CSF cell count, protein, and VDRL titer [96]. Eighty-six percent of symptomatic infants with congenital syphilis in this study had evidence of CNS disease. In contrast, only 1 of 12 asymptomatic newborns had laboratory evidence of CNS disease. The authors concluded that CNS invasion by *T. pallidum* is common in symptomatic congenital syphilis and uncommon in asymptomatic disease. A more recent study by Michelow et al. evaluated CNS involvement in 76 infants with untreated congenital syphilis using rabbit-infectivity testing of the CSF along with syphilis IgM immunoblotting and PCR on blood and CSF specimens [97]. Spirochetes were detected in the CSF in 17 of the 76 infants. CNS infection was best predicted by IgM immunoblotting of serum or PCR assay of serum or blood.

Sequelae from neurosyphilis include hydrocephalus, cranial nerve palsies, intellectual disability, seizures, strokes, deafness, blindness, general paresis, and behavioral/learning difficulties [89]. Neurologic manifestations of congenital syphilis that are evident during the first 2 years of life are infrequent [95]. When reported, the most common clinical types of CNS involvement with early congenital syphilis are acute leptomeningitis and chronic meningovascular syphilis. Leptomeningitis usually becomes evident at between 3 and 6 months of age. It is clinically indistinguishable from other bacterial causes of meningitis. The CSF typically contains 100–200 mononuclear cells/mm^3 and has an increased protein concentration and a positive serologic test for syphilis. This form of neurosyphilis responds to penicillin therapy [90].

Chronic meningovascular syphilis tends to follow a protracted and progressive course starting late in the first year of life. It usually results in communicating hydrocephalus and cranial nerve palsies. Cerebral infarctions from syphilitic endarteritis may also result in a variety of cerebrovascular syndromes, with paresis and seizures being the most consistent features [89]. Unfortunately, these later forms of neurosyphilis often do not respond to penicillin treatment.

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Neurologic involvement in late congenital syphilis is infrequent [98]. Interestingly, deafness, a common sequela of other congenital infections, is an uncommon finding in children with congenital syphilis.

Recommendations

Congenital syphilis is a devastating disease if not treated. Identification of infected mothers and neonates must be optimized. Serologic screening for gestational infection should be conducted early in pregnancy, during the third trimester (especially for high-risk women), and at delivery [92]. Even with adherence to these guidelines, some infants with congenital syphilis may be missed, probably because the maternal infection occurred immediately prior to delivery, providing insufficient time for an antibody response to develop, or the mothers received no treatment or inadequate treatment for syphilis. Thus, in areas where the infection is prevalent, retesting of infants presenting during the first weeks of life with symptoms or signs compatible with congenital syphilis may be prudent [89]. Screening should be with a nontreponemal test: VDRL or, more commonly, RPR. If the nontreponemal test is positive, one of the treponemal-specific tests should be performed to confirm maternal infection: typically either TP-PA, FTA-ABS, or TP-EIA. Maternal treatment history must be reviewed in detail if both nontreponemal and treponemal tests are positive. In addition, any mother with positive syphilis serology needs HIV testing, along with testing for other sexually transmitted infections, because co-infections are common.

The diagnosis of congenital syphilis should be considered in any neonate born to a mother with a reactive serologic test for syphilis. All infants should have a physical examination and nontreponemal antibody titer obtained. For accurate comparison, the nontreponemal test used must be the same for the infant and mother. Testing of cord blood is inadequate for screening because it can be contaminated by maternal blood and can yield false-positive results [99]. Criteria for further evaluation of neonates are listed in Table 32.2 [92,99]. Evaluation for congenital syphilis should also be considered for stillbirths occurring after 20 weeks' gestation and in neonates with unexplained prematurity or low birth weight, bullous skin lesions, maculopapular rashes, rhinitis, skeletal lesions, jaundice, hepatosplenomegaly, or lymphadenopathy [89,99].

At minimum, the diagnostic evaluation of infants suspected of having congenital syphilis includes physical examination, nontreponemal titers, long-bone radiographs, complete blood count, and CSF analysis. Further evaluation such as liver function tests, neuroimaging, chest radiograph, ophthalmologic examination, and auditory brain stem response should be considered if clinically indicated [99]. Long bone radiographs are suggested because 6–20% of asymptomatic infants will have detectable abnormalities [90]. Evaluation of CSF should include analysis of cell count, protein, and VDRL. The CSF VDRL titer is highly specific for neurosyphilis but has a sensitivity of only 22–69%, as opposed to PCR for *T. pallidum* DNA in the CSF, which is 75% sensitive and 96–100% specific [96]. Thus, if available, PCR cloud also be performed on CSF fluid. Finally, if possible, the placenta and umbilical cord should undergo histologic examination.

Ten days of parenteral aqueous crystalline penicillin G or penicillin G procaine is recommended for the treatment of symptomatic congenital syphilis in infants 4 weeks of age or younger. Aqueous crystalline penicillin G or penicillin G procaine is recommended because both provide adequate treatment for possible neurosyphilis; benzathine penicillin does not. This treatment regimen is considered prudent even if tests for neurosyphilis are negative because these tests may be falsely negative. Treatment is also indicated for asymptomatic infants born to women with untreated syphilis, inadequate treatment, treatment with a nonpenicillin regimen, and inadequate

Table 32.2 Criteria for Evaluation of Infants for Congenital Syphilis

Infants born to seropositive women who meet any of the following criteria should be thoroughly evaluated:
Mother had untreated syphilis.
Mother treated for syphilis during pregnancy with a nonpenicillin regimen (e.g., erythromycin).
Mother treated for syphilis fewer than 4 weeks before delivery.
Mother treated for syphilis during pregnancy with the appropriate penicillin regimen, but nontreponemal antibody titers did not decrease sufficiently after therapy (fourfold decline) to indicate an adequate response to treatment.
Mother did not have syphilis treatment well documented.
Mother was treated appropriately before pregnancy but did not have adequate serologic follow-up to ensure response to therapy and to rule out reinfection.

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documentation of treatment. In addition, treatment should be given to asymptomatic infants born to women treated within 1 month of delivery even if an appropriate regimen was given [92,99].

Treatment of asymptomatic infants born to a mother who received appropriate treatment without adequate nontreponemal titer decline is controversial. The controversy stems from the inability definitely to exclude neurosyphilis or congenital syphilis in at-risk infants. In addition, in late latent maternal infection, nontreponemal titers decline slowly and may remain stably positive at low titers (≤1:4). Thus, in some pregnant women, appropriate treatment may fail to produce a fourfold titer decline. Debate continues on how to manage infants in this scenario. Some advocate close observation and follow-up if the complete evaluation is negative, whereas others opt to treat these infants with a single dose of benzathine penicillin [92]. Consultation with local infectious disease experts is recommended. To date, though serology may be less reliable in HIV-infected women, there is no indication to alter maternal treatment or neonatal evaluation and treatment when caring for HIV-infected pregnant women and their children [99].

All infants with suspected or proven congenital syphilis, whether or not CNS involvement is confirmed, must undergo careful long-term evaluations of mental and motor function, hearing, and vision. In addition, nontreponemal tests should be monitored until they become nonreactive [99]. In the absence of fetal infection, the nontreponemal antibody titers should be decreasing by 3–4 months of age and should be undetectable in most infants by 6 months. If the infant was congenitally infected, adequate treatment should result in decreasing nontreponemal titers with disappearance by 6 months of age. If nontreponemal tests remain reactive beyond 6 months, reevaluation and retreatment may be indicated. Treponemal-specific antibodies may be detectable up to 15 months of age in uninfected neonates due to persistence of maternal transplacental antibodies. If antibodies persist beyond these limits, the infant should be reassessed and treated. In 85% of infected individuals, treponemal antibodies persist for life; therefore, these tests should not be monitored during follow-up assessments of congenitally infected children [93]. If the CSF VDRL was originally positive, it should be repeated at 6 months of age. If the CSF VDRL remains positive or if abnormal CSF indices persist, retreatment for possible neurosyphilis is indicated [99].

Varicella-Zoster Virus

Primary infection with VZV causes varicella (chickenpox), and reactivation of latent VZV infection results in herpes zoster (shingles). Although pregnant women occasionally develop varicella, this virus is an unusual cause of intrauterine or perinatal infection because even prior to routine immunization against varicella, more than 90% of women of childbearing age were already immune to VZV due to childhood illness [100]. In the prevaccine era, it was an uncommon infection in pregnant women, occurring in an estimated 0.4–0.7/1,000 pregnancies [101]. If an infection does occur during pregnancy, VZV rarely may be transmitted across the placenta, resulting in congenital or neonatal varicella infection.

Congenital varicella syndrome was first described in 1947 [102]. Infants with congenital varicella syndrome have characteristic cicatricial cutaneous scars, limb atrophy, rudimentary digits, chorioretinitis, and microcephaly [103]. In 1987, Alkalay et al. proposed three diagnostic criteria for congenital varicella syndrome, which included a documented maternal varicella infection in pregnancy, congenital cutaneous lesions in a dermatomal distribution, and evidence of congenital infection by immunologic proof (VZV-specific IgM at delivery) or zoster in infancy accompanied by a rise in VZV antibody titers (Table 32.3) [104]. In their study, 77% of infants fulfilling the diagnostic criteria for congenital varicella syndrome had abnormalities that included hypoplasia of the upper or lower extremities (80%), limb paresis (65%), hydrocephalus/cortical atrophy (35%), seizures (24%), Horner's syndrome (24%), intellectual disability (18%), and auditory palsy (6%). The region of neurologic involvement correlated well with the anatomic distribution of dermatomal disease.

Table 32.3 Proposed Diagnostic Criteria for Congenital Varicella Syndrome

Documented maternal varicella infection in pregnancy
Congenital cutaneous lesions in a dermatomal distribution
Evidence of congenital infection by either:
Immunologic proof of in utero varicella infection (VZV-specific IgM at delivery) or
Zoster in infancy accompanied by a rise in VZV antibody titers

Note: VZV, varicella-zoster virus; IgM, immunoglobulin M.

Table 32.4 Neurologic Abnormalities in Congenital Varicella Syndrome

Limb paresis
Hypoplasia of extremities (usually ipsilateral and distal to cutaneous abnormalities)
Seizures
Horner syndrome
Intellectual disability
Auditory nerve palsy
Hydrocephalus
Microcephaly
Cortical atrophy
CNS structural anomalies (prosencephalic cysts, glial fiber proliferation)
Encephalitis
Autonomic dysfunction
Ocular disease (chorioretinitis, microphthalmia, endophthalmitis, optic atrophy, cataracts)
Gastrointestinal dysmotility
Genitourinary dysfunction

The series of Enders et al. of 1,373 pregnant women with varicella during pregnancy is the largest experience to date [105]. Nine cases of congenital varicella and an additional 10 cases of zoster in infancy occurred in offspring of these women. The overall risk of congenital varicella syndrome was 1%. This risk increased to 2% if maternal infection occurred between 13 and 20 weeks' gestation.

VZV is a neurotropic virus. Neurologic damage is an important consequence of congenital varicella syndrome. Table 32.4 lists the various neurologic abnormalities that have been reported [103,105,106]. Autopsies of neonates with congenital varicella syndrome have demonstrated VZV virus in the cerebrum and spinal cord by dot blot and Southern blot hybridization [107]. Postmortem evaluations of suspected and confirmed congenital varicella syndrome cases report cortical and cerebellar necrosis, severe encephalopathy involving gray and white matter, and spinal cord disease including myelopathy, anterior horn cell loss, and gray matter gliosis [103].

Maternal varicella during the few days before and after delivery can result in transplacental infection or exposure to the virus during delivery [101]. This perinatal infection is not associated with congenital malformations but can be the cause of severe neonatal morbidity and mortality. Infants whose mothers develop varicella more than a week before delivery can be expected to escape infection or to have an uncomplicated illness, probably because the interval between the onset of maternal infection and birth provides sufficient time for transplacental transmission of VZV antibodies. In contrast, maternal chickenpox developing 5 days before or within 2 days following delivery poses a substantial risk to the newborn. The attack rate for perinatal infection under these circumstances is approximately 20%, and the incidence of fatal infection is about 30% [108]. Nosocomial exposure of high-risk infants can also result in neonatal varicella.

Infants who contract perinatal VZV during this high-risk period are typically well for the first 5–10 days of life. Infection is recognized thereafter with the typical cutaneous exanthema. The diagnosis is usually obvious because of the characteristic vesicular lesions and the recognition of recent maternal varicella. Progressive cutaneous infection is associated with life-threatening illness due to VZV pneumonia, encephalitis, hepatitis, and bleeding diathesis. Encephalitis is suggested by the occurrence of seizures accompanied by CSF and electroencephalogram (EEG) abnormalities. Because of the limited number of infants with perinatal VZV infection that have been reported, the risk of neurologic involvement has not been established.

Zoster, due to the reactivation of latent VZV, occurs during pregnancy but has not been associated with the classic features of congenital varicella syndrome. Enders et al. followed 366 women with zoster during pregnancy; none of these women had an affected newborn [105]. Infants whose mothers develop zoster late in pregnancy or immediately postpartum are not at risk for serious illness because these infants are protected by transplacentally acquired VZV antibodies.

In March 1995, the US Food and Drug Administration (FDA) approved licensure of a live attenuated vaccine for varicella. This vaccine is not approved for pregnant women or women who might conceive within 3 months following vaccination. In pregnant women who have inadvertently received varicella vaccine, there have been no reported cases of congenital varicella syndrome to date [109].

Recommendations

Pregnant women who are known to be susceptible to VZV infection and are exposed to active varicella lesions should be offered varicella-zoster immune globulin (VariZIG) as soon as possible, ideally within 96 hours, in order to prevent or lessen the severity of VZV infection [110]. Limited data suggest a benefit for VariZIG when given up to 10 days after exposure. It is possible, although not proven, that VariZIG may reduce the risk of congenital varicella infection. In the study by Enders et al., none of the 97 women who received VariZIG had an infant with congenital varicella syndrome [105].

VariZIG should be given to infants born to mothers whose onset of varicella is between 5 days before and 2 days after delivery [101]. Infants who develop varicella within the first 2 weeks of life should also be treated with intravenous acyclovir [110a, 110b]. Although controlled clinical evaluations of acyclovir treatment of infants with perinatal varicella are lacking, the drug prevents progressive VZV infection among other immunodeficient patients.

No intervention is required for term infants who are exposed to maternal zoster. These infants will have transplacentally acquired VZV antibodies and can be expected to be free of infection or to develop mild varicella.

Women who contract varicella during pregnancy should have ultrasounds performed to look for abnormalities associated with congenital varicella syndrome (e.g., limb hypoplasia, microcephaly, intrauterine growth restriction) [111]. The potential value of viral culture and PCR on the amniotic fluid of pregnancies complicated by varicella has been assessed and use of these tests should be discussed with an expert in perinatology [112].

Herpes Simplex Virus

The incidence of neonatal HSV infection in the United States is estimated to be 1/3,200 live births [113]. Mother-to-child transmission of HSV can occur as a congenital infection (5%), during the peripartum period (85%), or postnatally (10%) [114]. Peripartum and postnatal HSV infections are further classified into three disease categories: skin, eye, and/or mouth (SEM) disease; isolated CNS disease; and disseminated disease. Approximately 30% of neonatal infections primarily involve the CNS. An additional two-thirds of disseminated neonatal HSV disease involve the CNS as well, meaning that all combined, more than half of infants with neonatal HSV infection have CNS involvement [115].

Transmission of HSV to the Fetus and Newborn

Neonatal infection with HSV can be caused by either herpes simplex virus type 1 (HSV-1) or HSV-2. HSV-2 previously accounted for a majority of neonatal infections, but due to the increasing incidence of HSV-1 genital infections, HSV-1 is now the predominant cause in some populations [116]. More than 85% of neonates with HSV infection contract the virus perinatally though exposure to infected maternal secretions during labor and delivery. Nearly 80% of infected neonates are born to women who are asymptomatic during labor and delivery and have no known history of genital herpes [117]. Intrapartum asymptomatic HSV shedding by the mother may represent a primary infection or reactivation of latent virus from a previous genital HSV infection. In a study of almost 16,000 women prospectively cultured for HSV at delivery, 0.4% were found to have asymptomatic HSV shedding, regardless of their reported history of HSV infection [118]. Based on serologic evaluation, one-third of these women had primary genital infections, and two-thirds had recurrent infections. The attack rate among infants born to mothers with primary genital herpes at delivery is estimated to be 57% [113]. Fortunately, the attack rate for HSV infection among infants whose mothers are experiencing recurrent HSV shedding at delivery is substantially lower at 2% [113]. The difference in neonatal infection rates following primary versus recurrent maternal infection is due to many factors, including concentration of virus, site of viral excretion (cervix versus labia), and presence of transplacentally acquired protective antibodies in infants born to mothers with recurrent infection.

Postnatal exposure to HSV accounts for approximately 10% of neonatal infections [115]. These infections typically result from close contact with individuals who have active HSV-1 infection. These infections may be symptomatic or asymptomatic and cause the same spectrum of disease as seen with perinatal acquired infection. Nosocomial transmission of HSV from infant to infant, apparently by personnel or fomites, has also occurred in neonatal nurseries.

Fewer than 5% of neonatal HSV infections are congenital [119]. The risk factors for congenital HSV infection have not been determined. Affected infants have been born to mothers who were symptomatic and asymptomatic, as well as with primary and recurrent HSV infections during pregnancy [120]. HSV-2 is responsible for most congenital infections.

Clinical Manifestations and Consequences of Perinatal and Congenital HSV Infections

Although the rate and severity of neurologic abnormalities vary, SEM, isolated CNS, disseminated disease, and congenital infections have all been associated with neurologic deficits at follow-up. Approximately 45% of perinatal HSV infections are classified as SEM disease [121]. This mucocutaneous form of infection is characterized by vesicular lesions of the skin and mucosal surfaces with or without ocular disease. It is crucial to identify herpetic mucocutaneous lesions as soon as possible because without proper identification and treatment, infants with SEM disease often will progress to disseminated or CNS disease. In addition, during the pre–antiviral drug era, neurologic sequelae occurred in more than 25% of infants with localized SEM disease [122]. In infants limited to SEM disease, 5–10% will have evidence of neurologic impairment at follow-up [123]. One predictor of neurologic morbidity appears to be the frequency of mucocutaneous recurrences during the first 6 months of life [124]. With timely acyclovir treatment, though, the chance that the infant will escape neurologic sequelae exceeds 90%.

Thirty percent of neonatal HSV infections have isolated CNS involvement [121]. Neonatal HSV CNS disease usually occurs in infants who are about 2 weeks old (range 1–6 weeks). At presentation, some infants have active or resolving mucocutaneous lesions, but most do not. Only 65% of infants with CNS herpes have cutaneous lesions documented at any time during the course of their illness [121]. The signs of neonatal HSV CNS disease are often nonspecific and include fever or temperature instability, lethargy, and poor feeding. More specific signs include bulging fontanel, pyramidal tract signs, tremors, and seizures. The seizures often begin as focal, unilateral tonic-clonic movements that become generalized. Apnea is common. The CSF can be normal at the onset of symptoms but usually shows a mild lymphocytic pleocytosis (20–100 cells/mm^3) and elevated protein; the glucose may be normal or slightly low. Serial evaluations of the CSF usually show progressive abnormalities with a substantial increase in protein (up to 1 g/dL) and inflammatory cells [125]. The EEG is usually diffusely abnormal. CT scans of the brain may be normal or show diffuse enhancement. MRI is superior to CT scan in demonstrating subtle abnormalities early in infection. Focal CNS disease, typically in the temporal lobe, can occur via retrograde axonal transport, whereas diffuse brain involvement is more commonly associated with hematogenous spread of HSV. Cultures of the CSF for HSV have a low yield: less than one-third are positive. PCR of CSF is the preferred method to diagnose HSV meningoencephalitis [126]. The sensitivity of PCR on the CSF is 75–100%, with a specificity of 70–100% [127]. Although antiviral treatment of infants with neonatal HSV CNS disease reduces the mortality rate, 31% will go on to have neurodevelopmental impairment even if additional suppressive antiviral therapy is provided [128].

Disseminated disease represents 25% of cases of neonatal HSV infection [121]. Infants with disseminated herpes usually present during the first 2 weeks of life with fever and signs indistinguishable from bacterial sepsis. Disseminated HSV is often fulminant and associated with severe hepatitis, coagulopathy, pneumonitis, and possible concomitant encephalitis [115]. Unfortunately, infants with disseminated disease often lack cutaneous symptoms at presentation; 20% never develop mucocutaneous lesions. Disseminated neonatal herpes has a mortality rate of 85% if untreated [129]. The mortality rate for disseminated neonatal HSV infection is approximately 30%, even with appropriate antiviral therapy [130]. Infants who have had CNS involvement in the course of their disseminated disease often have neurologic sequelae if they survive.

In utero infection accounts for less than 5% of neonatal HSV. The consequences of in utero infection are devastating. Infants with intrauterine infection have skin vesicles or scars at birth, chorioretinitis in the first week of life, microphthalmia, and abnormal head CT scan. In one series of 13 infants infected in utero, all had multisystem disease [119]. Four died; six had severe neurologic sequelae, including hydranencephaly, brain atrophy, seizures, and severe developmental delay. Antiviral therapy does not reverse CNS damage sustained in utero.

Predictors of mortality and morbidity from neonatal HSV infections are outlined in Tables 32.5 and 32.6

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Table 32.5 Predictors of Mortality with Neonatal HSV Infection Based on Signs at Presentation

Coma or semicomatose state
Disseminated intravascular coagulation
Prematurity
Disseminated disease due to HSV-1

Note: Mortality was the same in those with CNS disease from HSV-1 and HSV-2.

Table 32.6 Predictors of Morbidity from Neonatal HSV Infection

Infection with HSV-2
Seizures
Extent of disease at presentation (disseminated, CNS, or SEM)
For SEM only, ≥3 mucocutaneous recurrences in 6 months after therapy

Note: HSV, herpes simplex virus; CNS, central nervous system; SEM, skin, eyes, and mouth.

[124]. Morbidity is defined as developmental delay of greater than 6 months, blindness, microcephaly, spastic quadriplegia, and/or seizures. The presence of seizures prior to the initiation of antiviral therapy significantly influences the incidence of neurologic deficits in survivors. In the era prior to high-dose (60 mg/kg/day) intravenous acyclovir, 93% of survivors with seizures had neurologic deficits compared with a 34% incidence of neurologic impairment in the absence of seizures [124]. The highest morbidity occurred in neonates with CNS disease, followed by those with disseminated disease. Only a small percentage of those with SEM disease had neurologic sequelae. As antiviral therapies have advanced, 1-year mortality has improved significantly in infants with CNS or disseminated disease. The rate of long-term neurodevelopmental impairment has improved for disseminated neonatal HSV disease, but neurodevelopmental outcomes in CNS disease remain unacceptably poor, with an estimated 31% of patients still having neurodevelopmental impairment at 1 year [131].

Recommendations

Prevention

Since most neonatal disease is acquired from maternal genital infection at the time of delivery, the first problem is to identify women with genital shedding of HSV at the onset of labor. If the mother has active genital lesions or prodromal symptoms consistent with genital HSV, cesarean delivery is recommended to avoid infant exposure [132]. Although some small reports suggest that the benefits of cesarean section are more likely to be realized if cesarean section is performed within 4–6 hours of membrane rupture, the American College of Obstetricians and Gynecologists (ACOG) recommends cesarean section regardless of the duration of membrane rupture [132].

Up to 1.4% of women with a past history of recurrent genital herpes will have HSV shedding without any lesions at the time of delivery [133]. Unfortunately, routine antepartum screening for HSV by history, physical examination, and virologic testing does not reliably predict who will be shedding HSV at the time of delivery. Women with active recurrent genital herpes should be offered suppressive antiviral therapy with oral acyclovir or valacyclovir beginning at 36 weeks of gestation [132]. Cesarean delivery for every woman with a past history of genital herpes (but no active lesions at the time of delivery) is not recommended by ACOG. Women who have had symptomatic primary genital herpes late in pregnancy may constitute a special subpopulation at greater risk of high-titer asymptomatic shedding; special consideration for cesarean section in these women may be necessary.

Diagnosis and Treatment

Isolation of HSV by viral culture remains the definitive method of diagnosing neonatal HSV infection. Viral culture of the CSF has a low yield, however, so detection of HSV DNA in CSF by PCR is routinely acceptable for defining CNS involvement in neonatal HSV infection [134]. Serologic tests are not routinely used because the majority of newborn infants have passive maternal HSV antibodies due to transplacental acquisition. Furthermore, absence of HSV antibodies does not rule out herpes because the infant may have acquired the infection late in gestation or postnatally as a result of primary maternal HSV or from a nonmaternal source. In addition, some infected neonates have delayed or no serologic response to infection. Currently, there is no reliable method for detection of HSV IgM.

Because the maternal history of herpes is not a reliable clue, infants with neonatal herpes will only be recognized if clinicians maintain a high index of suspicion and viral diagnostic procedures are included in the

evaluation of infants with suspicious mucocutaneous lesions, nonbacterial sepsis, or unexplained seizures. Timely antiviral therapy may result in increased survival and improved long-term outcome for neonates infected with HSV [124]. Prior to initiation of empirical parenteral acyclovir in an infant with suspected neonatal HSV infection, diagnostic specimens should be obtained. This includes obtaining swab specimens from the mouth, nasopharynx, conjunctivae, and anus for HSV culture (and, if desired, for HSV PCR), skin vesicular fluid for HSV culture and PCR, CSF specimens for PCR, whole blood for PCR, and measuring blood alanine aminotransferase (ALT) level [134].

High-dose parenteral acyclovir therapy (60 mg/kg/day) is recommended for the treatment of neonatal herpes. SEM disease should be treated for 14 days and CNS and disseminated disease for at least 21 days. In order to ensure viral clearance in patients with CNS disease, repeat HSV PCR should be performed on the CSF near the end of the 21-day course of therapy. If still positive, intravenous acyclovir should be continued for another 7 days, with repeat PCR on the CSF once again performed at the end of this extended course. Consultation with an infectious disease specialist is should be sought for any patient requiring extended therapy [134].

After completion of the appropriate course of intravenous acyclovir for neonatal HSV infection, a 6-month suppressive course of oral acyclovir has been shown to benefit both short- and long-term outcomes [128]. In the short term, infants with CNS and SEM disease had less frequent recurrences of skin lesions while receiving oral suppressive therapy at a dose of 300 mg/m^2 three times a day. Most notably, infants with CNS involvement who received the same oral suppressive acyclovir therapy after completion of their 21-day course of intravenous acyclovir had better long-term neurodevelopmental outcomes than the placebo group, who only received the initial course of intravenous acyclovir. Any infant diagnosed with neonatal HSV infection should have ongoing evaluation of developmental milestones through childhood, with appropriate referrals to speech, occupational, and physical therapy as needed.

References

1. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007; **17**: 253–76.
2. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev* 2013; **26**: 86–102.
3. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol* 2007; **17**: 355–63.
4. Stagno S, Reynolds DW, Huang ES, et al. Congenital cytomegalovirus infection. *N Engl J Med* 1977; **296**: 1254–8.
5. Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection: a longitudinal follow-up study. *Am J Dis Child* 1982; **136**: 896–901.
6. Fowler KB, McCollister FP, Dahle AJ, et al. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J Pediatr* 1997; **130**: 624–30.
7. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis* 2013; **57**(Suppl 4): S178–81.
8. Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. *Pediatrics* 1980; **66**: 758–62.
9. Boppana SB, Fowler KB, Vaid Y, et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 1997; **99**: 409–14.
10. Pass RF, Anderson B. Mother-to-child transmission of cytomegalovirus and prevention of congenital infection. *J Pediatr Infect Dis Soc* 2014; **3**: S2–6.
11. Boppana SB, Rivera LB, Fowler KB, et al. Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. *N Engl J Med* 2001; **344**: 1366–71.
12. Monif GR, Egan EA 2nd, Held B, Eitzman DV. The correlation of maternal cytomegalovirus infection during varying stages in gestation with neonatal involvement. *J Pediatr* 1972; **80**: 17–20.
13. Reynolds DW, Stagno S, Stubbs KG, et al. Inapparent congenital cytomegalovirus infection with elevated cord IgM levels: casual relation with auditory and mental deficiency. *N Engl J Med* 1974; **290**: 291–6.
14. Hanshaw JB, Scheiner AP, Moxley AW, et al. School failure and deafness after "silent" congenital cytomegalovirus infection. *N Engl J Med* 1976; **295**: 468–70.
15. Conboy TJ, Pass RF, Stagno S, et al. Intellectual development in school-aged children with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 1986; **77**: 801–6.

.033

16. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 1992; **90**: 862–6.

17. Dahle AJ, Fowler KB, Wright JD, et al. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol* 2000; **11**: 283–90.

18. Boppana SB, Fowler KB, Pass RF, et al. Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. *J Pediatr* 2005; **146**: 817–23.

19. Forner G, Abate D, Mengoli C, et al. High cytomegalovirus (CMV) DNAemia predicts CMV sequelae in asymptomatic congenitally infected newborns born to women with primary infection during pregnancy. *J Infect Dis* 2015; **212**: 67–71.

20. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome. *JAMA* 1986; **256**: 1904–8.

21. Boppana SB, Pass RF, Britt WJ, et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J* 1992; **11**: 93–9.

22. Stagno S, Pass RF, Alford CA. Perinatal infections and maldevelopment. *Birth Defects Original Article Series* 1981; **17**: 31–50.

23. McCracken GH Jr, Shinefield HM, Cobb K, et al. Congenital cytomegalic inclusion disease: a longitudinal study of 20 patients. *Am J Dis Child* 1969; **117**: 522–39.

24. Butt W, Mackay RJ, de Crespigny LC, et al. Intracranial lesions of congenital cytomegalovirus infection detected by ultrasound scanning. *Pediatrics* 1984; **73**: 611–4.

25. James SH, Kimberlin DW, Whitley RJ. Antiviral therapy for herpesvirus central nervous system infections: neonatal herpes simplex virus infection, herpes simplex encephalitis, and congenital cytomegalovirus infection. *Antiviral Res* 2009; **83**: 207–13.

26. Troendle Atkins J, Demmler GJ, Williamson WD, et al. Polymerase chain reaction to detect cytomegalovirus DNA in the cerebrospinal fluid of neonates with congenital infection. *J Infect Dis* 1994; **169**: 1334–7.

27. Noyola DE, Demmler GJ, Nelson CT, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 2001; **138**: 325–31.

28. Williamson WD, Desmond MM, LaFevers N, et al. Symptomatic congenital cytomegalovirus: disorders of language, learning, and hearing. *Am J Dis Child* 1982; **136**: 902–5.

29. Rivera LB, Boppana SB, Fowler KB, et al. Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 2002; **110**: 762–7.

30. Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143**: 16–25.

31. Kimberlin DW, Jester PM, Sanchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015; **372**: 933–43.

32. Wolf A, Cowen D, Paige BH. Toxoplasmic encephalomyelitis. III. A new case of granulomatous encephalomyelitis due to a protozoon. *Am J Pathol* 1939; **15**: 657–94.

33. McAuley JB. Congenital toxoplasmosis. *J Pediatr Infect Dis Soc* 2014; **3**: S30–5.

34. Lynfield R, Guerina NG. Toxoplasmosis. *Pediatr Rev* 1997; **18**: 75–83.

35. American Academy of Pediatrics. *Toxoplasma gondii* Infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds., *Red Book: 2015 Report of the Committee on Infectious Diseases*. Elk Grive Village, IL: American Academy of Pediatrics, 2015: 787–96.

36. Vogel N, Kirisits M, Michael E, et al. Congenital toxoplasmosis transmitted from an immunologically competent mother infected before conception. *Clin Infect Dis* 1996; **23**: 1055–60.

37. Lindsay DS, Dubey JP. *Toxoplasma gondii*: the changing paradigm of congenital toxoplasmosis. *Parasitology* 2011; **138**: 1829–31.

38. Hohlfeld P, Daffos F, Thulliez P, et al. Fetal toxoplasmosis: outcome of pregnancy and infant follow-up after in utero treatment. *J Pediatr* 1989; **115**: 765–9.

39. Foulon W, Villena I, Stray-Pedersen B, et al. Treatment of toxoplasmosis during pregnancy: a multicenter study of impact on fetal transmission and children's sequelae at age 1 year. *Am J Obstet Gynecol* 1999; **180**: 410–5.

40. SYROCOT (Systematic Review on Congenital Toxoplasmosis) Study Group, Thiebaut R, Leproust S, et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet* 2007; **369**: 115–22.

41. Prusa AR, Kasper DC, Pollak A, et al. The Austrian Toxoplasmosis Register, 1992–2008. *Clin Infect Dis* 2015; **60**: e4–10.

42. Hotop A, Hlobil H, Gross U. Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis* 2012; **54**: 1545–52.

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.033

43. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med* 2010; **7**.
44. Wallon M, Peyron F, Cornu C, et al. Congenital toxoplasma infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. *Clin Infect Dis* 2013; **56**: 1223–31.
45. Koppe JG, Loewer-Sieger DH, de Roever-Bonnet H. Results of 20-year follow-up of congenital toxoplasmosis. *Lancet* 1986; **1**: 254–6.
46. Stagno S, Reynolds DW, Amos CS, et al. Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegaloviral and *Toxoplasma* infections. *Pediatrics* 1977; **59**: 669–78.
47. Wilson CB, Remington JS, Stagno S, Reynolds DW. Development of adverse sequelae in children born with subclinical congenital *Toxoplasma* infection. *Pediatrics* 1980; **66**: 767–74.
48. Guerina NG, Hsu HW, Meissner HC, et al. Neonatal serologic screening and early treatment for congenital *Toxoplasma gondii* infection. The New England Regional Toxoplasma Working Group. *N Engl J Med* 1994; **330**: 1858–63.
49. Stillwaggon E, Carrier CS, Sautter M, McLeod R. Maternal serologic screening to prevent congenital toxoplasmosis: a decision-analytic economic model. *PLoS Neglect Trop Dis* 2011; **5**: e1333.
50. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis* 1994; **18**: 853–61; quiz 62.
51. McLeod R, Boyer K, Karrison T, et al. Outcome of treatment for congenital toxoplasmosis, 1981–2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. *Clin Infect Dis* 2006; **42**: 1383–94.
52. McAuley J, Boyer KM, Patel D, et al. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. *Clin Infect Dis* 1994; **18**: 38–72.
53. Roizen N, Swisher CN, Stein MA, et al. Neurologic and developmental outcome in treated congenital toxoplasmosis. *Pediatrics* 1995; **95**: 11–20.
54. Patel DV, Holfels EM, Vogel NP, et al. Resolution of intracranial calcifications in infants with treated congenital toxoplasmosis. *Radiology* 1996; **199**: 433–40.
55. Naessens A, Jenum PA, Pollak A, et al. Diagnosis of congenital toxoplasmosis in the neonatal period: a multicenter evaluation. *J Pediatr* 1999; **135**: 714–9.
56. Gilbert RE, Thalib L, Tan HK, et al. Screening for congenital toxoplasmosis: accuracy of immunoglobulin M and immunoglobulin A tests after birth. *J Med Screen* 2007; **14**: 8–13.
57. Olariu TR, Remington JS, McLeod R, et al. Severe congenital toxoplasmosis in the United States: clinical and serologic findings in untreated infants. *Pediatr Infect Dis J* 2011; **30**: 1056–61.
58. Foulon W, Pinon JM, Stray-Pedersen B, et al. Prenatal diagnosis of congenital toxoplasmosis: a multicenter evaluation of different diagnostic parameters. *Am J Obstet Gynecol* 1999; **181**: 843–7.
59. Wallon M, Franck J, Thulliez P, et al. Accuracy of real-time polymerase chain reaction for *Toxoplasma gondii* in amniotic fluid. *Obstet Gynecol* 2010; **115**: 727–33.
60. Dudgeon JA. Congenital rubella. *J Pediatr* 1975; **87**: 1078–86.
61. Reef SE, Frey TK, Theall K, et al. The changing epidemiology of rubella in the 1990s: on the verge of elimination and new challenges for control and prevention. *JAMA* 2002; **287**: 464–72.
62. Centers for Disease Control and Prevention. Increase in rubella and congenital rubella syndrome – United States, 1988–1990. *MMWR Morbid Mortal Wkly Rep*1991; **40**: 93–9.
63. Achievements in public health: elimination of rubella and congenital rubella syndrome – United States, 1969–2004. *Ann Pharmacother* 2005; **39**: 1151–2.
64. Centers for Disease Control and Prevention. Three cases of congenital rubella syndrome in the postelimination era – Maryland, Alabama, and Illinois, 2012. *MMWR Morbid Mortal Wkly Rep*2013; **62**:226–9.
65. Lambert N, Strebel P, Orenstein W, et al. Rubella. *Lancet* 2015; **385**: 2297–307.
66. Ujiie M, Nabae K, Shobayashi T. Rubella outbreak in Japan. *Lancet* 2014; **383**: 1460–1.
67. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982; **2**: 781–4.
68. Neu N, Duchon J, Zachariah P. TORCH infections. *Clin Perinatol* 2015; **42**: 77–103.
69. Meitsch K, Enders G, Wolinsky JS, et al. The role of rubella-immunoblot and rubella-peptide-EIA for the diagnosis of the congenital rubella syndrome during the prenatal and newborn periods. *J Med Virol* 1997; **51**: 280–3.
70. Mace M, Cointe D, Six C, et al. Diagnostic value of RT-PCR of amniotic fluid for prenatal diagnosis of congenital rubella infection in pregnant women with confirmed primary rubella infection. *J Clin Microbiol* 2004; **42**: 4818–20.

71. Ueda K, Nishida Y, Oshima K, Shepard TH. Congenital rubella syndrome: correlation of gestational age at time of maternal rubella with type of defect. *J Pediatr* 1979; **94**: 763–5.
72. Peckham CS. Clinical and laboratory study of children exposed in utero to maternal rubella. *Arch Dis Childhood* 1972; **47**: 571–7.
73. Frey TK. Neurological aspects of rubella virus infection. *Intervirology* 1997; **40**: 167–75.
74. Weil ML, Itabashi H, Cremer NE, et al. Chronic progressive panencephalitis due to rubella virus simulating subacute sclerosing panencephalitis. *N Engl J Med* 1975; **292**: 994–8.
75. Macfarlane DW, Boyd RD, Dodrill CB, Tufts E. Intrauterine rubella, head size, and intellect. *Pediatrics* 1975; **55**: 797–801.
76. Chang YC, Huang CC, Liu CC. Frequency of linear hyperechogenicity over the basal ganglia in young infants with congenital rubella syndrome. *Clin Infect Dis* 1996; **22**: 569–71.
77. Lane B, Sullivan EV, Lim KO, et al. White matter MR hyperintensities in adult patients with congenital rubella. *Am J Neuroradiol* 1996; **17**: 99–103.
78. Townsend JJ, Baringer JR, Wolinsky JS, et al. Progressive rubella panencephalitis: late onset after congenital rubella. *N Engl J Med* 1975; **292**: 990–3.
79. Desmond MM, Fisher ES, Vorderman AL, et al. The longitudinal course of congenital rubella encephalitis in nonretarded children. *J Pediatr* 1978; **93**: 584–91.
80. McIntosh ED, Menser MA. A fifty-year follow-up of congenital rubella. *Lancet* 1992; **340**: 414–5.
81. Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. *J Pediatr* 1978; **93**: 699–703.
82. Brown AS, Cohen P, Greenwald S, Susser E. Nonaffective psychosis after prenatal exposure to rubella. *Am J Psychiatry* 2000; **157**: 438–43.
83. Tanemura M, Suzumori K, Yagami Y, Katow S. Diagnosis of fetal rubella infection with reverse transcription and nested polymerase chain reaction: a study of 34 cases diagnosed in fetuses. *Am J Obstet Gynecol* 1996; **174**: 578–82.
84. Reef SE, Redd SB, Abernathy E, et al. The epidemiological profile of rubella and congenital rubella syndrome in the United States, 1998–2004: the evidence for absence of endemic transmission. *Clin Infect Dis* 2006; **43**(Suppl 3): S126–32.
85. Papania MJ, Wallace GS, Rota PA, et al. Elimination of endemic measles, rubella, and congenital rubella syndrome from the Western hemisphere: the US experience. *JAMA Pediatr* 2014; **168**: 148–55.
86. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommend Rep* 2013; **62**: 1–34.
87. Klass PE, Brown ER, Pelton SI. The incidence of prenatal syphilis at the Boston City Hospital: a comparison across four decades. *Pediatrics* 1994; **94**: 24–8.
88. Wharton M, Chorba TL, Vogt RL, et al. Case definitions for public health surveillance. *MMWR Recommend Rep* 1990; **39**: 1–43.
89. Kwak J, Lamprecht C. A review of the guidelines for the evaluation and treatment of congenital syphilis. *Pediatr Ann* 2015; **44**: e108–14.
90. Sung L, MacDonald NE. Syphilis: a pediatric perspective. *Pediatr Rev* 1998; **19**: 17–22.
91. Sanchez PJ. Laboratory tests for congenital syphilis. *Pediatr Infect Dis J* 1998; **17**: 70–1.
92. American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds., *Red Book: 2015 Report of the Committee on Infectious Diseases*. Elk Grove, IL: American Academy of Pediatrics, 2015: 755–68.
93. Stoll BJ. Congenital syphilis: evaluation and management of neonates born to mothers with reactive serologic tests for syphilis. *Pediatr Infect Dis J* 1994; **13**: 845–52; quiz 53.
94. Beeram MR, Chopde N, Dawood Y, et al. Lumbar puncture in the evaluation of possible asymptomatic congenital syphilis in neonates. *J Pediatr* 1996; **128**: 125–9.
95. Srinivasan G, Ramamurthy RS, Bharathi A, et al. Congenital syphilis: a diagnostic and therapeutic dilemma. *Pediatr Infect Dis* 1983; **2**: 436–41.
96. Sanchez PJ, Wendel GD Jr, Grimprel E, et al. Evaluation of molecular methodologies and rabbit infectivity testing for the diagnosis of congenital syphilis and neonatal central nervous system invasion by *Treponema pallidum*. *J Infect Dis* 1993; **167**: 148–57.
97. Michelow IC, Wendel GD Jr, Norgard MV, et al. Central nervous system infection in congenital syphilis. *N Engl J Med* 2002; **346**: 1792–8.
98. Fiumara NJ, Lessell S. Manifestations of late congenital syphilis: an analysis of 271 patients. *Arch Dermatol* 1970; **102**: 78–83.
99. Workowski KA, Bolan GA, CDC. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recommend Rep* 2015; **64**: 1–137.

100. Bialas KM, Swamy GK, Permar SR. Perinatal cytomegalovirus and varicella zoster virus infections: epidemiology, prevention, and treatment. *Clin Perinatol* 2015; **42**: 61–75.

101. American College of Obstetricians and Gynecologists. Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy (Practice Bulletin No. 151). *Obstet Gynecol* 2015; **125**: 1510–25.

102. Laforet EG, Lynch CL Jr. Multiple congenital defects following maternal varicella: report of a case. *N Engl J Med* 1947; **236**: 534–7.

103. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med* 1994; **330**: 901–5.

104. Alkalay AL, Pomerance JJ, Rimoin DL. Fetal varicella syndrome. *J Pediatr* 1987; **111**: 320–3.

105. Enders G, Miller E, Cradock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994; **343**: 1548–51.

106. Jones KL, Johnson KA, Chambers CD. Offspring of women infected with varicella during pregnancy: a prospective study. *Teratology* 1994; **49**: 29–32.

107. Scharf A, Scherr O, Enders G, Helftenbein E. Virus detection in the fetal tissue of a premature delivery with a congenital varicella syndrome: a case report. *J Perinatal Med* 1990; **18**: 317–22.

108. Brunell PA. Fetal and neonatal varicella-zoster infections. *Semin Perinatol* 1983; **7**: 47–56.

109. Wilson E, Goss MA, Marin M, et al. Varicella vaccine exposure during pregnancy: data from 10 years of the pregnancy registry. *J Infect Dis* 2008; **197**(Suppl 2): S178–84.

110. Ogilvie MM. Antiviral prophylaxis and treatment in chickenpox: a review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998; **36**(Suppl 1): 31–8.

110a. Smith CK, Arvin AM. Varicella in the fetus and newborn. *Semin Fetal Neonat Med* 2009; **14**: 209–17.

110b. Meyers JD. Congenital varicella in term infants: risk reconsidered. *J Infect Dis* 1974; **129**: 215–7.

111. Meyberg-Solomayer GC, Fehm T, Muller-Hansen I, et al. Prenatal ultrasound diagnosis, follow-up, and outcome of congenital varicella syndrome. *Fetal Diagn Ther* 2006; **21**: 296–301.

112. Mouly F, Mirlesse V, Meritet JF, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. *Am J Obstet Gynecol* 1997; **177**: 894–8.

113. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; **289**: 203–9.

114. Kimberlin DW. Herpes simplex virus infections of the newborn. *Semin Perinatol* 2007; **31**: 19–25.

115. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. *Clin Perinatol* 2015; **42**: 47–59.

116. Jones CA, Raynes-Greenow C, Issacs D. Population-based surveillance of neonatal HSV infection in Australia (1997–2011). *Clin Infect Dis* 2014; **59**(4): 525–31.

117. James SH, Sheffield JS, Kimberlin DW. Mother-to-child transmission of herpes simplex virus. *J Pediatr Infect Dis Soc* 2014; **3**: S19–23.

118. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med* 1991; **324**: 1247–52.

119. Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infections. *J Pediatr* 1987; **110**: 97–101.

120. Vasileiadis GT, Roukema HW, Romano W, et al. Intrauterine herpes simplex infection. *Am J Perinatol* 2003; **20**: 55–8.

121. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001; **108**: 223–9.

122. Kimberlin DW. Management of HSV encephalitis in adults and neonates: diagnosis, prognosis and treatment. *Herpes* 2007; **14**: 11–6.

123. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991; **324**: 444–9.

124. Whitley R, Arvin A, Prober C, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med* 1991; **324**: 450–4.

125. Kimberlin D. Herpes simplex virus, meningitis and encephalitis in neonates. *Herpes* 2004; **11**(Suppl 2): 65A–76A.

126. Lakeman FD, Whitley RJ, National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. *J Infect Dis* 1995; **171**: 857–63.

127. Kimberlin DW, Lakeman FD, Arvin AM, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. *J Infect Dis* 1996; **174**: 1162–7.

128. Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *N Engl J Med* 2011; **365**: 1284–92.

129. Whitley RJ, Nahmias AJ, Soong SJ, et al. Vidarabine therapy of neonatal herpes simplex virus infection. *Pediatrics* 1980; **66**: 495–501.

130. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001; **108**: 230–8.

131. James SH, Kimberlin DW. Neonatal herpes simplex virus infection. *Infect Dis Clin North Am* 2015; **29**(3): 391–400.

132. American College of Obstetricians and Gynecologists. Clinical management guidelines for obstetrician-gynecologists: management of herpes in pregnancy (Practice Bulletin No. 82). *Obstet Gynecol* 2007; **109**: 1489–98.

133. Arvin AM, Hensleigh PA, Prober CG, et al. Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. *N Engl J Med* 1986; **315**: 796–800.

134. American Academy of Pediatrics. Herpes Simplex. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds., *Red Book: 2015 Report of the Committee on Infectious Diseases*. Oak Grove, IL: American Academy of Pediatrics, 2015: 432–45.

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Chapter 33

Neurologic Complications of Perinatal Human Immunodeficiency Virus Infection

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Introduction

Since the initial description of acquired immune deficiency syndrome (AIDS) cases in infants and children more than 30 years ago [1], the epidemiology of pediatric human immunodeficiency virus type 1 (HIV) epidemic has changed significantly [2–4]. Most pediatric HIV infections occur through perinatal transmission [5]. Dramatic declines in the number of children with perinatally acquired HIV infection (PHIV+) have been reported in the United States and other high-income countries (HICs) due to prompt implementation of strategies to prevent mother-to-child transmission of HIV (PMTCT) [3,4]. Further, the availability of combination antiretroviral therapy (cART) has led to improved survival of HIV-infected children into adolescence and adulthood, changing most HIV infections into a chronic rather than an acute disease [6].

Progress has been made in PMTCT in many low- and middle-income countries (LMICs) due to increasing access to cART for HIV-positive mothers as well as uptake of highly effective combination antiretroviral (ARV) regimens to prevent mother-to-child HIV transmission during antepartum, intrapartum, and postnatal transmission of HIV during breastfeeding [7,8]. However, implementation of PMTCT programs have been slower in LMICs due to variety of health systems and other barriers [2,9–11].

The central nervous system (CNS) is a vulnerable target in infants and children with (PHIV+) [2,12]. Neurologic complications of pediatric HIV infection result in major morbidity and mortality [13–16]. The most common neurologic manifestation of perinatal HIV infection is HIV encephalopathy, followed by other sequelae, including developmental delay, behavioral problems, opportunistic infections (OIs) of the CNS, seizures, myopathy, and peripheral neuropathies [17].

The purpose of this chapter is to review the neurologic complications of perinatal HIV infection with a focus on the pathogenesis, clinical manifestations, and neuroimaging findings of HIV encephalopathy in infants. We also briefly summarize the epidemiology, clinical features, treatment, and prevention of perinatal HIV infection.

Epidemiology

United States

During the past three decades, the epidemiology and prevention of pediatric human immunodeficiency virus type 1 (HIV) epidemic have evolved dramatically in the United States and other HICs [3,4,18–20]. In the United States, children younger than 13 years have accounted for 0.05% and 0.8% of all estimated AIDS diagnoses in 2011 and cumulative AIDS diagnoses through 2011, respectively [21]. At the end of 2014, an estimated 11,500 cases children, adolescents and adults with PHIV+ live in the United States [22]. The racial and ethnic and geographic distribution of AIDS cases in children parallels that of women with AIDS. Perinatally acquired HIV infection has occurred more frequently among black not Hispanic (61%) and Hispanic (23%) children than among white non-Hispanic children [23,24].

The number of infants born with HIV has dropped from a high of 2,000 per year in the early 1990s to fewer than 60 in 2010 [21]. In the United States and other HICs, widespread implementation of routine antenatal HIV testing, initiation of three-drug cART during pregnancy for HIV-infected women, elective Cesarean section before labor and before membrane rupture; and complete avoidance of breastfeeding have resulted in mother-to-child transmission (MTCT) rates below 2% [25,26]. Virtual elimination of MTCT is a reality in many HICs; new perinatal infections are exceeding rare and occur due to missed prevention opportunities [27–30].

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Global

In LMICs, remarkable progress in implementation of PMTCT interventions has resulted in a decline of new PHIV+ infections by 47% between 2010 (300,000 cases) and 2016 (160,000 cases) [31]. MTCT rates of less than 5% have been noted in clinical trials and implementation programs [30]. However, many obstacles remain to elimination of PHIV+ worldwide, including low antenatal HIV testing rates, suboptimal coverage of PMTCT interventions, low early infant HIV diagnosis, delayed initiation of cART for pregnant and breastfeeding women, and stigma and discrimination faced by HIV-infected women [2,32]. More than 90% of HIV-infected children reside in sub-Saharan Africa [5]. Without treatment, over 50% of HIV-infected children die by their second birthday [33].

Perinatal HIV Transmission: Rates, Timing, and Risk Factors

Mother-to-child transmission of HIV can take place in utero via transplacental infection, intrapartum by exposure to maternal blood at the time of labor and delivery, and postnatally through breastfeeding [4,5]. Perinatal HIV transmission rates in the absence of specific interventions vary from about 15% to 30% among nonbreastfeeding HIV-infected women in the United States and Europe to 25% to 45% among breastfeeding populations in sub-Saharan Africa [34–38]. Most MTCT occurs during the intrapartum period. In the nonbreastfed infant, about one-third of transmissions occur during gestation and the remaining two-thirds during delivery, whereas in the breastfed infant, one-third to one-half of overall transmission may occur after delivery during lactation [8,38–40].

Many maternal, obstetric, infant, and viral-related factors may contribute to perinatal HIV transmission risk [36]. The maternal serum HIV RNA level is the strongest predictor of both intrauterine and intrapartum transmission [41]. However, transmission can occur rarely among pregnant women with low or undetectable serum levels of HIV around the time of labor and delivery [42]. Other maternal risk factors associated with higher transmission rates include women with AIDS, acute HIV infection during pregnancy, and low CD4 counts [41]. Obstetric risk factors associated with increased risk of transmission include vaginal delivery, rupture of membranes for more than 4 hours, chorioamnionitis, and invasive obstetric procedures [35]. Premature infants born to HIV-infected women have a higher rate of perinatal HIV infection than full-term infants. Studies evaluating the relative risk of HIV transmission associated with vaginal (versus cesarean) delivery have demonstrated decreased transmission with cesarean delivery [43,44].

In resource-poor settings, where breastfeeding is the cultural norm, postnatal transmission of HIV through breast milk remains a serious problem and carries an estimated risk of about 15% when breastfeeding is prolonged and continued into the second year of life [45]. Risk factors for breast milk HIV transmission include women seroconverting during lactation, high HIV DNA or RNA level in plasma and breast milk, longer duration of breastfeeding, mixed infant feeding, bleeding or cracked nipples, subclinical and clinical mastitis, and breast abscesses [36,46].

Neurologic Complications of Pediatric HIV Infection

Central nervous system (CNS) manifestations in patients with HIV infection may be due to direct effects of HIV viral infection or to secondary effects of OIs of the CNS that may occur in advanced stages of HIV/AIDS [47,48]. Children with PHIV+ are at increased risk of morbidity and mortality from neurologic complications compared with HIV-infected adult patients [15,17]. The impact and neurologic manifestations of children with PHIV+ infection are different from the neurologic sequelae in HIV-infected adults, who acquire infection at the time of CNS maturity (Table 33.1).

Children with PHIV+ typically present with neurobehavioral disturbances early in the clinical course prior to severe immunosuppression [48]. HIV disease progression and severe morbidity have been reported among children with PHIV+ in the ART era [49]. In 2013, only 25% of children in need of cART in LMICs received therapy, and thus infants with PHIV+ remain at risk for severe neurocognitive impairment in these settings [50]. Initiation of early cART in infants with PHIV+ may reduce the incidence of severe neurologic complications, but neurocognitive problems may persist despite undetectable viral load [14,17,51–53].

A myriad of other complex and diverse neurologic and neurobehavioral complications have been described in pediatric HIV infection [13–15,17], but only HIV encephalopathy will be discussed in detail

Table 33.1 Neurologic Manifestations of HIV Infection in Children and Adults

Features	Children	Adults
Syndrome	HIV-associated encephalopathy	AIDS-dementia complex
Target cells	Macrophages, microglia, astrocytes (minor role)	Macrophages, microglia astrocytes (central role)
Latent period	Short	Long
	Encephalopathy often the first AIDS-defining illness	
Clinical features	Motor, cognitive, and language functions impaired	Motor and cognitive functions deteriorate
Opportunistic CNS infections	Rare	Common
Cerebrovascular disease	Rare	Common

Table 33.2 Neurologic Complications of HIV Infection in Children

HIV encephalopathy
Behavioral or psychiatric problems (e.g., ADHD, anxiety disorders, depression)
Opportunistic infections of the CNS (e.g., CMV infection, TB)
Epilepsy
Cerebrovascular disease
Primary CNS lymphomas
Peripheral neuropathy
Myopathy

Note: ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; CMV, cytomegalovirus; TB, tuberculosis.
Source: Data from Refs. [13,14,17].

here (Table 33.2). Although the pathogenesis of pediatric neuroAIDS needs further research, the unique pathologic and CNS features of PHIV+ likely reflect the vulnerability of the immature infant brain to HIV infection [14,47,54–56].

HIV Encephalopathy

In the pre-ART era, neurologic disease in children with PHIV+ was most commonly recognized as HIV encephalopathy, an early primary HIV-associated CNS complication, often presenting in the first year of life [14,57–59]. In the pre-ART era, 20–60% of children with AIDS developed progressive encephalopathy, with a survival of 6–24 months [14,60–62]. In the current era of cART, the incidence of overt and rapidly progressive HIV encephalopathy has decreased dramatically but may be associated with more subtle and insidious CNS manifestations [63–66].

Pathogenesis

The neuropathogenesis of HIV encephalopathy is poorly understood [13,48,67]. Studies have shown that HIV is neurotropic and enters the CNS soon after primary infection and may persist in this compartment during the course of the infection [48,55]. CNS targets of HIV infection may be different in children and adults. In contrast to terminally differentiated cells of the mature nervous system of adults, the immature nervous system of children has mitotically active cells. Blood-derived macrophages, microglial cells, and their derivatives harbor HIV in the CNS [48,63,68]. The virus crosses the blood-brain barrier (BBB) via infected monocytes (i.e., macrophages and microglia) [69]. Pathology studies in infants with PHIV+ suggest indirect CNS injury due to perivascular cellular inflammation involving HIV-infected macrophages and multinucleated cells followed by infection of astocytes and activation of the neurotoxic cascade [70,71]. Direct infection of the neurons may also possibly occur [72].

Neuroinflammation is a vital component in the neuropathogenesis of HIV encephalopathy and appears to involve a cascade of viral proteins (especially transcriptional transactivator [Tat] and glycoprotein gp120), various proinflammatory cytokines (i.e.,

tumor necrosis factor & [TNF-α], interferon-γ [INF-γ], interleukin 12 [IL-12]) and chemokines, and neurotransmitters that promote ongoing inflammation, excitation, and overstimulation of the *N*-methly-D-aspartate type receptor (NMDAR) system [68,73–75]. This subsequently leads to neuronal injury and death secondary to apoptosis or necrosis, astrocytosis, and dendritic and synaptic damage [76]. Neural progenitors cells may also be involved in the neuropathogenesis of HIV encephalopathy [77].

Alteration of the BBB and entry of HIV-infected monocytes into the CNS with subsequent immune activation and viral tropism may play a key role in the development of HIV-associated neurocognitive disorders (HANDs) [73]. The chemokine receptors CCR5 and CXCR4 are expressed by neurons, astrocytes, and microglia. With chronic virus exposure, binding of HIV gp120 with the CXCR4 chemokine receptor may induce caspase-3-dependent neuronal apoptosis through activation of p38 mitogen-activated protein kinase (MAPK) [78]. p38 MAPK is also involved in the breakdown of the BBB and other pathologic processes such as macrophage activation, neurotoxicity, impairment of neurogenesis, and lymphocyte apoptosis [67,78]. Macrophage-secreted cathepsin B has been involved in HIV-induced neuronal apoptosis [79]. Recent studies have found that mannose-binding lectin (MBL) mediates subcellular localization and intracellular trafficking of gp120 complexes along neurites [80]. Genetic variants in the host restriction factor APOBEC3G are associated with disease progression and CNS impairment in HIV-infected children [81]. Data from neonatal rodent HIV-1 and perinatal simian immunodeficiency virus (SIV) models and clinical data indicate that hippocampus neurons are at greatest risk of injury from the neurotoxic cascade of HIV-1 proteins [67]. HIV clade-specific effects of neuropathologic manifestations have not been well studied in HIV-infected children [13,14, 67].

Pathology

Neuropathologic evidence of pediatric HIV-related CNS disease includes decreased brain weight, cortical atrophy, symmetric intracerebral calcifications, white matter changes, reactive astrocytosis, myelin pallor, inflammation of the CNS vasculature, and subcortical gray matter abnormalities of the basal ganglia, thalamus, claustrum, caudate, putamen, globus pallidus, and hippocampus [82,83]. HIV has been isolated from the brain of aborted fetuses from HIV-infected women and from the brain and cerebrospinal fluid (CSF) of HIV-infected children and adults with AIDS [84,85].

Clinical Manifestations

Symptoms of HIV encephalopathy in the newborn or young infant initially include delayed head control or delayed acquisition of a social smile and variable degrees of truncal hypotonia [57]. Subsequently, impairment of cognitive, behavioral, and motor functions becomes apparent. Typical findings include a loss of or failure to attain normal

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diagnosis of the most severe, rapidly progressive form of encephalopathy in an HIV-infected child is a marker of poor prognosis. Children with HIV infection can suffer from progressive encephalopathy, static encephalopathy, neuropsychiatric disorders, motor impairment, and cognitive decline [57–62]. Mild neurocognitive or behavioral deficits have been described in infants and children with PLHIV+ in the absence of overt HIV encephalopathy [63–66].

Neuroimaging

Characteristic computed tomographic (CT) findings of HIV encephalopathy in the pre-and post-cART periods include cerebral atrophy and bilateral symmetric calcification of the basal ganglia [16,59,61,87,88]. More recent studies using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have described subtle white matter changes and neuronal microstructural abnormalities in infants and children with PHIV+ who are receiving ART [88–90]. In one report, white matter signal abnormalities (WMSAs) on T2/FLAIR (primarily involving the frontal and parietal lobe white matter) were found in PLHIV+ infants who had received cART by 8 weeks of age, suggesting that the virus likely enters the CNS soon after acquisition of infection [89]. Subtle white matter microstructural abnormalities on DTI have been reported in ART-naive ("slow progressor") and ART-treated vertically infected children and adolescents [90]. Neuronal microstructural damage is suggested by decreased fractional anisotropy and axial diffusion and increased mean diffusivity and radial diffusion [90]. Abnormal metabolite levels in the frontal cortex and hippocampus have been described in HIV-infected children receiving ART [91].

Early Infant HIV Diagnosis

Virologic tests (HIV DNA or RNA assays) are needed for early infant HIV diagnosis and should be performed at 14–21 days of life, at 1–2 months of age, and at 4–6 months of age [21]. In infants and children younger than 18 months, HIV DNA polymerase chain reaction (PCR) is the preferred virologic test for detection of subtype B HIV virus, the predominant viral subtype prevalent in the United States. For suspected maternal non–subtype B virus infection, HIV RNA PCR should be used for early infant diagnosis [21]. An infant is diagnosed with HIV infection if two separate blood samples from two separate time points test positive for HIV DNA or RNA PCR assay [21].

Early Treatment

cART is the standard of care for most children with HIV infection. cART has evolved from simple nucleoside reverse-transcriptase inhibitor (NRTI) regimens of the 1980s and early 1990s to current complex regimens of NRTI in combination with protease inhibitors (PIs) or integrase strand transfer inhibitor or nonnucleoside reverse-transcriptase inhibitors (NNRTIs). The introduction of cART including NRTIs and NNRTIs, as well as combinations containing PIs, has resulted in dramatic reductions in mortality and morbidity in children [6]. Treatment of pediatric HIV infection with cART is associated with reduction in mortality, OIs, HIV encephalopathy and other complications, improvement in growth and neurodevelopment, improvement in virologic and immunologic parameters, and better quality of life [6].

Current US pediatric guidelines recommend immediate initiation of cART in all infants with PHIV+ who are younger than 12 months of age regardless of clinical symptoms or immune status or HIV RNA level [92]. The consideration of treatment initiation for asymptomatic infants is based on the rationale that infants are at highest risk of rapid disease progression to AIDS or death (even when immune degradation and virus replication are moderately well contained) and that there are no reliable clinical or laboratory markers to identify infants who will progress from those who will not [93]. Early treatment can result in complete cessation of viral replication and the preservation of normal immune function. A randomized, controlled trial conducted in South Africa (Children with HIV Early Antiretroviral Therapy [CHER]) showed that the initiation of cART within the first 3 months of life in asymptomatic PHIV+ infants with normal immune function resulted in a 76% reduction in mortality and a 75% reduction in HIV disease progression compared with infants not initiating cART until they met clinical or CD4 T-lymphocyte count (CD4 < 25%) criteria for starting cART [94].

Preferred cART regimens in neonates and infants with PHIV+ aged 14 days and older to younger than 3 months include two NRTIs (zidovudine/lamivudine or zidovudine/emtricitabine) plus a PI (lopinavir-ritonavir) [92]. Infants in whom HIV infection is diagnosed

while on ZDV prophylaxis should receive cART [92]. Because of adverse effects and drug interactions, not all agents can be paired in the regimens [92]. Resistance testing should be considered before starting cART in newly diagnosed infants younger than 12 months of age, especially if the mother has known or suspected infection with drug-resistant virus [92].

cART regimens are safe, effective, and well tolerated for long periods of time when started in early infancy [92]. Because the standards of care are still evolving, collaboration between the child's primary healthcare provider and an HIV treatment center is strongly suggested. Whenever possible, children should be enrolled in clinical trials; access and information can be obtained by calling 1-800-TRIALS-A (AIDS Clinical Trials Group [ACTG]) or 301-402-0696 (HIV & AIDS Malignancy Branch, National Cancer Institute). Several promising second-generation agents as well as new classes of antiretroviral agents are currently being evaluated in adult clinical trials, but pharmacokinetic and safety data are limited in infants [92]. These agents include duranavir (protease inhibitor), maraviroc (CCR5 antagonist), raltegravir (integrase inhibitor), and etravirine (newer NNRTI). Data are insufficient to recommend these agents as initial therapy of infants [92].

The rate of progression and severity of HIV encephalopathy are variable. cART in children may prevent, reduce, or improve neurologic manifestations of HIV infection [48,59,63]. The optimal cART regimen to treat HIV encephalopathy has not been established [95]. In early studies, ZDV continuous therapy improved cognitive performance and reduced brain atrophy in a small study of symptomatic HIV-infected children [96]. cART was more effective than monotherapy in improving age-appropriate neurocognitive scores in young children with symptomatic HIV [97]. CNS penetration differs substantially among current antiretroviral drugs [65]. Of the available agents, zidovudine has the best penetration into the CSF, followed by stavudine and high-dose abacavir [95]. In an observational study, high-CNS-penetrating cART regimens were significantly associated with improved survival in a subset of children with established HIV encephalopathy [65]. A CHER neurologic substudy demonstrated improved neurodevelopmental outcomes among children at 11 months of age in the early ART arm compared with children in the delayed treatment arm [98]. Thus physicians are challenged to find adequate drug combinations to prevent and treat both CNS and systemic manifestations of HIV infection.

Treatment of infected infants with cART is complex given the risk of virologic failure, ART compliance issues due to complex and demanding regimens, difficulties in developing pediatric formulations, immature drug metabolism, lack of age-specific pharmacokinetic data to guide pediatric dosing, toxicity, and development of drug resistance [36,92]. A family-centered approach involving a multidisciplinary team to integrate medical, social, and psychosocial support is critical.

Neurocognitive Issues in Pediatric HIV Infection

Among untreated children with PHIV+, the prevalence of neurocognitive impairment is over 50% [17]. Infants with HIV encephalopathy and severe immunosuppression are at highest risk of neurocognitive impairment [59]. In the era of cART, a wide spectrum of neurodevelopmental deficits has been described in infants with PHIV+, including fine and gross motor deficits, cognitive delay, verbal comprehension impairment, executive functioning problems, working memory deficits, visual-spatial integration problems, abnormal muscle tone, spasticity, and seizure disorder [15,17,48,67,99]. The improved survival of PHIV+ children into adolescence and adulthood in the cART era has led to the recognition of a less severe form of neurocognitive dysfunction with a profound impact on quality of life [13,63–66]. In one recent report, youth with PHIV+ with a history of encephalopathy demonstrated cognitive slowing and self-reported metacognitive problems [100]. Perinatally HIV-exposed, uninfected (PHEU) youths may also exhibit problems with executive function [100]. It is important to recognize the difficulty in evaluating the impact of the direct effects of HIV infection on neurodevelopment. Multiple confounding variables affecting neurodevelopment are often present in PHIV+ and PHEU-infected children and adolescents. These variables include prematurity, low birth weight, prenatal drug exposure, antiviral drug toxicities, nutritional deficits, endocrine abnormalities, and the socioeconomic impacts of disease (e.g., poverty, disrupted caregiving, family mental health problems) [16,100]. Furthermore, secondary CNS complications of infection may be present. Thus it is often not possible to isolate HIV's direct impact on

neurodevelopment from the effects of these other variables. Children infected with HIV also display a wide range of behavioral or psychological problems, including learning and attention-deficit-hyperactivity disorders, anxiety disorders, depression, autistic behavior, and social withdrawal [14,66].

Other CNS Complications

Secondary neurologic complications of HIV infection include OIs, epilepsy, cerebrovascular disease (e.g., strokes secondary to hemorrhage or ischemic insults), and CNS neoplasms (e.g., primary CNS lymphomas) [13,14]. OIs of the CNS are less common in children than in adults with HIV infection. When these infections do occur in children, they are often diagnosed in those over 6 years of age with CD4 counts below 200. CNS opportunistic pathogens include *Cryptococcus*, toxoplasmosis, cytomegalovirus, herpes simplex virus, *Candida* spp., JC virus, syphilis, and *Mycobacterium* tuberculosis [13,14]. Primary CNS lymphomas, non-Hodgkin's lymphoma with CNS metastases, and strokes are rare in children.

Challenges to Perinatal HIV Prevention and Treatment

Despite significant advances in perinatal HIV prevention, around 57 HIV-infected babies were born in the United States in 2010 primarily due to missed opportunities to implement effective interventions [21,27–29]. Reported barriers to elimination of MTCT include inadequate prenatal care (especially in women with substance abuse), lack of antenatal HIV testing, acquisition of new infection in women later in pregnancy and during breastfeeding, and poor maternal adherence to ART during pregnancy [21,27–29]. Knowledge of a women's HIV status during labor is crucial for providing ARV prophylaxis for those who test positive and their HIV-exposed infants to prevent perinatal transmission [21]. Routine antenatal HIV testing ("opt-out" approach) is recommended for all women as soon as pregnancy is confirmed [21]. To reduce missed prevention opportunities, repeat testing in the third trimester of pregnancy is recommended for high-risk women to detect new infections as well as rapid HIV testing of women who present in labor with unknown HIV status. Other challenges include preventing new incident HIV infections in women of childbearing age, especially adolescent girls of minority race or ethnicity.

Despite the scale-up of pediatric HIV care and treatment services in LMICs in recent years, only 25% of children in need of ART were receiving treatment by end of 2013 [50]. Barriers to treatment in LMICs include delay in identification of infected infants due to lack of diagnostic testing for early infant HIV diagnosis, poor health systems and weak linkages resulting in high dropout rates in the PMTCT cascade, and lack of prioritization and advocacy for pediatric treatment [2,9–11].

Future Directions

There is a need for studies to better delineate the complex pathogenesis and neurobiology of early CNS infection in children with PHIV+. More effective screening and increased access to different neuroimaging techniques are crucial to address neurologic complications early in the disease process [88]. However, access to neuroimaging studies remains a challenge in LMICs [13]. Early initiation of cART in PHIV+ appears to be crucial in preserving immune function and preventing HIV encephalopathy. Future longitudinal studies are needed to fully understand the timing and varied spectrum of neurocognitive deficits affecting infants, children, and adolescents with PHIV+ [13]. In addition, interventions for HIV-associated vasculopathy and seizure disorders are urgently needed, especially for affected children and adolescents in LMICs [13,14].

References

1. Centers for Disease Control and Prevention. Unexplained immunodeficiency and opportunistic infections in infants – New York, New Jersey, California. *MMWR Morbid Mortal Wkly Rep* 1982; **31**: 665–7.
2. Prendergast AJ, Essajee S, Penazzato M. See comment in PubMed Commons below HIV and the Millennium Development Goals. *Arch Dis Child* 2015; **100**(Suppl 1): S48–52.
3. Abrams EJ, Myer L. Can we achieve an AIDS-free generation? Perspectives on the global campaign to eliminate new pediatric HIV infections. *J Acquir Immune Defic Syndr* 2013; **63**(Suppl 2): S208–12.
4. Hurst SA, Appelgren KE, Kourtis AP. Prevention of mother-to-child transmission of HIV type 1: the role of neonatal and infant prophylaxis. *Expert Rev Anti-infect Ther* 2015; **13**: 169–81.
5. Mofenson LM. Prevention in neglected subpopulations: prevention of mother-to-child

transmission of HIV infection. *Clin Infect Dis* 2010; **50**(Suppl 3): S130–48.

6. See comment in PubMed Commons below Mofenson LM, Cotton MF. The challenges of success: adolescents with perinatal HIV infection. *J Int AIDS Soc* 2013; **16**: 18650.
7. Rakhmanina NY, van den Anker JN. Pharmacologic prevention of perinatal HIV infection. *Early Hum Dev* 2014; **90**(Suppl 1):S13–5.
8. White AB, Mirjahangir JF, Horvath H, et al. Antiretroviral interventions for preventing breast milk transmission of HIV. *Cochrane Database Syst Rev* 2014; **10**: CD011323.
9. Tenthani L, Haas AD, Tweya H, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ("Option B+") in Malawi. *AIDS* 2014; **28**: 589–98.
10. Shaffer N, Abrams EJ, Becquet R, et al. Option B+ for prevention of mother-to-child transmission of HIV in resource-constrained settings: great promise but some early caution. *AIDS* 2014; **28**: 599–601
11. Colvin CJ, Konopka S, Chalker JC, et al. A systematic review of health system barriers and enablers for antiretroviral therapy (ART) for HIV-infected pregnant and postpartum women. *PLoS One* 2014; **9**: e108150.
12. Tardieu M, Tejiokem M, Nguefack S. Virus-induced lesions and the fetal brain: examples of the transmission of HIV-1 and CMV from mother to offspring. *Handb Clin Neurol* 2013; **112**: 1103–8.
13. Wilmshurst JM, Donald KA, Eley B. Update on the key developments of the neurologic complications in children infected with HIV. *Curr Opin HIV AIDS* 2014; **9**: 533–8.
14. Donald KA, Hoare J, Eley B, Wilmshurst JM. Neurologic complications of pediatric human immunodeficiency virus: implications for clinical practice and management challenges in the African setting. *Semin Pediatr Neurol* 2014; **21**:3–11.
15. Samia P, Petersen R, Walker KG, et al. Prevalence of seizures in children infected with human immunodeficiency virus. *J Child Neurol* 2013; **28**: 297–302.
16. Donald KA, Walker KG, Kilborn T, et al. HIV Encephalopathy: pediatric case series description and insights from the clinic coalface. *AIDS Res Ther* 2015; **12**: 2.
17. Govender R, Eley B, Walker K, et al. Neurologic and neurobehavioral sequelae in children with human immunodeficiency virus (HIV-1) infection. *J Child Neurol* 2015; **26**: 1355–64.
18. Recommendations of the US Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus, 2014. Available at www.cdc.gov/mmwr/preview/mmwrhtml/00032271.htm (accessed August 30, 2015).
19. Centers for Disease Control and Prevention. Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome. *MMWR Morbid Mortal Wkly Rep* 1985; **34**: 721–6.
20. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States, 2014. Available at www.aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf (accessed August 30, 2015).
21. American Academy of Pediatrics. Human immunodeficiency virus infection, in Kimberlin DW, Brady MT, Jackson MA, Long SS, eds., *Red Book*, 30th edn. Elk Grove, IL: American Academy of Pediatrics, 2015:453–76.
22. Centers for Disease Control and Prevention. HIV among pregnant women, infants and children, 2017. Available at www.cdc.gov/hiv/risk/gender/pregnantwomen/facts/index.html (accessed July 28, 2017).
23. Centers for Disease Control and Prevention. HIV surveillance report, 2010. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/ (accessed August 21, 2015).
24. Centers for Disease Control and Prevention. Racial/ethnic disparities among children with diagnoses of perinatal HIV infection – 34 states, 2004–2007. *MMWR Morbid Mortal Wkly Rep* 2010; **59**:97–101.
25. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr* 2002; **29**: 484–94.
26. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. *AIDS* 2014; **28**: 1049–57.
27. Nesheim S, Taylor A, Lampe MA, et al. A framework for elimination of perinatal transmission of HIV in the United States. *Pediatrics* 2012; **130**: 738–44.
28. Whitmore SK, Taylor AW, Espinoza L, et al. Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. *Pediatrics* 2012; **129**:e74–81.
29. Camacho-Gonzalez AF, Kingbo MH, Boylan A, et al. Missed opportunities for prevention of mother-to-child transmission in the United States. *AIDS* 2015; **29**: 1511–15.
30. UNAIDS. *2014 Progress Report on the Global Plan towards the Elimination of New HIV Infections among Children by 2015 and Keeping Their Mothers Alive.*

Geneva: Joint United Nations Programme on HIV/AIDS, 2014.

31. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS, 2017. Available at http://www.unaids.org/en/resources/fact-sheet (accessed July 28, 2017).
32. Piot P, Abdool Karim SS, Hecht R, et al. Defeating AIDS: advancing global health. *Lancet* 2015; **386**: 171–218.
33. Newell ML, Coovadia H, Cortina-Borja M, et al. Ghent International AIDS Society (IAS) Working Group on HIV Infection in Women and Children. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 2004; **364**: 1236–43.
34. Working Group on Mother-to-Child Transmission of HIV Infection. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr* 1995; **8**: 506–10.
35. European Collaborative Study. Vertical transmission of HIV-1: maternal immune status and obstetric factors. *AIDS* 1996; **10**: 1675–81.
36. Shetty AK, Maldonado YA. Human immunodeficiency virus/Acquired immunodeficiency syndrome in the infant. In Wilson C, Nizet V, Maldonado YA, Remington JS, Klein, JO (eds.), *Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant*, 8th edn. Philadelphia: Elsevier/Saunders, 2015: 619–74.
37. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; **331**: 1173–80.
38. DeCock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000; **283**: 1175–82.
39. Thorne C, Newell ML. Prevention of mother-to-child transmission of HIV infection. *Curr Opin Infect Dis* 2004; **17**: 247–52.
40. Stevens J, Hermione L. Mother to child transmission of HIV: what works and how much is enough? *J Infect* 2014; **69**(Suppl 1): S56–62.
41. Magder LS, Mofenson L, Paul ME, et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir Immune Defic Syndr* 2005; **38**: 87–95.
42. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *N Engl J Med* 1996; **335**: 1621–9.
43. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 11: a meta-analysis of 15 prospective studies. *N Engl J Med* 1999; **340**: 977–87.
44. European Mode of Delivery Collaboration. Elective cesarean section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomized clinical trial. *Lancet* 1999; **353**: 1035–9.
45. Kuhn L, Sinkala M, Kankasa C, et al. High uptake of exclusive breastfeeding and reduced early post-natal HIV transmission. *PLoS One* 2007; **2**: e1363.
46. Rollins N, Coovadia HM. Breastfeeding and HIV transmission in the developing world: past, present, future. *Curr Opin HIV AIDS* 2013; **8**: 467–73.
47. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. *Lancet* 2005; **4**: 543–55.
48. Van Rie, HPR, Dow A, Robertson K. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. *Eur J Paediatr Neurol* 2007; **11**: 1–9.
49. Pearson DA, McGrath NM, Nozycee M, et al. Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning. Pediatric AIDS Clinical Trials 152 Study Team. *Pediatrics* 2000; **106**: e76.
50. UNAIDS. *Report on the Global AIDS Epidemic 2013*. Geneva: Joint United Nations Programme on HIV/AIDS, 2013.
51. van Arnhem LA, Bunders MJ, Scherpbier HJ, et al. Neurologic abnormalities in HIV-1 infected children in the era of combination antiretroviral therapy. *PLoS One* 2013; **8**: e64398.
52. Foster CJ, Biggs RL, Melvin D, et al. Neurodevelopmental outcomes in children with HIV infection under 3 years of age. *Dev Med Child Neurol* 2006; **48**: 677–82.
53. Crowell CS, Malee KM, Yogev R, Muller WJ. Neurologic disease in HIV-infected children and the impact of combination antiretroviral therapy. *Rev Med Virol* 2014; **24**: 316–31.
54. Tardieu M, Le CJ, Persoz A, et al. HIV-1-related encephalopathy in infants compared with children and adults. French Pediatric HIV Infection Study and the SEROCO Group. *Neurology* 2000; **54**: 1089–95.
55. Sturdevant CB, Dow A, Jabara CB, et al. Central nervous system compartmentalization of HIV-1 subtype C variants early and late in infection in young children. *PLOS Pathog* 2012; **8**: e1003094.
56. Gorry PR, Bristol G, Zack JA, et al. Macrophage tropism of human immunodeficiency virus type 1 isolates from brain and lymphoid tissues predict

neurotropism independent of coreceptor specificity. *J Virol* 2001; **75**: 10073–89.

57. Cooper ER, Hanson C, Diaz C, et al. Encephalopathy and progression of human immunodeficiency virus disease in a cohort of children with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1998; **132**: 808–12.
58. Labato MN, Caldwell MB, Ng P, et al. Encephalopathy in children with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1995; **126**: 710–15.
59. Chiriboga CA, Fleishman S, Champion S, et al. Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active anti-retroviral therapy (HAART). *J Pediatr* 2005; **146**: 402–7.
60. Belman AL, Ultmann MH, Horoupian D, et al. Neurologic complications in infants and children with acquired immune deficiency syndrome. *Ann Neurol* 1985; **18**: 560–6.
61. Epstein LG, Sharer LR, Oleske JM, et al. Neurologic manifestations of human immunodeficiency virus infection in children. *Pediatrics* 1986; **78**: 678–87.
62. Mintz M, Rapaport R, Oleske JM, et al. Progressive encephalopathy in children with acquired immunodeficiency syndrome. *Am J Dis Child* 1989; **143**: 771–4.
63. Mitchell CD, HIV-1 encephalopathy among perinatally infected children: neuropathogenesis and response to highly active antiretroviral therapy. *Ment Retard Dev Disabil Res Rev* 2006; **12**: 216–22.
64. Nachman SA, et al., Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med* 2009; **163**: 164–71.
65. Patel K, et al., Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. *AIDS* 2009; **23**: 1893–901.
66. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J Int AIDS Soc* 2013; **16**:18603.
67. Heather C, Swang M, Lawrence J, et al. Of mice and monkeys: can animal models be utilized to study neurological consequences of pediatric HIV-1 infection. *ACS Chem Neurosci* 2015; **6**: 1276–89.
68. Bissel SJ, Wiley CA. Human immunodeficiency virus infection of the brain: pitfalls in evaluating infected/affected cell populations. *Brain Pathol* 2004; **14**:97–108.
69. Persidsky Y, Zheng J, Miller D, Gendelman HE. Mononuclear phagocytes mediate blood-brain barrier compromise and neuronal injury during HIV-1-associated dementia. *J Leukocyt Biol* 2001; **68**(3): 413–22.
70. Blumberg BM, Gelbard HA, Epstein LG. HIV-1 infection of the developing nervous system: central role of astrocytes in pathogenesis. *Virus Res* 1994; **32**: 253–67.
71. Tornatore C, Chandra R, Berger JR, Major EO. HIV-1 infection of subcortical astrocytes in the pediatric central nervous system. *Neuolrogy* 1994; **44**: 481–7.
72. Canto-Nogues C, Sanchez-Ramon S, Alvarez S, et al. HIV-1 infection of neurons might account for progressive HIV-1-associated encephalopathy in children. *J Mol Neurosci* 2005; **27**:79–89.
73. Chen MF, Gill AJ, Kolson DL. Neuropathogenesis of HIV-associated neurocognitive disorders: roles for immune activation, HIV blipping and viral tropism. *Curr Opin HIV AIDS* 2014; **9**: 559–64.
74. Kaul M. HIV's double strike at the brain: neuronal toxicity and compromised neurogenesis. *Front Biosci* 2008; **13**: 2484–94.
75. Foster SB, Lu M, Glaze DG, et al. Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. *Clin Immunol* 2012; **144**:13–23.
76. Epstein LG, Gelbard HA. HIV-1-induced neuronal injury in the developing brain. *J Leukocyt Biol* 1999; **65**: 453–7.
77. Schwartz L, Major EO. Neural progenitors and HIV-1-associated central nervous system disease in adults and children. *Curr HIV Res* 2006; **4**: 319–27.
78. Medders KE, Kaul M. Mitogen-activated protein kinase p38 in HIV infection and associated brain injury. *J Neuroimmun Pharmacol* 2011; **6**: 202–15.
79. Rodriguez-Franco EJ, Cantres-Rosario YM, Plaud-Valentin M, et al. Dysregulation of macrophage-secreted cathepsin B contributes to HIV-1-linked neuronal apoptosis. *PLoS One* 2012; **7**:e36571.
80. Teodorof C, Divakar S, Soontornniyomkij B, et al. Intracellular mannose binding lectin mediates subcellular trafficking of HIV-1 gp120 in neurons. *Neurobiol Dis* 2014; **69**:54–64.
81. Singh KK, Wang Y, Gray KP, et al. Genetic variants in the host restriction factor APOBEC3G are associated with HIV-1-related disease progression and central nervous system impairment in children. *J Acquir Immune Defic Syndr* 2013; **62**:197–203.
82. Tornatore C, Chandra R, Berger JR, Major EO. HIV-1 infection of subcortical astrocytes in the pediatric central nervous system. *Neurology* 1994; **44**: 481–7.
83. da Cunha A, Mintz M, Eiden LE, Sharer LR. A neuronal and neuroanatomical correlate of HIV-1 encephalopathy

relative to HIV-1 encephalitis in HIV-1 infected children. *J Neuropathol Exp Neurol* 1997; **56**: 974–87.

84. Lyman YD, Kress Y, Kure K, et al. Detection of HIV in fetal central nervous tissue. *AIDS* 1990; **4**: 917–20.
85. Levy JA, Shimabukuro J, Hollander H, et al. Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. *Lancet* 1985; **2**: 586–8.
86. European Collaborative Study. Neurologic signs in young children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 1990; **9**: 402–6.
87. George R, Andronikou S, du Plessis AM, et al. Central nervous system manifestations of HIV infection in children. *Pediatr Radiol* 2009; **39**: 575–85.
88. Hoare J, Ransford GL, Phillips N, et al. Systematic review of neuroimaging studies in vertically transmitted HIV positive children and adolescents. *Metab Brain Dis* 2014; **29**: 221–9.
89. Ackermann C, Andronikou S, Laughton B, et al. White matter signal abnormalities in children with suspected HIV-related neurologic disease on early combination antiretroviral therapy. *Pediatr Infect Dis J* 2014; **33**: e207–12.
90. Hoare J, Fouche JP, Phillips N, et al. White matter micro-structural changes in ART-naïve and ART-treated children and adolescents infected with HIV in South Africa. *AIDS* 2015; **29**: 1793–801.
91. Hoare J, Fouche JP, Spottiswoode B, et al. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naive "slow progressors." *J Neurovirol* 2012; **18**: 205–12.
92. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf (accessed July 28, 2017).
93. Abrams EJ, Kuhn L. Should treatment be started among all HIV-infected children and then stopped?, *Lancet* 2003; **362**: 1595–6.
94. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008; **359**: 2233–44.
95. Saavedra-Lozano J, Ramos JT, Sanz F, et al. Salvage therapy with abacavir and other reverse transcriptase inhibitors for human immunodeficiency-associated encephalopathy. *Pediatr Infect Dis J* 2006; **25**: 1142–52.
96. DeCarli C, Fugate L, Falloon J, et al. Brain growth and cognitive improvement in children with human immunodeficiency virus-induced encephalopathy after 6 months of continuous infusion zidovudine therapy. *J Acquir Immune Defic Syndr* 1991; **4**: 585–92.
97. McCoig C, Castrejon MM, Castano E, et al. Effects of combination antiretroviral therapy on cerebrospinal fluid HIV RNA, HIV resistance, and clinical manifestations of encephalopathy. *J Pediatr* 2002; **141**:36–44.
98. Laughton B, Cornell M. Grove D, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. *AIDS* 2012; **26**: 1685–90.
99. Cohen S, Ter Stege JA, Geurtsen GJ, et al. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin Infect Dis* 2015; **60**: 1111–19.
100. Nichols SL, Brummel SS, Smith RA, et al. Executive functioning in children and adolescents with perinatal HIV infection. *Pediatr Infect Dis J* 2015; **34**: 969–75.

Chapter

34 Inborn Errors of Metabolism and Single-Gene Disorders with Features of Neonatal Encephalopathy

Gregory M. Enns

Introduction

Inborn errors of metabolism and abnormalities in many single genes related to neuronal function can present in the neonatal period and have clinical, biochemical, and neuroradiologic features similar to those of neonatal encephalopathy caused by environmental factors, such hypoxia, ischemia, or in utero infection. *Neonatal encephalopathy* may be defined as a clinical syndrome characterized by a subnormal level of consciousness or seizures and often associated with respiratory difficulties and diminished tone and reflexes in an infant born following at least 35 weeks of gestation [1]. Both genetic disorders and neonatal encephalopathy secondary to environmental factors, such as hypoxic-ischemic encephalopathy (HIE), may be associated with severe neurologic distress, metabolic acidosis, and multiorgan system involvement. Perinatal asphyxia affects 2–4/1,000 neonates, with encephalopathy occurring in 25% and death in an additional 30% [2]. The patterns of brain injury may be different when HIE and genetic disorders are compared. However, some genetic disorders can have neuroradiologic findings similar to those seen in HIE. Inborn errors are rare individually, but as a group, they affect approximately 1/1,000 neonates [3]. It is particularly crucial to consider inborn errors of metabolism in the differential diagnosis of patients who present with nonspecific features suggestive of sepsis or asphyxia. Prompt diagnosis not only may prevent mortality or significant morbidity but also may allow the clinician to provide the family with accurate genetic counseling. Although expanded newborn screening using tandem mass spectrometry (MS/MS) will detect a number of metabolic disorders, this testing will miss many inborn errors of metabolism that present with HIE-like features. In such cases, specialized testing is required in order to establish a diagnosis. In this chapter, patterns of brain injury and systemic complications that occur in HIE and genetic disorders are reviewed, with a concentration on inborn errors of metabolism. Specific inborn errors of metabolism and single-gene disorders with clinical presentations commonly encountered in patients with HIE are discussed further.

Patterns of Brain Injury in HIE and Inborn Errors of Metabolism

Neonatal hypoxic-ischemic brain injury may be caused by localized infarction or a diffuse ischemic insult. Focal ischemic infarction in the neonate typically presents with lethargy, hypotonia, or seizures. Most infarcts occur in full-term infants and are localized to the distribution of an artery, especially the middle cerebral artery and its branches. Reported causes of focal infarction include cardiac disorders, emboli, infection, coagulation abnormalities, and birth asphyxia, although in many cases an etiology is never found [4]. Metabolic causes of focal ischemia are listed in Table 34.1 but will not be reviewed in this chapter.

Diffuse hypoxic-ischemic injury affects different brain regions depending on the duration and severity of the insult, the gestational age of the infant, and the presence or absence of systemic stress [5]. Mild to moderate cerebral hypotension with impaired brain vascular autoregulation results in the shunting of blood from the anterior to posterior circulation in order to maintain blood flow to the basal ganglia, brainstem, and cerebellum. Brain damage thus is restricted to the cerebral hemisphere intervascular boundary zones (*watershed regions*) [4,6,7]. Because the location of the watershed regions changes with brain maturation, different patterns of cerebral damage are encountered in premature and term infants. Mild to moderate cerebral hypotension in premature infants results in periventricular white matter injury, with sparing of the cerebral cortex and subcortical white matter. By the thirty-fourth to

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Table 34.1 Inborn Errors of Metabolism Associated with Stroke in Childhood

Organic acidurias
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
Glutaric aciduria type 1
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type 2)
3-Methylcrotonyl-CoA carboxylase deficiency
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
Aminoacidemias
Homocystinuria
Methylenetetrahydrofolate reductase (MTHFR) deficiency
Urea cycle disorders
Ornithine transcarbamylase deficiency
Carbamyl phosphate synthetase deficiency
Mitochondrial disorders
MELAS
Leigh syndrome
Cytochrome oxidase (complex IV) deficiency
Lysosomal storage disorders
Fabry disease
Cystinosis
Other
Congenital disorders of glycosylation
Sulfite oxidase deficiency
Molybdenum cofactor deficiency
Phosphoglycerate kinase deficiency
Hyperlipoproteinemia
Menkes disease
Purine nucleoside phosphorylase deficiency

Note: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.
Source: Adapted from Schwartz & Barkovich [10].

thirty-sixth weeks of gestation, the watershed areas have shifted peripherally to include the subcortical white matter and cerebral cortex. Therefore, term infants who sustain brain injury as a result of mild to moderate hypotension have damage primarily in the cortex and underlying subcortical and periventricular white matter [7].

Severe cerebral hypotension, with complete or near-complete interruption of the cerebral blood supply, results in deep gray matter (especially thalami and basal ganglia) and brainstem damage [8]. In this case, the shunting of blood is not sufficient to prevent deep gray matter damage. Damage to white matter and the cerebral cortex is a later sequela to profound hypotension. Profound cerebral hypotension also causes different patterns of brain injury depending on brain maturity [6,7]. In the early third trimester, the thalami and brainstem have the highest metabolic activity and relative blood flow. The thalami, brainstem, basal ganglia, and perirolandic region have the highest metabolic activity from the middle of the third trimester through 40 weeks of gestation. By the end of the first postnatal month, the visual cortex has an increased metabolic activity and is susceptible to damage. The basal ganglia remain highly vulnerable to injury from HIE or other environmental stress factors until approximately age 3 years [9].

The pattern of brain involvement also depends on the duration of injury. In general, the longer and more severe the episode of hypotension, the more likely it is that brain injury will occur. Short episodes of poor perfusion secondary to hypotension are unlikely to cause brain injury; autoregulatory mechanisms may compensate for hypotension of short duration. Longer episodes of hypotension severe enough for autoregulation to be unable to compensate are more likely to cause brain damage [10].

In contrast to the patterns of brain injury encountered in classic HIE, metabolic disorders may affect different areas of the brain [9,11]. Whereas head MRI evaluation in HIE may show hyperintense signal in the putamen (with relative sparing of the anterior putamen) and thalamus, metabolic disorders affect other structures. Metabolic conditions with differential involvement of white and gray matter are listed in Tables 34.2 through 34.4. Disorders of mitochondrial energy metabolism may present with a wide spectrum of lesions, but abnormal hyperintense signal in the globus pallidus and periatrial white matter of the centrum semiovale is often present [9]. Pyruvate dehydrogenase deficiency, organic acidemias, carbon monoxide or cyanide poisoning, and hypothermic circulatory arrest during cardiac surgery have been associated with similar abnormal signals in the globus pallidus [9,11]. Mitochondrial disorders may also

Table 34.2 Inborn Errors of Metabolism Primarily or Only Involving Gray Matter

Cortical gray matter
Neuronal ceroid lipofuscinosis
Sialidosis
Polymerase γ deficiency (Alpers syndrome)
Deep gray matter
Prolonged striatal T2 signal
Mitochondrial disorders: MELAS, Leigh syndrome
3-Methylglutaconic acidemia types 1 and 4
α-Ketoglutaric acidemia
Propionic acidemia[a]
Wilson disease[a]
Hypoglycemia[b]
Juvenile Huntington disease
Short (hypointense) globus pallidus T2 signal
Pantothenate kinase–associated neurodegeneration
Prolonged (hyperintense) globus pallidus T2 signal
Methylmalonic acidemia
Isovaleric acidemia
β-Ketothiolase deficiency
Succinate semialdehyde dehydrogenase deficiency
Guanidinoacetate methyltransferase deficiency
Pyruvate dehydrogenase (E2) deficiency
Kernicterus
Prolonged (hyperintense) T2 in subthalamic nucleus
Leigh syndrome
Kernicterus
Cerebellum and brainstem
Leigh syndrome
Wilson disease
Propionic acidemia
3-Methylglutaconic acidemia types 1 and 4
β-Ketothiolase deficiency
Glutaric acidemia type 1
Dihydropyrimidine dehydrogenase deficiency
Biotin-responsive basal ganglia disease
Cerebrotendinous xanthomatosis

Note: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.
[a]May have white matter involvement.
[b]In older infants, adolescents, and adults.
Source: Adapted from Barkovich & Patay [11].

Table 34.3 Inborn Errors of Metabolism Involving White Matter Only

Subcortical white matter (U fibers) early
Macrocephaly
Alexander disease
Normal head circumference
4-Hydroxybutyric aciduria[a]
Galactosemia
Aicardi-Goutières syndrome
Deep white matter early
Pons/medulla corticospinal tract involvement
Peroxisomal disorders
No specific brainstem tracts involved
Phenylketonuria
Maple syrup urine disease[b]
5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency
Disorders of cobalamin metabolism
Metachromatic leukodystrophy
Sjögren-Larsson syndrome
Hypomyelination
Pelizaeus-Merzbacher disease
Trichothiodystrophy
Sialuria
3-Phosphoglycerate dehydrogenase deficiency
Nonspecific white matter pattern
Glycine encephalopathy
3-Hydroxy-3-methylglutaryl coenzyme A lyase deficiency
Urea cycle disorders

[a]Cerebellar atrophy may also be present.
[b]Cerebellar and cerebral peduncle involvement may also be present.
Source: Adapted from Barkovich & Patay [11].

present with isolated white matter disease, Leigh syndrome, or even normal MRI findings [11]. Different patterns of abnormality may suggest other underlying inborn errors of metabolism. For example, basal ganglia "metabolic strokes" have been associated with methylmalonic and propionic acidemias [12]. It is important to emphasize that normal head imaging does not exclude the presence of an inborn error of metabolism [9].

Table 34.4 Inborn Errors of Metabolism Involving Both Gray and White Matter

Cortical gray matter and white matter only
Cortical dysplasia
Muscle-eye-brain disease
Walker-Warburg syndrome
Fukuyama muscular dystrophy
Other congenital muscular dystrophies
Absent cortical dysplasia
Polymerase γ deficiency (Alpers syndrome)
Menkes disease
Abnormal bones
Mucopolysaccharidoses
Lipid storage disorders
Peroxisomal disorders
Deep gray matter and white matter involvement
Primary thalamic involvement
GM1 gangliosidosis
GM2 gangliosidosis
Krabbe disease
Wilson disease
Primary globus pallidus involvement
Canavan disease
Methylmalonic acidemia
L-2-Hydroxyglutaric aciduria
Maple syrup urine disease
Mitochondrial disorders: Kearns-Sayre syndrome
Fucosidosis
Urea cycle disorders[a]
Primary striatal involvement
Organic acidemias: biotinidase deficiency, multiple carboxylase deficiency, glutaric aciduria type 1, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, α-ketoglutaric acidemia, β-ketothiolase deficiency, malonic acidemia, 3-methylglutaconic aciduria, propionic acidemia
Molybdenum cofactor deficiency
Mitochondrial disorders: MELAS, Leigh syndrome
Biotin-responsive basal ganglia disease
Wilson disease

Note: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.
[a]With insular involvement.
Source: Adapted from Barkovich & Patay [11].

The mechanisms underlying the differential effects of HIE and metabolic disorders on the brain have been the subject of much study [2,13–21]. The position of deep gray matter nuclei within the basal ganglia motor loop circuitry may be particularly important in determining the location of brain injury [2,18]. HIE following severe asphyxia results in electroencephalographic (EEG) and positron emission tomographic (PET) patterns suggestive of activity in corticothalamic, thalamocortical, and corticoputaminal excitatory projections with strong glutamate innervations [18]. Such hyperexcitability in these circuits may cause the characteristic thalamus and putamen lesions seen in HIE via glutamate-mediated toxicity [15]. Areas of the brain with a high concentration of glutamate innervations may be particularly vulnerable to injury during asphyxia because of damage sustained to nerve terminal glutamate reuptake pumps and subsequent high levels of synaptic glutamate. Glutamate has the potential to bind to postsynaptic *N*-methyl-D-aspartate (NMDA) receptors, causing membrane-bound calcium channels to open and subsequent influx of Ca^{2+} and cell death, mediated in part by mitochondrial damage and augmentation of nitric oxide and carbon monoxide production [2,16,19,21]. Released nitric oxide combines with superoxide to form peroxynitrite, which, in turn, leads to DNA damage, depletion of cellular energy, and cell death [16]. While the cortex, putamen, and thalamus are activated by such a glutamate excitatory stimulus, the globus pallidus is inhibited, resulting in relative sparing of this structure from damage [18]. This "neuronal circuitry" hypothesis may explain the selective pattern of involvement of deep gray structures in HIE despite the close proximity and similar vascular supply of these structures. Nitric oxide produced by nitric oxide synthase following NMDA receptor activation also inhibits mitochondrial respiratory chain complex IV (cytochrome oxidase), which elicits further production of superoxide and peroxynitrate. Mitochondrial release of proapoptotic proteins follows, resulting in caspase- and apoptosis-inducing factor-dependent cell death [20]. Adenosine monophosphate–activated protein kinase (AMPK), an enzyme expressed throughout the brain and activated in response to ATP depletion, has also been implicated in the pathophysiology of HIE. AMPK activity in the short term may have beneficial effects, including downregulating pathways that consume energy

and upregulating bioenergetic and antioxidant pathways via stimulation of peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α). However, prolonged activation of AMPK may promote cell death through the production of a Bcl-2 protein that is involved in mitochondrial permeabilization [21].

Toxic and metabolic disorders that affect mitochondrial energy metabolism (e.g., kernicterus, pyruvate dehydrogenase complex deficiency, respiratory chain disorders) may also lead to neuronal injury by diminishing the ability of mitochondria to maintain membrane potentials. Neuronal subacute membrane depolarization could result in subsequent opening of postsynaptic voltage-dependent NMDA and sodium channels with resulting cellular injury [14,18]. The globus pallidus appears to be particularly vulnerable in metabolic disorders because of the relatively high basal firing rate of pallidal neurons [18]. This predisposition to oxidative stress could also be related to the relatively high concentration of brain NMDA receptors in neonates compared with adults [13,17]. In addition, mitochondrial damage may lead to decreased expression of hypoxia-inducible factor 1 (HIF-1), a transcription factor that induces genes coding for erythropoietin, vascular endothelial growth factor, glycolytic enzymes, and glucose transporters. HIF-1 appears to be important in an adaptive response to hypoxia because of its role in stimulating cellular glucose uptake, increasing glycolytic capacity, and enhancing tissue O_2 delivery [22]. In short, the pathogenesis of neurologic damage in both HIE and biochemical disorders that may present with HIE-like features converges at the mitochondria.

Clinical Features of HIE and Inborn Errors of Metabolism

Neonates progress through distinctive stages of neurologic impairment following asphyxia severe enough to cause HIE [5]. Seizures occur in 50–70% of acutely asphyxiated neonates and tend to start between 30 minutes to 24 hours after birth, with an earlier occurrence signifying a more severe asphyxial insult [5]. In addition to CNS complications seen in perinatal asphyxia, systemic involvement of multiple organs, including heart, liver, and kidneys, may also occur (Table 34.5). Such damage to other organs may contribute to the severity of brain injury. The possibility that neonatal encephalopathy is associated with peripartum or intrapartum hypoxia-ischemia is increased in the presence of low Apgar scores (<5 at 5 and 10 minutes), fetal umbilical artery acidemia (pH < 7.0, base deficit ≥ 12 mmol/L, or both), distinct patterns of MRI abnormalities, and multisystem organ failure [1]. Bradycardia, pallor, cyanosis, decreased or absent respirations, and diminished or absent reflex activity may be present. A combined metabolic and respiratory acidosis is characteristic. Other metabolic findings include hypoglycemia, hypocalcemia, hyponatremia (secondary to the syndrome of inappropriate antidiuretic hormone secretion [SIADH]), and multiple electrolyte abnormalities from renal dysfunction. Hyperammonemia may occur if hepatic dysfunction is severe [5,23].

Table 34.5 Systemic Complications of HIE

Cardiomyopathy
Hepatic necrosis
Acute tubular necrosis
Adrenal insufficiency
Necrotizing enterocolitis
Meconium aspiration syndrome
Persistent fetal circulation
Thrombocytopenia
Hypoglycemia
Hypocalcemia
Hyperammonemia
SIADH

Note: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Inborn errors of metabolism may also present with severe neurologic illness and the involvement of multiple organ systems. A high index of suspicion and specific laboratory investigations are necessary to diagnose a metabolic disorder presenting with symptoms and signs suggestive of HIE (Table 34.6). The onset of symptoms of metabolic disease is often postnatal, appearing after an interval period of apparent good health and following a normal pregnancy. This interval may be as short as a few hours or last several days or even longer. Because an asphyxial insult may occur at any time in the prenatal period, the absence of a significant obstetric event does not exclude HIE as a cause of neonatal distress but may raise the suspicion of an underlying metabolic condition. A

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Table 34.6 Laboratory Investigations in Neonates with a Suspected Inborn Error of Metabolism

Routine investigations
Complete blood count + differential
Urinalysis
Electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium
Liver enzymes
Creatine kinase
Blood gases
CSF glucose, protein, erythrocytes, and leukocytes
Cultures of blood, urine, and CSF
Basic metabolic investigations
Ammonia
Lactate, pyruvate
Serum amino acids
Urine organic acids
Carnitine levels (total, free, and esterified carnitine)
Acylcarnitine profile
Further metabolic investigations[a]
Blood ketone bodies
CSF lactate, amino acids, neurotransmitters, and 4-aminobutyric acid levels[b]
Very long-chain fatty acid analysis
Plasma and urine guanidinoacetate and creatine levels
Urine *S*-sulfocysteine
Urine homocitrulline
Urine purines and pyrimidines
Cultured fibroblasts for specific enzymology[c]
Muscle biopsy for histochemistry, mitochondrial respiratory chain activities
DNA analysis[d]

[a]These investigations are performed on an individual basis depending on the presentation.

[b]Simultaneous serum glycine should be obtained for the investigation of glycine encephalopathy (nonketotic hyperglycinemia).

[c]Fibroblast analysis is often used for assay of fatty acid oxidation disorders, some mitochondrial disorders, and disorders of pyruvate metabolism. Other tissues (e.g., liver, muscle) may also be useful for enzyme analysis.

[d]DNA analysis is routinely available for most metabolic disorders, including many mitochondrial disorders. Comprehensive seizure gene panels or whole-exome sequencing may be useful diagnostic studies if biochemical markers of a specific disorder are absent.

sentinel hypoxic or ischemic peripartum or intrapartum event, such as a ruptured uterus, severe abruptio placentae, umbilical cord prolapse, amniotic fluid embolus, maternal cardiovascular collapse, or fetal exanguination, increases the likelihood that an environmental factor is involved in the pathogenesis of neonatal encephalopathy [1]. In general, if the degree of neonatal metabolic distress seems out of proportion to known obstetric or environmental factors, there is a higher likelihood that an inborn error of metabolism is present. The persistence or increasing levels of markers of metabolic disease (e.g., lactic acid and ammonia) despite vigorous therapy may also point to an underlying metabolic problem. Because most inborn errors of metabolism are characterized by autosomal recessive or maternal inheritance, obtaining a detailed family history is crucial. Parental consanguinity or a history of a previously affected child also increases the probability that neonatal distress is secondary to an underlying inborn error of metabolism.

Other indicators of metabolic imbalance include an anion gap acidosis, lactic acidosis, hyperammonemia, and hypoglycemia, but these markers are not invariably present (Table 34.7). It is apparent that the clinician may have difficulty distinguishing HIE from a metabolic disorder because similar signs and symptoms occur in both conditions. Furthermore, these conditions are not mutually exclusive. An asphyxial insult may constitute the initial environmental stress that unmasks an underlying inborn error of metabolism, or a debilitating metabolism disorder may predispose an infant to a difficult delivery. The following sections summarize specific genetic diseases according to their typical presentations in the neonatal period. These clinical classifications are general guidelines only because genetic disorders may present in atypical ways.

Isolated Seizures

Up to 9% of infants admitted to neonatal intensive care units have seizures [24]. The most common causes of neonatal seizures are HIE, intracranial hemorrhage, electrolyte abnormalities, infection, CNS malformations, drug exposure and withdrawal, and inborn errors of metabolism [25]. Metabolic disorders that may present with isolated neonatal seizures, without other obvious routine laboratory or clinical markers of an underlying inborn error of

Table 34.7 Inborn Errors of Metabolism with Features of HIE

Isolated seizures
Glycine encephalopathy (nonketotic hyperglycinemia)
Sulfite oxidase (molybdenum cofactor) deficiency
Pyridoxine-responsive seizures
Pyridoxal-responsive seizures
3-Phosphoglycerate dehydrogenase deficiency[a]
Glutamine synthetase deficiency
Asparagine synthetase deficiency
4-Aminobutyrate aminotransferase (GABA transaminase) deficiency
Dihydropyrimidine dehydrogenase deficiency
Guanidinoacetate methyltransferase (GAMT) deficiency
Glucose transporter defect (GLUT-1 deficiency syndrome)
Peroxisomal disorders[a]
Mitochondrial disorders[a]
Mitochondrial glutamate transporter deficiency
Organic acidemias[a,b]
Lactic acidosis, hypotonia, and systemic involvement
Pyruvate dehydrogenase deficiency[b]
Pyruvate carboxylase deficiency[b]
Fatty acid oxidation defects[b,c]
Mitochondrial disorders
3-Methylglutaconic aciduria
α-Ketoglutarate dehydrogenase deficiency
Fumaric aciduria[d]
Severe ketoacidosis
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
Multiple acyl coenzyme A dehydrogenase deficiency (glutaric aciduria type 2)[d]
Holocarboxylase synthetase deficiency (multiple carboxylase deficiency)[e]
3-Hydroxyisobutyric aciduria[e]
Lethargy without metabolic acidosis
Maple syrup urine disease[e]
Mevalonic acidemia[d]
Lethargy with hyperammonemia
Urea cycle defects
HHH (hyperornithinemia, hyperammonemia, homocitrullinuria) syndrome
Lysinuric protein intolerance
Other disorders
Fructose-1,6-diphosphatase deficiency[f,g]
Glycogen storage disorders types I, II, III, VIII[f,g]

[a]These conditions commonly have other systemic manifestations (see text).

[b]Hyperammonemia may also be present.

[c]Lactic acidosis is usually not prominent, except in long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency and trifunctional protein deficiency or if there is systemic hypoperfusion.

[d]Dysmorphic features and head MRI abnormalities are commonly present.

[e]Metabolic acidosis may occur later in the course of disease.

[f]Lactic acidosis may be severe.

[g]Hypoglycemia with hepatomegaly is commonly present. An enlarged heart is present in glycogen storage disorder type II and may be present in glycogen storage disorder type VIII.

metabolism, are relatively rare and include glycine encephalopathy (nonketotic hyperglycinemia); sulfite oxidase deficiency (either isolated or as part of molybdenum cofactor deficiency); α-amino adipic semialdehyde dehydrogenase deficiency (pyridoxine-dependent epilepsy); pyridox(am)ine 5'-phosphate oxidase deficiency (pyridoxal-responsive seizures); disorders of serine, glutamine, or asparagine synthesis; 4-aminobutyrate aminotransferase (GABA transaminase) deficiency; dihydropyrimidine dehydrogenase deficiency; guanidinoacetate methyltransferase (GAMT) deficiency; glucose transporter (GLUT-1) deficiency; and mitochondrial glutamate transporter deficiency [26–28]. Peroxisomal disorders, mitochondrial disorders, congenital disorders of glycosylation, organic acidemias, and urea cycle defects may also have seizures as part of a neonatal presentation, but other organ system involvement or characteristic routine laboratory abnormalities (e.g., hyperammonemia, lactic acidemia, or metabolic acidosis) should guide the clinician to the underlying diagnosis [29-32]. Disorders with an isolated seizure presentation, in contrast, may not have concomitant acidosis, hypoglycemia, or electrolyte abnormalities. Routine metabolic studies are also normal; specific

investigations on blood, CSF, or urine are required to make a diagnosis [33,34]. Diagnosis of these biochemical genetic disorders can also be confirmed by gene sequencing. In addition to inborn errors of metabolism, single-gene disorders affecting a variety of proteins related to neurologic function, including voltage-gated electrolyte channels, modulation of synaptic vesicle release, synaptic structure, neuronal cell transcription, and cell signaling, have also been implicated in causing early-onset seizures (Table 34.8) [26,27,35–38].

Glycine Encephalopathy (Nonketotic Hyperglycinemia)

Glycine encephalopathy is an autosomal recessive condition characterized by the accumulation of large amounts of glycine in body fluids because of defective glycine cleavage system function. Symptoms include lethargy, apnea, profound hypotonia, feeding difficulty, hiccups, and seizures. Approximately two-thirds of patients will have symptoms appear within 48 hours of delivery, but symptoms may occur as early as 6 hours of life. The electroencephalogram (EEG) is characterized by a burst-suppression pattern in the first 2 weeks of life. Head CT evaluation may show cerebral and cerebellar volume loss with hypoattenuation of the periventricular white matter. Head MRI studies show delayed myelination early. Progressive cerebral atrophy, agenesis of the corpus callosum, and atrophic basal ganglia may also occur [39–41]. Routine laboratory evaluations and organic acid analysis are normal. The only consistent abnormality is an elevated glycine concentration in urine, plasma, and CSF. A CSF-to-plasma glycine ratio greater than 0.08 is diagnostic of glycine encephalopathy. CSF and blood samples for glycine analysis should be obtained as near to simultaneously as possible to allow for an accurate calculation of the glycine ratio. Elevated CSF glycine has also been reported in HIE, but a normal CSF-to-plasma glycine ratio would be expected in this case [42]. Definitive diagnosis requires enzymatic analysis of liver glycine cleavage system activity or gene sequencing [43]. Treatment with sodium benzoate and dextromethorphan (a noncompetitive NMDA receptor antagonist) may improve symptoms but is not curative. Survivors often display minimal cognitive development and may have seizures recalcitrant to therapy.

Sulfite Oxidase Deficiency and Molybdenum Cofactor Deficiency

Sulfite oxidase deficiency may occur in isolation or combined with xanthine oxidase deficiency (molybdenum cofactor deficiency). Patients typically present with drug-resistant seizures in the first few days of life. EEG shows a bust-suppression pattern. In the neonatal period, head MRI shows T2 prolongation of the white matter and caudate nuclei consistent with edema. In the subacute phase, the basal ganglia may have abnormalities similar to those seen in acute asphyxia [44]. Encephalomalacia with cystic changes, especially in subcortical regions, may also mimic HIE [45]. MRI may also show cerebral and cerebellar atrophy, dysgenesis of the corpus callosum, dilated ventricles, and abnormal thalami [46]. Routine laboratory evaluations and urine organic acid analysis are normal, although a low uric acid level may be noted in molybdenum cofactor deficiency. Elevated *S*-sulfocysteine in plasma or urine is diagnostic. (*Note:* *S*-sulfocysteine content is not routinely reported on serum or urine amino acid analyses; a specific assay must be performed.) Gene sequencing may be used to confirm the diagnosis; isolated sulfite oxidase deficiency is caused by mutations in *SUOX*, and three other genes (*MOCS1, MOSC2*, and *GPHN*) may cause molybdenum cofactor deficiency [46]. These conditions are autosomal recessive traits. There is no current therapy for isolated sulfite oxidase deficiency, and most cases result in profound mental retardation or early death. Substitution therapy with intravenous cyclic pyranopterin monophosphate (cPMP), a molybdenum precursor, has shown promise in patients with molybdenum cofactor deficiency caused by *MOSC1* mutations [47].

Pyridoxine-Dependent Seizures

Pyridoxine-dependent seizures are caused primarily by α-amino adipic semialdehyde dehydrogenase (antiquin) deficiency, a defect in the cerebral lysine degradation pathway [48,49]. Genetic heterogeneity exists, and the overall birth incidence is approximately 1/160,000 [48,50]. Patients may present on the first day of life with flaccidity, abnormal eye movements, and irritability. Shock, hypothermia, hepatomegaly, and abdominal distension suggestive of intestinal obstruction also occur [51]. EEG shows intermittent or continuous generalized slow-wave activity with or without focal or multifocal spike or

Table 34.8 Select Single-Gene Disorders Associated with Early Infantile Epileptic Encephalopathy (EIEE)

Gene	Protein function	Clinical findings	Brain imaging
ARX	Transcription factor	Microcephaly Burst suppression Infantile spasms Various seizure types Hypotonia Dystonia Movement disorder Cognitive impairment	Cerebral atrophy Cerebellar atrophy T2 hyperintensities in globus pallidus, putamen
CDKL5	Serine-threonine kinase	Microcephaly Infantile spasms Various seizure types Hypotonia Dystonia Movement disorder Rett syndrome-like Absent speech Autistic spectrum disorder Cognitive impairment	Cerebral atrophy Cerebellar atrophy Delayed myelination
DNM1	GTP-binding protein, synaptic transmission	Infantile spasms Various seizure types Hypotonia Absent speech Autistic spectrum disorder Cognitive impairment	Cerebral atrophy
GRIN1	NMDA receptor subunit	Microcephaly Various seizure types Abnormal eye movements Movement disorder Cognitive impairment	Cerebral atrophy Cerebellar atrophy Thin corpus callosum
KCNQ2	Voltage-gated potassium channel	Burst suppression Tonic seizures Seizure resolution Hypotonia Dystonia Spasticity	Cerebral edema Thin corpus callosum Abnormalities in basal ganglia and thalamus Decreased posterior white matter

Table 34.8 (cont.)

Gene	Protein function	Clinical findings	Brain imaging
KCNT1	Sodium-activated potassium channel	Burst suppression MMPSI Hypotonia Spasticity Absent speech Cognitive impairment	Cerebral atrophy Thin corpus callosum Delayed myelination
MECP2	Transcription factor	Microcephaly Intractable seizures Hypotonia Movement disorder Respiratory failure Developmental delay Rett syndrome (females) Cognitive impairment	Cerebral atrophy Polymicrogyria
PIGA	Biosynthesis of cell surface glycolipid	Burst suppression	Delayed myelination
PLCβ1	Cell signal transduction	Infantile spasms MMPSI Various seizure types Hypotonia Spasticity Cognitive impairment	Cerebral atrophy Thin corpus callosum
PNKP	DNA repair	Microcephaly Various seizure types Behavior abnormalities Cognitive impairment	
SCN1A	Voltage-gated sodium channel	Myoclonic seizures MMPSI Various seizure types Ataxia Movement disorder Cognitive impairment	Cerebral atrophy Cerebellar atrophy Cerebral edema Thin corpus callosum Temporal lobe abnormalities
SCN2A	Voltage-gated sodium channel	Burst suppression Infantile spasms Hypotonia Movement disorder Spasticity Cognitive impairment	Cerebral atrophy Delayed myelination Thin corpus callosum

Table 34.8 (cont.)

Gene	Protein function	Clinical findings	Brain imaging
SPTAN1	Cytoskeletal protein	Microcephaly	Cerebral atrophy
		Infantile spasms	Cerebellar atrophy
		Spasticity	Brainstem atrophy
		Cognitive impairment	Hypomyelination
			Thin corpus callosum
STXBP1	Synaptic vesicle release	Burst suppression	Cerebral atrophy
		Various seizure types	Delayed myelination
		Hypotonia	Thin corpus callosum
		Absent speech	
		Cognitive impairment	

Note: GTP, guanosine triphosphate; MMPSI, malignant migrating partial seizures of infancy; NMDA, *N*-methyl-D-aspatate.

spike and wave activity. Patients may have brain abnormalities, including generalized brain atrophy, cerebellar hypoplasia, white matter volume loss, and a thin corpus callosum [49]. Approximately 10% of neonatal cases have features suggestive of HIE [52]. Initial diagnosis is clinical, with documented response of seizures to intravenous pyridoxine (vitamin B_6). Markedly elevated levels of pipecolic acid and α-amino adipic semialdehyde are present in urine, plasma, and CSF, but detection requires specialized laboratory methods. Antiquitin (*ALDH7A1*) mutation analysis provides final confirmation of the diagnosis [48]. An entity previously referred to as *folinic acid–responsive seizures*, in which seizures may occur as early as 2 hours after birth, is also caused by mutations in the *ALDH7A1* gene [53–55]. Folinic acid supplementation, in addition to pyridoxine, may be of benefit in some patients with α-amino adipic semialdehyde dehydrogenase deficiency, although the biochemical basis for this remains unclear [55].

Pyridoxal-Responsive Seizures

Pyridoxal phosphate is a cofactor for aromatic L-amino acid decarboxylase (AADC), threonine dehydratase, and the glycine cleavage enzyme. Some infants with intractable neonatal seizures have increased concentrations of threonine, glycine, and AADC metabolites in the CSF, suggesting a cellular deficiency of pyridoxal phosphate. Signs of fetal distress may be noted. These infants respond to pyridoxal phosphate (30 mg/kg/day) but not pyridoxine supplementation [56]. Mutations in the gene coding for pyridox(am)ine 5'-phosphate oxidase (PNPO) are associated with pyridoxal-responsive seizures [57]. Prompt treatment with pyridoxal phosphate results in amelioration of seizures and normal development or moderate psychomotor delay. Severe mental retardation with or without early death occurs in children with late or no treatment [56].

Disorders of Amino Acid Synthesis

Disorders of serine, glutamine, and asparagine synthesis primarily affect the brain and typically present with congenital microcephaly and severe encephalopathy, although microcephaly is not invariably present [58–63]. 3-Phosphoglycerate dehydrogenase (3-PGD) deficiency is a disorder of serine synthesis that causes intractable seizures, congential microcephaly, irritability, hyperexcitability, severe psychomotor retardation, hyperexcitability, spastic tetraparesis, feeding difficulties, and growth retardation. Brain MRI may show hypomyelination, cortical and subcortical atrophy, and corpus callosum hypoplasia [59]. Decreased serine in fasting plasma and CSF is a biochemical marker for 3-PGD deficiency [58]. Treatment of 3-PGD deficiency with supplementation of L-serine with or without glycine may result in decreased seizure frequency, but the effect of therapy on head growth and psychomotor development has been disappointing [59]. Glutamine synthetase (GS) deficiency was initially reported in neonates with severe neonatal encephalopathy, early death, and brain abnormalities, including marked immaturity with hyperintense white matter, enlarged ventricles, subependymal cysts, and almost complete agyria [60]. A milder clinical course and longer survival have since

been documented. One patient who did not require resuscitation at birth developed seizures during the second week of life and was noted to have severe developmental delay in early childhood. Abnormal and reduced white matter, a thin corpus callosum, enlarged CSF spaces, and atrophic basal ganglia were present [61]. Low plasma and CSF glutamine levels provide clues to the underlying diagnosis of GS deficiency. Patients with GS deficiency also have had mild hyperammonemia (<100 μmol/L). Glutamine supplementation may improve symptoms in some instances [61]. Asparagine synthetase (AS) deficiency is also associated with congenital microcephaly, profound developmental delay, and early-onset seizures. Brain MRI has shown generalized atrophy, prominent CSF spaces, delayed myelination, decreased size of the pons, and simplified gyri [62]. Low CSF asparagine levels may be present in AS deficiency [63]. These disorders of amino acid synthesis are inherited as autosomal recessive traits, and gene sequencing is used to confirm the diagnosis.

GABA Transaminase Deficiency

GABA transaminase catalyzes the first step in the conversion of GABA (γ-aminobutyric acid), a CNS-inhibitory neurotransmitter, to succinic acid. Clinical features of GABA transaminase deficiency include neonatal seizures, lethargy, hypotonia, hyperreflexia, and a high-pitched cry. MRI may show agenesis of the corpus callosum, abnormal white matter, and cerebellar hypoplasia. Only a few patients with GABA transaminase deficiency have been reported, but diagnosis will be missed unless GABA is measured in plasma or CSF [64,65].

Purine and Pyrimidine Disorders

Dihydropyrimidine dehydrogenase deficiency is a disorder of pyrimidine metabolism that is associated with a variety of neurologic findings, including isolated neonatal seizures and head imaging abnormalities, such as delayed myelination and brainstem white matter abnormalities [66,67]. Disorders of purine metabolism, including adenylosuccinate lyase deficiency and AICAR transformylase deficiency, can also present with neonatal or infantile encephalopathy and developmental delay [68,69]. A urine screen for purine and pyrimidine metabolites is helpful in detecting these conditions, although some cases of adenylosuccinate lyase deficiency may be detected only after measuring succinylpurines in the CSF.

Guanidinoacetate Methyltransferase (GAMT) Deficiency

GAMT deficiency is a disorder of creatine metabolism characterized by low plasma creatine levels and elevated guanidinoacetate. Patients typically present in infancy with seizures, developmental delay, unusual behavior, and extrapyramidal signs, but this condition has also been diagnosed in neonates. Guanidinoacetate may be assayed in plasma by tandem mass spectrometry. An absence of the creatine peak may be detected on brain magnetic resonance spectroscopy. Treatment with creatine monohydrate and a low-protein diet with restricted arginine and increased ornithine may improve symptoms [70,71].

GLUT-1 Deficiency Syndrome

GLUT-1 protein is the major glucose transporter in the blood-brain barrier. Mutations in the *GLUT1* gene result in haploinsufficiency of this hexose carrier and severe clinical symptoms, including seizures, acquired microcephaly, and developmental delay. Patients have presented as early as the third week of life, but relatively few cases have been reported in the literature. The GLUT-1 deficiency syndrome is an autosomal dominant condition. Characteristic diagnostic findings are a reduced CSF glucose concentration (hypoglycorrhachia) and reduced erythrocyte glucose transporter activity. Peripheral blood glucose and other routine metabolic evaluations are normal. Seizures may stop and children may show a dramatic recovery with the institution of a ketogenic diet [72,73].

Peroxisomal Disorders

Peroxisomal disorders that may present with neonatal seizures include neonatal adrenoleukodystrophy, Zellweger syndrome, and infantile Refsum disease [29]. Most are inherited as autosomal recessive traits, although another form of adrenoleukodystrophy that presents in childhood and rhizomelic chondrodysplasia punctata are X-linked. Clinical features in the neonatal period include severe hypotonia and seizures refractory to therapy. Seizures may be grand mal or myoclonic, and EEG typically shows multifocal spike discharges [29]. Head imaging in Zellweger syndrome may show subependymal cysts reminiscent of those found in HIE, as well as profound hypomyelination and cerebral cortex malformations [74,75]. Anterior frontal and temporal lobe microgyri or perisylvian

and perirolandic cortex pachygyria may be present. A spectrum of similar brain abnormalities may occur in other peroxisomal disorders, although head imaging may also appear normal in these conditions [74]. Patients with peroxisomal disorders may also have prominent ophthalmologic and systemic findings, including large fontanel, cataracts, retinitis pigmentosa, dysmorphic features, hepatomegaly, hepatic fibrosis, and renal cysts. Despite the occasional presence of subependymal cysts, the presence of other characteristic features should make distinguishing these conditions from HIE relatively straightforward. Plasma elevation of very long-chain fatty acids, bile acid intermediates, and phytanic acid and decreased erythrocyte plasmalogens are biochemical markers for these conditions. No effective therapy is currently available.

Mitochondrial Disorders

These conditions may rarely present with neonatal seizures but more commonly feature hypotonia and lactic acidosis. Multiorgan system involvement is also typical of mitochondrial disease [30,31,76–81]. However, severe neonatal epilepsy with a burst-suppression pattern may occur in an autosomal recessive condition caused by impaired mitochondrial glutamate transport secondary to mutations in *SLC25A22*, the gene coding for a mitochondrial glutamate/H^+ symporter [82]. Mitochondrial respiratory chain disorders are discussed further below.

Organic Acidemias and Urea Cycle Disorders

Seizures may occur in neonates with classic organic acidemias and urea cycle defects but are usually not the major manifestation of these disorders. Overwhelming ketoacidosis, hyperammonemic coma, and characteristic serum amino acids and urine organic acids are usually present. Combined D-2– and L-2-hydroxyglutaric aciduria is a condition that presents with neonatal-onset encephalopathy and intractable seizures [83]. Mevalonic aciduria may present with severe neurologic involvement and seizures, without a metabolic acidosis. However, other findings, including dysmorphic features, hepatosplenomegaly, recurrent fevers, and anemia, are more typical [84]. Interestingly, an unusual pattern of organic acid excretion may occur in neonates with severe tissue hypoxia in the absence of an underlying genetic defect [85].

Early-Infantile Epileptic Encephalopathies (EIEEs)

With the increasing clinical availability of multiple-gene epilepsy panels and whole-exome or genome sequencing, a number of single-gene disorders with a neonatal or infantile encephalopathy presentation have been identified [37,38,86,87]. As a whole, these conditions are commonly classified as early-infantile epileptic encephalopathies (EIEEs), and selected examples are shown in Table 34.8. In general, EIEEs are conditions that are caused by abnormalities in genes related to various areas of neuronal function, such as voltage-gated ion channels, synapse integrity or transmission, intracellular signal transduction, and transcription factors important in brain development [35,36,88,89]. *Ohtahara syndrome*, or *EIEE with supression burst*, is sometimes used to refer to a category of most severe age-related epileptic encephalopathy in children [90]. In general, the EIEEs are a group of disorders that share a spectrum of phenotypic findings. Many neonates present with seizures with an underlying burst-suppression pattern and with time develop different seizure patterns, such as West syndrome and Lennox-Gastaut syndrome. Brain imaging findings are variable and range from relatively normal to nonspecific supra- and infratentorial abnormalities (Table 34.8). In some cases, neonatal cerebral edema and basal ganglia changes may raise concern for a hypoxic-ischemic insult [91,92].

Rett syndrome is an X-linked disorder that typically affects girls, who present with acquired microcephaly, stereotypical movements, and developmental regression, and it was thought to be lethal in males prior to birth. However, boys with Rett syndrome caused by mutations in *MECP2* have been described with a nonspecific neonatal encephalopathy and periventricular leukomalacia [93]. Similarly, mutations in the X-linked gene *CDKL5* primarily affect girls and cause a variety of phenotypes, including a Rett-like syndrome and X-linked infantile spasm syndrome. However, *CDKL5* mutations have also been described in boys with profound cognitive impairment and intractable early-onset seizures [94]. A congenital form of Rett syndrome has also been described in girls who harbor de novo mutations in *FOXG1*. Hypotonia, decreased interaction, and irritability are common features in the neonatal period, and children go on to develop severe microcephay, jerky movements, and epilepsy [95].

Depending on the clinical features, disorders associated with EIEE are often diagnosed by comprehensive

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epilepsy gene panel testing or whole-exome sequencing. Family history is often negative for similarly affected individuals because many mutations affecting genes that cause EIEE are de novo.

Lactic Acidosis, Hypotonia, and Systemic Involvement

Disorders of pyruvate metabolism, tricarboxylic acid cycle disorders, fatty acid oxidation defects, and mitochondrial disease may present in the neonatal period with neuromuscular abnormalities, lactic acidosis, and other systemic manifestations, including cardiomyopathy, liver disease, and renal tubular defects. Anomalies may be present on head imaging, including thinning or agenesis of the corpus callosum and basal ganglia lesions, but the classic findings of HIE are typically absent [18,74].

Disorders of Pyruvate Metabolism

Pyruvate dehydrogenase complex (PDHC) deficiency is the most common defect in oxidative metabolism that features persistent lactic acidosis [96,97]. Most often a defect in the E1α component of the multimeric PDHC is the underlying cause of this disorder. E1α deficiency is X-linked. Defects in the E2, protein X, E3, and PDH phosphatase components of the PDHC are rare autosomal recessive conditions. Although PDHC deficiency often presents later in infancy, a neonatal form exists that is characterized by lactic acidosis and severe neurologic compromise with hypotonia. Subtle dysmorphic features may be present. In contrast to the acidosis associated with tissue hypoxia, ketosis is often present in primary lactic acidemias. Hyperammonemia has also been reported in some patients [96,97]. Head MRI shows findings typical of Leigh syndrome in about 50% of patients. Cerebral and cerebellar atrophy, delayed myelination, and agenesis of the corpus callosum can be seen [74]. Patients may respond to a diet low in carbohydrate and high in fat. Dichloroacetate reduces lactate in most patients but is not standard therapy. Some variants have also shown a response to high-dose thiamine administration.

The complex form of pyruvate carboxylase deficiency presents with severe neonatal lactic acidosis, hyperammonemia, citrullinemia, and hyperlysinemia. This disorder has been described in patients of European, Egyptian, and Saudi Arabian descent. Most patients with the severe form die by age 3 months. A simple (Native American) form presents with developmental delay or lactic acidosis in infancy. Both forms are autosomal recessive. No effective treatment is available [97].

Tricarboxylic Acid Cycle Defects

α-Ketoglutarate dehydrogenase deficiency may present with lactic acidemia, hypotonia, hepatomegaly, and elevated creatine kinase immediately after birth. Patients have elevated α-ketoglutarate in the urine and a low-normal plasma β-hydroxybutyrate-to-acetoacetate ratio [98]. A combined deficiency of α-ketoglutarate dehydrogenase and pyruvate dehydrogenase has also been described in neonates with lactic acidosis, hypoglycemia, and neurologic abnormalities, including seizures. The combined defects may be caused by lipoamide dehydrogenase deficiency because this enzyme is integral to both α-ketoglutarate dehydrogenase and PDHC [99]. Patients with fumarase deficiency (fumaric aciduria) may have lactic acidosis, dysmorphic features, and congenital brain malformations, including polymicrogyria, decreased white matter volume, ventriculomegaly, open operculum, angulation of the frontal horns, and brainstem hypoplasia [100]. Treatment of these conditions is supportive.

Fatty Acid Oxidation Defects

Although the most common defect of fatty acid β-oxidation, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, typically presents later in infancy or childhood with a Reye syndrome-like illness, significant neonatal disease may occur [101]. Other fatty acid oxidation disorders may present in the neonatal and early-infantile periods with greater frequency. Short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein (TFP) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, carnitine palmitoyl transferase II (CPT II) deficiency, and carnitine-acylcarnitine translocase (CAT) deficiency have been described in neonates [102–105]. Systemic manifestations include cardiomyopathy, hepatopathy, Reye syndrome-like illness, and muscle weakness and hypotonia. The creatine kinase level may be very elevated, and prominent myoglobinuria may lead to renal tubular dysfunction and renal failure. A "salt and pepper" retinopathy

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has been reported in LCHAD deficiency but usually appears in later childhood. A history of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome may be elicited from a heterozygous mother carrying a fetus with LCHAD deficiency [106]. Lactic acidosis is more commonly encountered in long-chain fatty acid oxidation disorders but may not be a prominent feature unless present as part of terminal illness. Patients typically have hypoketotic or nonketotic hypoglycemia, although increased production of ketone bodies may be seen in SCHAD deficiency. Marked hyperammonemia is atypical but may occur (e.g., CAT and VLCAD deficiency) [103]. Urine organic acid analysis typically shows elevated dicarboxylic acids of characteristic chain length depending on the underlying disorder. Plasma total carnitine levels are typically low, with an elevation in the esterified carnitine fraction and esterified-to-free-carnitine ratio. An acylcarnitine profile may detect pathognomonic compounds characteristic of specific fatty acid oxidation disorders. However, fibroblast enzymology or intracellular acylcarnitine profile analysis with or without DNA mutation analysis may be needed to establish the diagnosis with certainty. Treatment includes avoidance of fasting, low-fat diet, and carnitine supplementation in patients who survive the neonatal period. Medium-chain triglycerides may be useful in long-chain defects [102].

Mitochondrial Disease

The mitochondrial electron transport chain is coded for by the coordinated action of both nuclear and mitochondrial genomes. These conditions therefore may exhibit either Mendelian (autosomal recessive, autosomal dominant, X-linked) or maternal (mitochondrial) inheritance [78]. Dysfunction of any organ system, either alone or in combination, may occur when mitochondrial function is abnormal. However, neuromuscular signs and symptoms occur most commonly. Children who have mitochondrial disorders, caused by either nuclear or mitochondrial DNA defects, may first come to medical attention as neonates [30,31,76, 77,79–81,107–113]. Hypotonia, lethargy, deafness, dystonia, and seizures are common features. Cataracts and retinal pigmentary abnormalities may also be present. Systemic involvement includes cardiomyopathy, bone marrow suppression, hepatic disease, and renal dysfunction. Antenatal findings include polyhydramnios, oligohydroamnios, hydrops fetalis, intrauterine growth retardation, arthrogryposis, decreased movement, and cardiomyopathy [30,31]. Severe asphyxia and early death may occur [114].

Although some patients with mitochondrial disease may only have nonspecific white matter abnormalities including edema or delayed myelination, gray matter involvement is relatively common, especially affecting the dorsal midbrain, thalami, and globi pallidi [18,113]. Leigh syndrome (subacute necrotizing encephalomyopathy) is another manifestation of mitochondrial dysfunction, although affected children tend to present after the neonatal period. The clinician must maintain a high index of suspicion because these disorders are often difficult to diagnose. For example, a patient initially diagnosed with HIE after presenting with fetal distress, metabolic acidosis, and seizures at 4 hours of age was later documented to have complex IV (cytochrome oxidase) deficiency [81]. Cerebral edema and subsequent multicystic encephalomalacia have also been described in mitochondrial disease patients presenting with neonatal-onset seizures and severe encephalopathy [112]. Elevated lactate-to-pyruvate ratio (>25), β-hydroxybutyrate-to-acetoacetate ratio (>1.0), and urine organic acids with tricarboxylic acid cycle intermediates or other compounds suggestive of mitochondrial dysfunction offer clues to diagnosis. Although a muscle biopsy may show changes suggestive of mitochondrial disease, ragged red fibers are rarely encountered in children, and histopathology may appear normal or have nonspecific findings. Definitive diagnosis is made by mitochondrial respiratory chain analysis in muscle or other tissue or the detection of a pathogenic mutation in mitochondrial or nuclear DNA. Various vitamin "cocktails" have been attempted, but there is no proven effective therapy for most of these conditions.

Severe Ketoacidosis

Classic organic acidemias often present in the neonatal period or infancy with overwhelming illness and ketoacidosis with an elevated anion gap. Prominent lactic acidosis is uncommon, but mild-to-moderate elevations may occur, especially if there is superimposed tissue hypoperfusion. Diagnosis of these disorders is relatively straightforward and is based on detection of characteristic metabolites in serum amino acids and urine organic acids.

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Organic Acidemias

Methylmalonic acidemia (MMA), propionic acidemia (PA), isovaleric acidemia (IVA), glutaric aciduria, type II (multiple acyl CoA dehydrogenase deficiency (MADD)), and holocarboxylase synthetase deficiency (multiple carboxylase deficiency (MCD)) are autosomal recessive conditions that may present in neonates with lethargy, vomiting, and severe ketoacidosis. Neonatal seizures have also been reported, but are not common. Renal cysts and dysmorphic features frequently occur in MADD with neonatal presentation. An odor of "sweaty feet" may also be noted in patients with MADD or IVA. Routine labs often show neutropenia, hypoglycemia, and a metabolic acidosis. Lactic acidosis is usually not a prominent feature, except in MCD and some cases of MMA. Head MRI may show abnormal T2 prolongation in the periventricular white matter and lesions in the basal ganglia, especially the globus pallidus (MMA) or putamen and caudate nucleus (PA) [74]. Characteristic organic acids in urine make diagnosis of these conditions relatively straightforward.

Affected individuals with 3-hydroxyisobutyric aciduria may also present in the neonatal period with overwhelming ketoacidosis. In addition, patients may have lactic acidosis, dysmorphic features, and congenital brain malformations, including intracerebral calcifications, lissencephaly, pachygyria, polymicrogyria, agenesis of the corpus callosum, and an indistinct gray and white matter interface [115]. Glutaric aciduria type I may also feature severe brain anomalies, including frontotemporal atrophy, delayed myelination, and basal ganglia changes, but this disorder tends to present later in infancy [74].

Therapy of organic acidemias consists of dietary restriction of specific amino acids in some conditions and the prompt treatment of acute episodes of ketoacidosis. Supplementation with carnitine and specific cofactors (e.g., vitamin B_{12} in some forms of MMA or biotin in MCD) is an important therapeutic intervention.

Lethargy without Metabolic Acidosis or Hyperammonemia

Maple Syrup Urine Disease

Children with maple syrup urine disease (MSUD) typically present in the first few days to weeks of life, after appearing normal at birth. Feeding difficulty and vomiting may be the initial symptoms. By the end of the first week, lethargy and progressive neurologic deterioration occur unless appropriate treatment is started. A markedly hypertonic infant with opisthotonus is typical. The characteristic odor is present by the time neurologic symptoms develop, but not all patients have a "maple syrup" smell. Metabolic acidosis is uncommon until later in the course of disease. Neuroimaging is normal in the first few days of life. Characteristic head MRI findings develop with time, including profound localized edema in the deep cerebellar white matter, dorsal brainstem, cerebral peduncles, posterior limb of the internal capsule, perirolandic white matter, and globi pallidi. Generalized cerebral hemisphere edema may also be present. Delayed, or abnormal, myelination is common [74]. Emergency management includes measures to decrease the levels of branched-chain amino acids (BCAAs) rapidly (e.g., hemodialysis, BCAA-free enteral or parenteral nutrition, and the prevention of catabolism). Restricting intake of branched-chain amino acids while providing adequate nutrition and prompt treatment of intercurrent illnesses are the cornerstones of chronic management. Thiamine supplementation may help in some cases of MSUD.

Mevalonic Aciduria

Mevalonic aciduria is an autosomal recessive disorder of cholesterol biosynthesis that may present in the neonatal period with lethargy, hypotonia, or other signs of neurologic dysfunction without a metabolic acidosis. Patients may have dysmorphic features, cataracts, hepatosplenomegaly, recurrent fevers without identifiable infectious agents, and anemia [84,116].

Lethargy with Hyperammonemia

Neonatal hyperammonemia is the predominant laboratory finding in urea cycle disorders, although other inborn errors of metabolism cause hyperammonemia by a secondary inhibition of urea cycle function. Pyruvate carboxylase deficiency, organic acidemias, carnitine-acylcarnitine translocase deficiency, lysinuric protein intolerance, and the HHH (hyperornithinemia-hyperammonemia-homocitrullinuria) syndrome may be associated with neonatal hyperammonemia. Prominent hyperammonemia (>10× elevation) has also been reported in patients with perinatal asphyxia, likely secondary to hepatic

dysfunction. Other common associations with perinatal asphyxia, such as severe fetal bradycardia, low Apgar scores, and the need for prolonged resuscitation following delivery, typically are present in such instances [23]. In contrast, patients with inborn errors of metabolism, including urea cycle disorders, typically appear normal at birth, without perinatal distress, following an uneventful pregnancy.

Urea Cycle Disorders

Patients with urea cycle disorders (*N*-acetylglutamate synthetase deficiency, carbamyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, argininosuccinic acid synthetase deficiency [citrullinemia], and argininosuccinic acid lyase deficiency) typically present with lethargy, poor feeding, and hyperpnea with a respiratory alkalosis in the first few days of life. Sepsis is often initially suspected, and unless an ammonia level is checked, these infants may die of unknown cause early in the neonatal period. Aside from ornithine transcarbamylase deficiency, which is X-linked, these are autosomal recessive conditions. Progression to deep coma supervenes, necessitating intubation and mechanical ventilation. Head imaging is nonspecific in these disorders but may show cerebral edema. Head MRI in the subacute phase (days of life 3–7) may resemble HIE, with edema in both gray and white matter and gray matter T1 shortening. Damage to the cortex and underlying white matter, similar to ischemic injury, may be present in the chronic phase [74]. Diagnosis is based on characteristic serum amino acid patterns and urine orotic acid concentration. Enzymology on fibroblasts or hepatocytes may be needed to confirm the diagnosis. DNA analysis may also be performed. Initial emergency treatment consists of hemodialysis, protein restriction, provision of adequate fluids and calories to prevent catabolism, intravenous ammonia-scavenging medications (sodium benzoate and sodium phenylacetate), and intravenous arginine hydrochloride. Chronic therapy includes protein restriction, oral nitrogen-scavenging medications, and arginine or citrulline supplementation.

HHH Syndrome

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an autosomal recessive condition caused by defective transport of ornithine into mitochondria, resulting in a secondary inhibition of the urea cycle. Most patients present in infancy with lethargy, intermittent hyperammonemia, failure to thrive, developmental delay, and ataxia, but HHH syndrome may present in neonates with nonspecific signs and symptoms related to hyperammonemia. Diagnosis is made by detecting characteristic metabolites in blood and urine. Treatment includes protein restriction.

Lysinuric Protein Intolerance

Defective transport of basic amino acids across the basilateral membrane of epithelial cells is the fundamental defect in lysinuric protein intolerance. Patients typically present in infancy with hyperammonemia, vomiting, diarrhea, and failure to thrive. Inheritance is autosomal recessive. Serum concentrations of ornithine, lysine, and arginine are low, whereas citrulline, glutamine, and alanine tend to be elevated. There is increased urinary excretion of lysine, ornithine, and arginine. Moderate protein restriction and citrulline supplementation are the primary therapies.

Cerebral Calcification

Intracranial calcification has been associated with severe HIE and TORCH infections but may also occur secondary to genetic disorders. These genetic conditions have sometimes been referred to as *pseudo-TORCH syndrome*, although given the identification of specific mutations in a number of genes, this imprecise term is probably best avoided [117]. Aicardi-Goutières syndrome (AGS) is characterized by early-onset encephalopathy, with some individuals having a neonatal presentation reminiscent of in utero infection. Such neonates may have seizures, hepatosplenomegaly, elevated liver transaminases, and thrombocytopenia. Brain imaging shows intracranial calcification with variable involvement of the basal ganglia, cerebellar dentate nuclei, and cerebellum. Cortical, cerebellar, and brainstem atrophy, as well as white matter disease, may also occur. CSF may show a lymphocytosis and elevated interferon-α, although levels may normalize in the first few years of life. AGS demonstrates genetic heterogeneity with mutations in a variety of cellular nuclease genes, including *TREX1, RNASEH2A*, and *RNASEH2C* being associated with disease [118]. AGS is inherited in most cases as an autosomal recessive condition, but less frequently de novo autosomal dominant mutations may also occur in *TREX1*-related disease. A syndrome of intractable neonatal seizures,

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subependymal calcification, hemorrhagic brain distruction, and congenital cataracts has been described in neonates with autosomal recessive mutations in the gene encoding junctional adhesion molecule 3 (*JAM3*) [119]. Band-like calcification with simplified gyration and polymicrogyria (BLC-PMG) is another autosomal recessive condition that manifests with clinical and neuroradiologic features that are common in congenital infections. Neonates with BLC-PMG have a prominent band of cortical gray matter calcification and calcification in the cerebellum and basal ganglia, as well as microcephaly, early-onset seizures, and profound developmental delay [120].

Other Disorders

Glycogen Storage Disorders

Glycogen storage disorders (GSDs) and disorders of gluconeogenesis may cause hypoglycemia and lactic acidosis in neonates. However, differentiation from HIE and other inborn errors of metabolism should be straightforward. GSD type I patients may have hepatomegaly at birth and symptomatic hypoglycemia, but most patients become symptomatic in infancy. GSD type III (debrancher enzyme deficiency) tends to be a more mild condition but may present in neonates. Rarely, GSD type IV (branching enzyme deficiency) has been associated with severe neurologic findings at birth and early death [121]. GSD type 0 (glycogen synthetase deficiency) may present with ketotic hypoglycemia and lactic acidosis without prominent hepatomegaly. GSD type VIII (phosphorylase kinase deficiency) may be inherited as an autosomal recessive or X-linked condition. Clinical features include hepatomegaly, myopathy, and a fatal infantile variant with cardiomyopathy. Pompe disease (GSD type II, a glucosidase deficiency) may also present with neonatal cardiomyopathy and marked hypotonia secondary to a skeletal myopathy [122].

Disorders of Gluconeogenesis

Fructose-1,6-bisphosphatase deficiency may present with severe neonatal metabolic acidosis. Routine laboratory tests show hypoglycemia and lactic acidosis. Patients typically respond well to intravenous fluids containing dextrose and bicarbonate. Avoidance of fasting is the mainstay of therapy for gluconeogenesis disorders [122].

Congenital Disorders of Glycosylation (CDGs)

These disorders are caused by abnormalities in the enzymes responsible for the glycosylation of proteins and lipids. CDG-Ia, the most common subtype, is characterized by mild dysmorphic features, abnormal fat distribution, inverted nipples, strabismus, and hypotonia. Protein-losing enteropathy, nephrotic syndrome, cardiomyopathy, and pericardial effusion are other common features. The head MRI shows cerebellar hypoplasia, but this may not be obvious in neonates [32]. These conditions should be considered, in addition to mitochondrial disorders, in neonates who have mulitsystem involvement.

Other Neonatal Myopathies and Encephalomyopathies

Patients with inherited myopathies (e.g., centronuclear myopathy) may also present with neonatal distress, hypotonia, and signs suggestive of HIE [122]. In addition to dysmorphic features, such as broad nasal bridge, anteverted nares, and low-set ears, neonates with Smith-Lemli-Opitz syndrome may have generalized seizures [123]. Cathepsin D deficiency is a congenital form of neuronal ceroid lipofuscinosis characterized by prenatal deceleration of head growth, microcephaly, intractable neonatal seizures, apnea, respiratory failure, and early death. Seizures may also be present prenatally [124]. Initial symptoms of GM3 synthase deficiency, a disorder of complex ganglioside synthesis, start in the neonatal or early-infantile period with irritability, poor feeding, and failure to thrive but progress to include severe epilepsy, developmental stagnation, and regression [125]. Menkes disease is an X-linked disorder that typically presents with neurodegeneration, sparse and coarse hair, and connective tissue abnormalities, but refractory neonatal seizures may also occur [126]. Monoamine neurotransmitter disorders may present in infancy and be associated with developmental delay, seizures, and pyramidal and extrapyramidal features, hence mimicking the presentation of other neurologic disorders, including HIE and cerebral palsy. Diagnosis requires specialized testing of CSF neurotransmitter metabolites or gene sequencing [127].

Summary

Inborn errors of metabolism and a number of single-gene disorders not primarily involved in metabolism may present in neonates with features of HIE. In

contrast to children with HIE, neonates with metabolic disorders often have an unremarkable delivery and an apparent normal period lasting hours to days. However, a traumatic delivery or prematurity may constitute environmental stress factors that unmask an underlying inborn error of metabolism; the absence of a normal period, therefore, does not exclude these disorders from consideration. Although patients with biochemical genetic disorders and HIE, in general, have different obstetric histories and may have different head imaging findings, in practice, it may be difficult to distinguish these conditions because they also share many clinical, radiologic, and laboratory features. There is a tendency to evaluate neonates for a possible underlying metabolic disorder only after more common conditions have been excluded. It is crucial for the clinician to consider biochemical genetic disorders in all neonates with nonspecific features suggestive of sepsis or asphyxia on initial presentation. Rapid diagnosis and management may prevent death or significant morbidity. By obtaining appropriate laboratory investigations, the clinician can provide the family with the best chance of arriving at a diagnosis for their child during an extremely stressful time. Establishing a diagnosis permits not only optimal management of the child but also accurate genetic counseling. Tandem mass spectrometry (MS/MS) testing for a wide variety of aminoacidemias, organic acidemias, and fatty acid oxidation defects continues to be integrated into newborn screening programs throughout the world. Such technology provides new hope for the early diagnosis and treatment of inborn errors of metabolism, which collectively account for significant neonatal morbidity and mortality. However, MS/MS newborn screening will not detect many metabolic disorders that may masquerade as HIE, so neonatologists must continue to have a high index of suspicion in order to arrive at a definitive diagnosis. State-of-the-art next-generation sequencing tests, such as comprehensive epilepsy gene panels, whole-exome sequencing, and whole-genome sequencing have identified a number of genetic disorders that can present with seizures and will undoubtedly play an increasingly important role in the evaluation of the encephalopathic neonate.

References

1. American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Executive summary: neonatal encephalopathy and neurologic outcome. *Obstet Gynecol*, 2014; **123**(4): 896–901.
2. Biagas K., Hypoxic-ischemic brain injury: advancements in the understanding of mechanisms and potential avenues for therapy. *Curr Opin Pediatr* 1999; **11**(3): 223–8.
3. Greene CL, Goodman SI. Catastrophic metabolic encephalopathies in the newborn period: evaluation and management. *Clin Perinatol* 1997; **24**(4): 773–86.
4. Khong PL, et al. MRI of neonatal encephalopathy. *Clin Radiol* 2003; **58**(11): 833–44.
5. Vannucci RC. Hypoxic-ischemic encephalopathy. *Am J Perinatol* 2000; **17**(3): 113–20.
6. Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. *AJNR Am J Neuroradiol* 1995; **16**(9): 1837–46.
7. Barkovich AJ, et al. Perinatal asphyxia: MR findings in the first 10 days. *AJNR Am J Neuroradiol* 1995; **16**(3): 427–38.
8. Roland EH, et al. Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. *Ann Neurol* 1998; **44**(2): 161–6.
9. Hoon AH Jr, et al. Brain magnetic resonance imaging in suspected extrapyramidal cerebral palsy: observations in distinguishing genetic-metabolic from acquired causes. *J Pediatr* 1997; **131**(2): 240–5.
10. Schwartz ES, Barkovich AJ. Brain and spine injuries in infancy and childhood. In *Pediatric Neuroimaging*. Philadelphia: Lippincott Williams & Wilkins, 2012: 240–366.
11. Barkovich AJ, Patay Z. Metabolic, toxic, and inflammatory brain disorders. In Barkovich AJ, Raybaud C, eds., *Pediatric Neuroimaging*. Philadelphia: Lippincott Williams & Wilkins, 2012: 81–239.
12. Haas RH, et al. Acute basal ganglia infarction in propionic acidemia. *J Child Neurol* 1995; **10**(1): 18–22.
13. Greenamyre T, et al. Evidence for transient perinatal glutamatergic innervation of globus pallidus. *J Neurosci* 1987; **7**(4): 1022–30.
14. Penn AA, et al. Kernicterus in a full term infant. *Pediatrics* 1994; **93**(6 Pt 1): 1003–6.
15. Ankarcrona M. et al. Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. *Neuron* 1995; **15**(4): 961–73.
16. Eliasson MJ, et al. Poly(ADP-ribose) polymerase gene disruption renders mice resistant to cerebral ischemia. *Nat Med* 1997; **3**(10): 1089–95.
17. Johnston MV. Hypoxic and ischemic disorders of infants and children: lecture for 38th Meeting of Japanese Society of Child Neurology, Tokyo, Japan, July 1996. *Brain Dev* 1997; **19**(4): 235–9.
18. Johnston MV, Hoon AH Jr. Possible mechanisms in infants for selective basal ganglia damage from

asphyxia, kernicterus, or mitochondrial encephalopathies. *J Child Neurol* 2000; **15**(9): 588–91.

19. Shi Y, et al. Role of carbon monoxide and nitric oxide in newborn infants with postasphyxial hypoxic-ischemic encephalopathy. *Pediatrics* 2000; **106**(6): 1447–51.
20. Blomgren K, Hagberg H. Free radicals, mitochondria, and hypoxia-ischemia in the developing brain. *Free Radic Biol Med* 2006; **40**(3): 388–97.
21. Rousset CI, et al. Mitochondria and perinatal brain injury. *J Mater Fetal Neonatal Med* 2012; **25**(Suppl 1): 35–8.
22. Agani FH, et al. The role of mitochondria in the regulation of hypoxia-inducible factor 1 expression during hypoxia. *J Biol Chem* 2000; **275**(46): 35863–7.
23. Goldberg RN, et al. Hyperammonemia associated with perinatal asphyxia. *Pediatrics* 1979; **64**(3): 336–41.
24. Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. *J Perinatol* 1999; **19**(1): 40–3.
25. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med* 2013; **18**(4): 185–91.
26. Van Hove JL, Lohr NJ. Metabolic and monogenic causes of seizures in neonates and young infants. *Mol Genet Metab* 2011; **104**(3): 214–30.
27. Noh GJ, Tavyev Asher YJ, Graham JM Jr. Clinical review of genetic epileptic encephalopathies. *Eur J Med Genet* 2012; **55**(5): 281–98.
28. Papetti L, et al. Metabolic epilepsy: an update. *Brain Dev* 2013; **35**(9): 827–41.
29. Takahashi Y, et al. Epilepsy in peroxisomal diseases. *Epilepsia* 1997; **38**(2): 182–8.
30. Gire C, et al. Clinical features and neuroradiological findings of mitochondrial pathology in six neonates. *Childs Nerv Syst* 2002; **18**(11): 621–8.
31. von Kleist-Retzow JC, et al. Antenatal manifestations of mitochondrial respiratory chain deficiency. *J Pediatr* 2003; **143**(2): 208–12.
32. Enns GM, et al. Clinical and molecular features of congenital disorder of glycosylation in patients with type 1 sialotransferrin pattern and diverse ethnic origins. *J Pediatr* 2002; **141**(5): 695–700.
33. Hoffmann GF, Surtees RA, Wevers RA. Cerebrospinal fluid investigations for neurometabolic disorders. *Neuropediatrics* 1998; **29**(2): 59–71.
34. Hyland K, Arnold LA. Value of lumbar puncture in the diagnosis of infantile epilepsy and folinic acid-responsive seizures. *J Child Neurol* 2002; **17**(Suppl 3): 3S48–55; discussion 3S56.
35. Mastrangelo M, Leuzzi V. Genes of early-onset epileptic encephalopathies: from genotype to phenotype. *Pediatr Neurol* 2012; **46**(1): 24–31.
36. Nordli DR Jr. Epileptic encephalopathies in infants and children. *J Clin Neurophysiol* 2012; **29**(5): 420–4.
37. Epi KC, et al. De novo mutations in epileptic encephalopathies. *Nature* 2013; **501**(7466): 217–21.
38. Veeramah KR, et al. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. *Epilepsia* 2013; **54**(7): 1270–81.
39. Bekiesiniska-Figatowska M, Rokicki D, Walecki J. MRI in nonketotic hyperglycinaemia: case report. *Neuroradiology* 2001; **43**(9): 792–3.
40. del Toro M, et al. Progressive vacuolating glycine leukoencephalopathy with pulmonary hypertension. *Ann Neurol* 2006; **60**(1): 148–52.
41. Mourmans J, et al. Sequential MR imaging changes in nonketotic hyperglycinemia. *Am J Neuroradiol* 2006; **27**(1): 208–11.
42. Roldan A, et al. Glycine and other neurotransmitter amino acids in cerebrospinal fluid in perinatal asphyxia and neonatal hypoxic-ischaemic encephalopathy. *Acta Paediatr* 1999; **88**(10): 1137–41.
43. Meyer S, et al. A novel missense mutation in a neonate with nonketotic hyperglycinemia. *Pediatr Neurol* 2010; **43**(5): 363–7.
44. Eyaid WM, et al. An inborn error of metabolism presenting as hypoxic-ischemic insult. *Pediatr Neurol* 2005; **32**(2): 134–6.
45. Topcu M, et al. Molybdenum cofactor deficiency: report of three cases presenting as hypoxic-ischemic encephalopathy. *J Child Neurol* 2001; **16**(4): 264–70.
46. Bayram E, et al. Molybdenum cofactor deficiency: review of 12 cases (MoCD and review). *Eur J Paediatr Neurol* 2013; **17**(1): 1–6.
47. Schwahn BC, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. *Lancet* 2015; **386**(10007): 1955–63.
48. Plecko B, et al. Biochemical and molecular characterization of 18 patients with pyridoxine-dependent epilepsy and mutations of the antiquitin (*ALDH7A1*) gene. *Hum Mutat* 2007; **28**(1): 19–26.
49. Scharer G, et al. The genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy due to mutations in *ALDH7A1*. *J Inherit Metab Dis* 2010; **33**(5): 571–81.
50. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. *Arch Dis Child* 1999; **81**(5): 431–3.

51. Baxter P, et al. Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. *Dev Med Child Neurol* 1996; **38**(11): 998–1006.
52. Haenggeli CA, Girardin E, Paunier L. Pyridoxine-dependent seizures, clinical and therapeutic aspects. *Eur J Pediatr* 1991; **150**(7): 452–5.
53. Hyland K, et al. Folinic acid responsive seizures: a new syndrome? *J Inherit Metab Dis* 1995; **18**(2): 177–81.
54. Torres OA, et al. Folinic acid-responsive neonatal seizures. *J Child Neurol* 1999; **14**(8): 529–32.
55. Gallagher RC, et al. Folinic acid-responsive seizures are identical to pyridoxine-dependent epilepsy. *Ann Neurol* 2009; **65**(5): 550–6.
56. Hoffmann GF, et al. Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy. *J Inherit Metab Dis* 2007; **30**(1): 96–9.
57. Mills PB, et al. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase. *Hum Mol Genet* 2005; **14**(8): 1077–86.
58. Jaeken J. Genetic disorders of gamma-aminobutyric acid, glycine, and serine as causes of epilepsy. *J Child Neurol* 2002; **17**(Suppl 3): 3S84–7; discussion 3S88.
59. Kraoua I, et al. 3-Phosphoglycerate dehydrogenase deficiency: description of two new cases in Tunisia and review of the literature. *Neuropediatrics* 2013; **44**(5): 281–5.
60. Haberle J, et al. Congenital glutamine deficiency with glutamine synthetase mutations. *N Engl J Med* 2005; **353**(18): 1926–33.
61. Haberle J, et al. Glutamine supplementation in a child with inherited GS deficiency improves the clinical status and partially corrects the peripheral and central amino acid imbalance. *Orphanet J Rare Dis* 2012; **7**: 48.
62. Ruzzo EK, et al. Deficiency of asparagine synthetase causes congenital microcephaly and a progressive form of encephalopathy. *Neuron* 2013; **80**(2): 429–41.
63. Alfadhel M, et al. Asparagine synthetase deficiency: new inborn errors of metabolism. *JIMD Rep* 2015; **22**: 11–6.
64. Medina-Kauwe LK, et al. 4-Aminobutyrate aminotransferase (GABA-transaminase) deficiency. *J Inherit Metab Dis* 1999; **22**(4): 414–27.
65. Parviz M, et al. Disorders of GABA metabolism: SSADH and GABA-transaminase deficiencies. *J Pediatr Epilepsy* 2014; **3**(4): 217–27.
66. Au KM, et al. Diagnosis of dihydropyrimidine dehydrogenase deficiency in a neonate with thymine-uraciluria. *Hong Kong Med J* 2003; **9**(2): 130–2.
67. Enns GM, et al. Head imaging abnormalities in dihydropyrimidine dehydrogenase deficiency. *J Inherit Metab Dis* 2004; **27**(4): 513–22.
68. Marie S, et al. AICA-ribosiduria: a novel, neurologically devastating inborn error of purine biosynthesis caused by mutation of ATIC. *Am J Hum Genet* 2004; **74**(6): 1276–81.
69. Jurecka A, et al. Adenylosuccinate lyase deficiency. *J Inherit Metab Dis* 2015; **38**(2): 231–42.
70. Stockler S, et al. Guanidinoacetate methyltransferase deficiency: the first inborn error of creatine metabolism in man. *Am J Hum Genet* 1996; **58**(5): 914–22.
71. Gordon N. Guanidinoacetate methyltransferase deficiency (GAMT). *Brain Dev* 2010; **32**(2): 79–81.
72. De Vivo DC, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med* 1991; **325**(10): 703–9.
73. De Vivo DC, Leary L, Wang D. Glucose transporter 1 deficiency syndrome and other glycolytic defects. *J Child Neurol* 2002; **17**(Suppl 3): S15–23; discussion S24–5.
74. Barkovich AJ. *Pediatric Neuroimaging*, 3rd edn. Philadelphia: Lippincott, Williams & Wilkins, 2000: 71–156, 162–205.
75. Norman MG, et al. Perinatal hemorrhagic and hypoxic-ischemic lesions. In Norman MG, ed., *Congenital Malformations of the Brain: Pathological and Genetic Aspects*. Oxford University Press, 1995: 419–23.
76. Birch-Machin MA, et al. Fatal lactic acidosis in infancy with a defect of complex III of the respiratory chain. *Pediatr Res* 1989; **25**(5): 553–9.
77. von Dobeln U, et al. Fatal neonatal lactic acidosis with respiratory insufficiency due to complex I and IV deficiency. *Acta Paediatr* 1993; **82**(12): 1079–81.
78. Zeviani M, Bertagnolio B, Uziel G. Neurological presentations of mitochondrial diseases. *J Inherit Metab Dis* 1996; **19**(4): 504–20.
79. Muraki K, et al. Severe lactic acidosis and neonatal death in Pearson syndrome. *J Inherit Metab Dis* 1997; **20**(1): 43–8.
80. Procaccio V, et al. Nuclear DNA origin of mitochondrial complex I deficiency in fatal infantile lactic acidosis evidenced by transnuclear complementation of cultured fibroblasts. *J Clin Invest* 1999; **104**(1): 83–92.
81. Willis TA, et al. Cytochrome oxidase deficiency presenting as birth asphyxia. *Dev Med Child Neurol* 2000; **42**(6): 414–7.

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82. Molinari F, et al. Impaired mitochondrial glutamate transport in autosomal recessive neonatal myoclonic epilepsy. *Am J Hum Genet* 2005; **76**(2): 334–9.
83. Muntau AC, et al. Combined D-2- and L-2-hydroxyglutaric aciduria with neonatal onset encephalopathy: a third biochemical variant of 2-hydroxyglutaric aciduria? *Neuropediatrics* 2000; **31**(3): 137–40.
84. Hoffmann GF, et al. Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. *Pediatrics* 1993; **91**(5): 915–21.
85. Bakkeren JA, et al. Organic aciduria in hypoxic premature newborns simulating an inborn error of metabolism. *Eur J Pediatr* 1977; **127**(1): 41–7.
86. Martin HC, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. *Hum Mol Genet* 2014; **23**(12): 3200–11.
87. Ohba C, et al. *GRIN1* mutations cause encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders. *Epilepsia* 2015; **56**(6): 841–8.
88. Nicita F, et al. The genetics of monogenic idiopathic epilepsies and epileptic encephalopathies. *Seizure* 2012; **21**(1): 3–11.
89. Tavyev Asher YJ, Scaglia F. Molecular bases and clinical spectrum of early infantile epileptic encephalopathies. *Eur J Med Genet* 2012; **55**(5): 299–306.
90. Pavone P, et al. Ohtahara syndrome with emphasis on recent genetic discovery. *Brain Dev* 2012; **34**(6): 459–68.
91. Dedek K, et al. Neonatal convulsions and epileptic encephalopathy in an Italian family with a missense mutation in the fifth transmembrane region of *KCNQ2*. *Epilepsy Res* 2003; **54**(1): 21–7.
92. Tang S, et al. Encephalopathy and *SCN1A* mutations. *Epilepsia* 2011; **52**(4): e26–30.
93. Schanen NC, et al. Neonatal encephalopathy in two boys in families with recurrent Rett syndrome. *J Child Neurol* 1998; **13**(5): 229–31.
94. Mirzaa GM, et al. *CDKL5* and *ARX* mutations in males with early-onset epilepsy. *Pediatr Neurol* 2013; **48**(5): 367–77.
95. Mencarelli MA, et al. Novel *FOXG1* mutations associated with the congenital variant of Rett syndrome. *J Med Genet* 2010; **47**(1): 49–53.
96. Byrd DJ, et al. Neonatal pyruvate dehydrogenase deficiency with lipoate responsive lactic acidaemia and hyperammonaemia. *Eur J Pediatr* 1989; **148**(6): 543–7.
97. Robinson BH, et al. Disorders of pyruvate carboxylase and the pyruvate dehydrogenase complex. *J Inherit Metab Dis* 1996; **19**(4): 452–62.
98. Bonnefont JP, et al. Alpha-ketoglutarate dehydrogenase deficiency presenting as congenital lactic acidosis. *J Pediatr* 1992; **121**(2): 255–8.
99. Haworth JC, et al. Lactic acidosis in three sibs due to defects in both pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complexes. *Pediatrics* 1976; **58**(4): 564–72.
100. Kerrigan JF, et al. Fumaric aciduria: clinical and imaging features. *Ann Neurol* 2000; **47**(5): 583–8.
101. Wilcken B, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet* 2007; **369**(9555): 37–42.
102. Duran M, et al. 3-Hydroxydicarboxylic aciduria due to long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency associated with sudden neonatal death: protective effect of medium-chain triglyceride treatment. *Eur J Pediatr* 1991; **150**(3): 190–5.
103. Stanley CA, et al. Brief report: a deficiency of carnitine-acylcarnitine translocase in the inner mitochondrial membrane. *N Engl J Med* 1992; **327**(1): 19–23.
104. Bertrand C, et al. Very long chain acyl-CoA dehydrogenase deficiency: identification of a new inborn error of mitochondrial fatty acid oxidation in fibroblasts. *Biochim Biophys Acta* 1993; **1180**(3): 327–9.
105. Hintz SR, et al. Early neonatal diagnosis of long-chain 3-hydroxyacyl coenzyme a dehydrogenase and mitochondrial trifunctional protein deficiencies. *Mol Genet Metab* 2002; **75**(2): 120–7.
106. Ibdah JA, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med* 1999; **340**(22): 1723–31.
107. Agsteribbe E, et al. A fatal, systemic mitochondrial disease with decreased mitochondrial enzyme activities, abnormal ultrastructure of the mitochondria and deficiency of heat shock protein 60. *Biochem Biophys Res Commun* 1993; **193**(1): 146–54.
108. Briones P, et al. A new case of multiple mitochondrial enzyme deficiencies with decreased amount of heat shock protein 60. *J Inherit Metab Dis* 1997; **20**(4): 569–77.
109. Poggi GM, et al. Fatal neonatal outcome in a case of muscular mitochondrial DNA depletion. *J Inherit Metab Dis* 2000; **23**(7): 755–7.
110. Valnot I, et al. Mutations of the *SCO1* gene in mitochondrial cytochrome c oxidase deficiency with

neonatal-onset hepatic failure and encephalopathy. *Am J Hum Genet* 2000; **67**(5): 1104–9.

111. Seyda A, et al. A novel syndrome affecting multiple mitochondrial functions, located by microcell-mediated transfer to chromosome 2p14-2p13. *Am J Hum Genet* 2001; **68**(2): 386–96.

112. Mayr JA, et al. Lipoic acid synthetase deficiency causes neonatal-onset epilepsy, defective mitochondrial energy metabolism, and glycine elevation. *Am J Hum Genet* 2011; **89**(6): 792–7.

113. Huemer M, et al. Clinical, morphological, biochemical, imaging and outcome parameters in 21 individuals with mitochondrial maintenance defect related to FBXL4 mutations. *J Inherit Metab Dis* 2015; **38**(5): 905–14.

114. Nakano Y, et al. Fatal case of mitochondrial DNA depletion with severe asphyxia in a newborn. *Pediatr Int* 2011; **53**(2): 240–2.

115. Chitayat D, et al. Brain dysgenesis and congenital intracerebral calcification associated with 3-hydroxyisobutyric aciduria. *J Pediatr* 1992; **121**(1): 86–9.

116. Burlina AB, Bonafe L, Zacchello F. Clinical and biochemical approach to the neonate with a suspected inborn error of amino acid and organic acid metabolism. *Semin Perinatol* 1999; **23**(2): 162–73.

117. Livingston JH, et al. Intracranial calcification in childhood: a review of aetiologies and recognizable phenotypes. *Dev Med Child Neurol* 2014; **56**(7): 612–26.

118. Rice G, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. *Am J Hum Genet* 2007; **81**(4): 713–25.

119. Mochida GH, et al. A homozygous mutation in the tight-junction protein JAM3 causes hemorrhagic destruction of the brain, subependymal calcification, and congenital cataracts. *Am J Hum Genet* 2010; **87**(6): 882–9.

120. O'Driscoll MC, et al. Recessive mutations in the gene encoding the tight junction protein occludin cause band-like calcification with simplified gyration and polymicrogyria. *Am J Hum Genet* 2010; **87**(3): 354–64.

121. Escobar LF, et al. Neonatal presentation of lethal neuromuscular glycogen storage disease type IV. *J Perinatol* 2012; **32**(10): 810–3.

122. Tein I. Neonatal metabolic myopathies. *Semin Perinatol* 1999; **23**(2): 125–51.

123. Garcia CA, et al. Neurological involvement in the Smith-Lemli-Opitz syndrome: clinical and neuropathological findings. *Dev Med Child Neurol* 1973; **15**(1): 48–55.

124. Siintola E, et al. Cathepsin D deficiency underlies congenital human neuronal ceroid-lipofuscinosis. *Brain* 2006; **129**(Pt 6): 1438–45.

125. Simpson MA, et al. Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase. *Nat Genet* 2004; **36**(11): 1225–9.

126. Jain P, et al. Menkes disease: an important cause of early onset refractory seizures. *J Pediatr Neurosci* 2014; **9**(1): 11–6.

127. Kurian MA, et al. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. *Lancet Neurol* 2011; **10**(8): 721–33.

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Chapter

35

Acidosis and Alkalosis

Ronald S. Cohen

Introduction

As part of normal homeostasis, normal physiologic processes fairly tightly control the pH of arterial blood. Healthy adults maintain a reasonably stable pH ranging from 7.35 to 7.45, and the initial pH after birth can range from 7.11 to 7.36. *Acidosis* (low pH) and *alkalosis* (high pH) occur commonly when there are disturbances of the body's normal physiology. This can result from either a pathologic process or medical interventions. When due to or temporally associated with a pathologic process, the abnormal pH may be blamed for any long-term consequences of that event. Similarly, when a medication or treatment results in an abnormal pH, any long-term consequences may be assigned to that intervention. In both situations, it may not be clear whether the underlying physiologic disturbance is responsible for the adverse long-term outcome or the abnormal pH played a role and, if so, how important that role may have been.

Acidosis

Acidosis is known to accompany ischemia and has been used as a marker for tissue hypoxia and damage. However, it is unclear whether acidosis per se is a cause of injury. To examine this issue, we need to separate the two clinical subtypes of acidosis – respiratory and metabolic.

Respiratory Acidosis

Respiratory acidosis occurs when carbon dioxide (CO_2), produced by metabolism, builds up in the body and dissolves in the bloodstream. The reaction of CO_2 with water (H_2O) results in the production of hydrogen ions (H^+) and bicarbonate (HCO_3^-). Because pH is defined as the inverse log of the concentration of hydrogen ions, as more CO_2 builds up in the bloodstream, more H^+ is produced, and the lower the pH becomes. In extrauterine life, the CO_2 that is produced by the body's metabolism is excreted through the lungs. Of course, in utero, CO_2 produced by fetal metabolism must cross the placenta and be excreted through the mother's lungs. Fetal respiratory acidosis usually reflects failure of the placenta to meet the demands of fetal metabolism rather than failure of maternal lung function. After birth, respiratory acidosis usually indicates an inability of the lungs to meet the demands of the body's metabolism. If either lung or placental function is inadequate to meet the metabolic needs of the patient, hypoxemia can coexist commonly with respiratory acidosis. When this occurs clinically, apportioning the causality for any injury to either the hypoxemia or the acidosis is difficult, if not impossible. However, situations exist where there is predominantly respiratory acidosis, and these allow us to determine the effect of this alone.

Allowing a higher arterial partial pressure of CO_2 ($PaCO_2$), or *permissive hypercapnia*, has been suggested as a safer method of mechanical ventilation [1–5]. Theoretically, using less pressure or smaller tidal volumes while on mechanical ventilation and allowing a moderate degree of respiratory acidosis to occur potentially would be less traumatic to the lungs than using more aggressive mechanical ventilation to achieve a lower "normal" $PaCO_2$. Since oxygenation target levels are not changed with this strategy, these patients generally are not any more hypoxemic than control patients ventilated using standard $PaCO_2$ target levels. Thus the impact of respiratory acidosis per se might be discernible.

Increasing $PaCO_2$ results in lower pH, causing increased cerebral blood flow due to vasodilation. This has been demonstrated in animals and human neonates [6–12]. The data suggest that newborn animals are less responsive than adults. Nevertheless, the possibility that hypercapnia could cause cerebral

vasodilation in neonates raises a concern for possible intraventricular hemorrhage (IVH), and there are some data to support this.

Early on, hypercapnic acidosis was identified as a risk factor for IVH [13,14]. More recently, a retrospective review found that maximum $PaCO_2$ was a dose-dependent predictor of severe IVH [15]. The babies with IVH were smaller and more premature, but the retrospective nature of this study limits its strength. The patients with no IVH had a mean maximum $PaCO_2$ of about 61 mmHg, whereas the median maximum $PaCO_2$ for patients with grades 3 and 4 IVH was about 74 mmHg ($p < 0.0001$), somewhat higher than the usual target range even with permissive hypercapnia. This was also higher than their target range, pointing out the risk of overshooting the upper limit in the clinical "real world." In a study that is not a randomized, controlled trial (RCT), it is impossible to know whether the $PaCO_2$ is causal or just a proxy for worse lung disease. Severe IVH per se might result in an increased $PaCO_2$. In particular, these authors have pointed out the risk of developing acute hypercarbia, and thus increased cerebral blood flow during surfactant administration [16]. They used an intraarterial continuous $PaCO_2$ monitoring device that demonstrated marked acute swings that otherwise would not have been detected using standard intermittent blood-gas sampling. They suggest that the incidence of undetected extreme hypercapnia could be much higher than suspected clinically. This group has also observed that cerebral blood flow is not well autoregulated and increases more with blood pressure than with changes in $PaCO_2$ over the more usual range of permissive hypercapnia [17]. Furthermore, another retrospective analysis suggested that both base deficit and, more important, arterial pH may be more strongly associated with severe IVH [18].

Acute changes in $PaCO_2$ may be just as important, if not more so, as prolonged exposure to specific levels, for which there may be acclimatization by the cerebral vasculature. In newborn lambs, the cerebral blood flow returns to baseline after 6 hours of hyperventilation [19]. However, acute normalization of the $PaCO_2$ resulted in an abrupt increase (up to 140%) in cerebral blood flow. Theoretically, this abrupt overperfusion could result in hemorrhage. A large (n = 849) single-center retrospective analysis showed that the time-weighted average of $PaCO_2$ was less predictive of severe IVH than high, low, and changes in $PaCO_2$ levels [20]. This study, being retrospective, was not able to look at acute changes in $PaCO_2$. Nevertheless, the association of severe IVH with extremes of $PaCO_2$ and changes in $PaCO_2$, more than the time-weighted average, suggests that fluctuations may be significant. Furthermore, because the association was with severe (i.e., grades 3 and 4) IVH, and not with smaller bleeds, the authors speculate that the fluctuations may result in the extension of existing small hemorrhages.

The relationship between $PaCO_2$ and cerebral blood flow in neonates may be more complicated than initially presumed. New data suggest that this relationship is minimal on the first day of life but becomes more pronounced over the next two days [21]. Additionally, the relationship may not be linear; there appears to be a "break point" in the mid-50 mmHg range. Further complicating this is the role of blood pressure, with this having a greater impact on cerebral blood flow at levels of $PaCO_2$ above the break point. Thus a newborn may be more tolerant of hypercapnia on day 1 than later, and the combination of hypertension and hypercapnia may be more dangerous than either alone.

Additional data supporting the theory that moderate hypoventilatory acidosis may be benign for both the lung and the brain are available from animal studies. Using the rat model with unilateral carotid ligation, Vannucci et al. studied the impact of hypoxia versus hypercarbia [22]. They exposed rats after ligation to hypoxic gas (8% O_2) mixed with varying levels of CO_2 (0%, 3%, 6%, or 9%). All groups had similar PaO_2 levels, about 34.7 mmHg, with average $PaCO_2$ levels of 26, 42, 54, and 71 mmHg, respectively. Animals were exposed to the different gas mixtures for 2.5 hours and then sacrificed at 30 days. Brain pathology was scored on a 0–5 scale. Exposure to hypocarbic conditions resulted in worse scores than normocarbia. Increasing CO_2 exposure to 6% further decreased brain pathology, with 9% doing about as well as 3%. The authors concluded that "hypocapnia aggravates perinatal hypoxic-ischemic brain damage while mild hypercapnia is neuroprotective, at least in the immature rat." Further studies by the same group found that higher levels of hypercarbia (>80 mmHg) were associated with lower cerebral blood flow and worse brain damage [23]. Studies in rabbits on the effects of hypercarbia on the circulation also showed improved cardiac output and tissue perfusion until $PaCO_2$ levels greater than 100 mmHg [24]. Studies on

neurons in vitro found that acidosis resulted in decreased apoptosis [25]. Thus the $PaCO_2$ levels associated with well-controlled permissive hypercarbia, if carefully maintained without rapid swings, may be neuroprotective on the cellular level, whereas CO_2 levels that are either very high or swing dramatically may alter cardiovascular function in ways that may be deleterious.

Further animal studies have demonstrated many theoretical benefits of moderate hypercapnia. Looking specifically at lung injury, studies have shown not only less lung injury with permissive hypercapnia but also a protective effect of inhaled CO_2, without lowered ventilator settings [26]. Thus CO_2 itself, not the altered ventilator strategy, may be lung protective. These same authors found that buffering the pH while breathing CO_2 actually attenuated this protective effect [27]. The impact of hypercapnia on other organ systems has also been investigated. Hypercapnic acidosis appears to be protective of the myocardium in postischemic animal models [28].

Clinical trials of permissive hypercapnia have thus far been somewhat reassuring, though perhaps not definitive. Though most studies have been positive, including two RCTs [2,29], one study was stopped early when there was a trend toward worse outcome in the hypercapnic "minimal ventilation" group [30]. This small study did have target ranges for $PaCO_2$ of 55–65 mmHg, higher than most other studies. Combining these data with the results discussed earlier regarding higher levels of $PaCO_2$ and IVH does raise a concern about an upper limit to "how high can you go" with permissive hypercapnia [15]. Nevertheless, the authors of the stopped trial have continued to support studies of permissive hypercapnia and consider it "a safe and effective management strategy to decrease morbidity from bronchopulmonary dysplasia" [31]. More recently, MRI data from a small subset of babies (11 in each group) that were in a RCT of hypercapnic ($PaCO_2$ 50–60 mmHg) versus normocapnic ($PaCO_2$ 35–45 mmHg) found no difference in conventional MRI findings but a small difference favoring normocapnia for fractional anisotropy [32]. Though interesting, the effect was small and the implications unclear.

Permissive hypercapnia may be gaining in acceptance clinically. A recent review of blood gas results from 173 European neonatal intensive care units (NICUs) found a low incidence of hypocapnia (4%) but a fairly high incidence of hypercapnia (31%) [33]. The authors concluded that "permissive hypercapnia has found its way into daily clinical practice."

Metabolic Acidosis

Metabolic acidosis in neonates usually is secondary to other pathologic processes such as significant hypoxemia, hypovolemia, shock, or an underlying genetic disorder. The presence of a significant metabolic acidosis is one of the generally accepted hallmarks of a perinatal hypoxic-ischemic event [34]. When a hypoxic-ischemic event results in metabolic acidosis, this generally is due to an increase in the serum lactate level induced by anaerobic metabolism [35]. Thus a metabolic acidosis frequently accompanies a hypoxic-ischemic event that may result in neurologic injury. Other chapters address the implications of metabolic acidosis as a marker for perinatal hypoxia-ischemia. The question to address here is, can metabolic acidosis itself cause neurologic injury? To sort this out, we need to look for evidence that lactic acidosis per se induces neurologic injury and that treating metabolic acidosis has an impact on neurologic outcome.

The data linking metabolic acidosis itself to neurologic injury are remarkably slim. There are metabolic disorders (e.g., microvillus inclusion disease [36]) that are known to cause recurrent or prolonged episodes of acidosis without resulting CNS injury. In a large cohort of patients with mitochondrial disorders known to cause lactic acidosis, poor outcome was associated with early onset of symptoms but was not correlated with plasma lactate levels or metabolic status [37]. Patients with MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke) syndrome have qualified for cardiac transplantation [38].

Is there laboratory evidence for lactic acid toxicity? Interestingly, the data suggest that lactic acid may actually be neuroprotective. First, substantial evidence suggests that lactate is a metabolic substrate for the brain [39,40]. Hypoxic stress may increase lactate consumption by the brain [41,42]. A study of rat brain cells in culture has shown that exposure to very low pH (≤6.6) is toxic to brain cells [43]. However, incubation with very high concentrations of lactate (up to 100 mM) did not induce cell death. When lactate was perfused into the brains of unanesthetized rats, there was slowing and suppression of pyramidal cell firing that was completely reversible [44]. This appeared to be due to lactate suppression of

glucose metabolism but only occurred at supraphysiologically high concentrations (10 mM). With lactate alone at physiologic levels (1 mM), nerve cell ATP levels were reduced; with lactate (1 mM) and glucose present at physiologic levels, ATP levels increased. Thus it may be that lactate metabolism can keep brain cells alive when glucose cannot be metabolized in part by reducing their metabolic activity.

Germane to this discussion is the question of the role of sodium bicarbonate therapy in the NICU because this is probably the most common treatment for metabolic acidosis. If metabolic acidosis is harmful, then treating it should be helpful. Indeed, despite minimal data to support its use, sodium bicarbonate has been widely used in neonatology for varying indications [45]. It is commonly given during resuscitation to correct acidosis either documented or suspected. Nevertheless, its efficacy for this remains unclear. There are understandably few RCTs looking at this issue. One, from India, studied the impact of sodium bicarbonate 1.8 mEq/kg versus dextrose 5% given to "asphyxiated" neonates requiring positive-pressure ventilation. The cord pH of the two groups was low (7.01 base, 7.05 dextrose), but in follow-up at 1, 6, 12, and 24 hours, there were no differences in blood gases between the groups [46]. There was also no significant difference in long- or short-term outcomes [47]. If anything, the nonsignificant trend was worse for the bicarbonate-treated group for outcomes such as cerebral edema (52% versus 30%), encephalopathy (74% versus 63%), and need for inotropes (44% versus 28.6%). The Cochrane analysis states: "There is insufficient evidence from randomized, controlled trials to determine whether the infusion of sodium bicarbonate reduces mortality and morbidity in infants receiving resuscitation in the delivery room at birth" [48]. A more recent study of the effects of sodium bicarbonate in very low-birth-weight infants found that though this treatment could improve base deficit and pH, it resulted in no improvement in blood pressure, oxygen saturation, $PaCO_2$, or lactate [49]. More significantly, there was no improvement in cerebral, renal, or splanchnic regional oxygen saturation and fractional tissue oxygen extraction.

Alkalosis

Alkalosis, like acidosis, can either be respiratory or metabolic. Both are most commonly iatrogenic in the newborn period, though rare metabolic disorders can result in either. Because many of these are associated with primary neurologic dysfunction, it is hard to assess the impact of alkalosis on the brain when it complicates these syndromes. Thus, analogous to situations in which hypoxemia accompanies acidosis, it is sometimes difficult to ascribe outcome to alkalosis per se or the underlying genetic cause.

Respiratory Alkalosis

Respiratory alkalosis occurs when $PaCO_2$ levels are decreased, a situation known as *hypocapnia*. This reverses the reaction described earlier under "Respiratory Acidosis," decreasing the concentration of H^+ in the blood and thus raising the pH. In neonates, this usually occurs during mechanical ventilation, though less commonly CNS, cardiac, pulmonary, infectious, or metabolic disorders may cause an infant to hyperventilate while breathing spontaneously, resulting in respiratory alkalosis [50]. Hypocapnia, like its inverse, hypercapnia, has effects on the circulation of several organ systems.

Both pH and $PaCO_2$ have long been known to affect pulmonary vasculature tone in newborn animals, with alkalosis causing decreased pulmonary vascular resistance [51,52]. Thus Peckham and Fox advocated intentional hyperventilatory alkalosis (the opposite of permissive hypercapnia) as a treatment for persistent pulmonary hypertension of the newborn (PPHN) [53]. This became a common treatment for this high-mortality condition for the next several years [54,55]. Initial follow-up studies reported good neurologic outcomes [56–58]. However, concerns were soon raised about an association between respiratory alkalosis and hearing loss [55,59,60]. It was not completely clear that the hearing loss and other neurologic sequelae of PPHN were due to the treatment or were related to the perinatal factors associated with the disease itself, such as asphyxia, hypoxemia, meconium staining, and infection. However, the duration of hyperventilatory alkalosis appeared to correlate with poor neurologic outcome [61], suggesting that the alkalosis per se, and not other factors, may be the cause. Also, follow-up of babies with PPHN from the pre–hyperventilatory alkalosis era did not find this association with hearing loss, suggesting that it may be related to the treatment and not the disease or its causes [62]. More recent studies of long-term outcome for patients with PPHN treated with newer modalities, such as inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO), show variable results for hearing

outcomes, but it is unclear how many patients were hyperventilated and for how long before meeting criteria for the new treatment. At least one study correlated post-ECMO hearing loss with profound hypocarbia prior to initiating ECMO, further strengthening this association [63]. Interestingly, even though some animal and human data suggest that alkalosis induced by bicarbonate infusion would decrease pulmonary artery pressure as well as hyperventilation does [64–66], there are recent animal data to question the efficacy of bicarbonate buffering to reverse hypoxic pulmonary vasoconstriction [67]. Clinical data have not supported the efficacy of this treatment for neonatal PPHN. In fact, at least one study suggests that metabolic alkalosis treatment (e.g., intravenous sodium bicarbonate) may be associated with a worse outcome for PPHN [68].

The connection between hyperventilatory alkalosis and hearing loss may have a plausible biological explanation. Cerebral blood flow is pH dependent, as discussed earlier, and may be reduced by alkalosis in animal and human neonates [19,69–72]. This relationship may be more important in term infants who get PPHN than in sick premature infants, whose cerebral circulation may lose the ability to respond to pH and become "pressure passive" [73]. Animal data suggest that auditory centers may be particularly vulnerable in the newborn period because of a very high metabolic rate compared with other brain regions [74,75]. Thus it is reasonable to theorize that the high metabolic demand of auditory centers may not be met when cerebral blood flow is decreased by hypocapnic alkalosis. Again, there are animal data to support this theory because decreased levels of brain energy stores have been reported in piglets exposed to normoxemic but hypocapnic ventilation [76,77]. The otherwise healthy normal human neonate might tolerate this. But if you add hypoxemia and hypotension, two situations that commonly coexist with PPHN, then you may have a scenario where the high metabolic demands may not be met. Furthermore, experimental data mentioned earlier indicate that hypocapnia may potentiate hypoxemic brain injury in rats [22]. Given the current availability of both iNO and ECMO treatments, it would seem prudent today to minimize the duration of exposure of neonates with PPHN to hyperventilatory alkalosis. Alkalinization with sodium bicarbonate appears to offer little value and may add risk and thus should be limited, too [68]. Until more is known, all patients with PPHN need close neurodevelopmental follow-up and monitoring for sensorineural hearing loss. This hearing loss may be progressive and may not show up for some years [78,79], and thus early screening alone is not adequate.

An association between hypocapnia and periventricular leukomalacia (PVL) has been noted in many studies over many years and with different modes of ventilation [80–83]. A study of high-frequency oscillatory ventilation (HFOV) found increased intracranial hemorrhages and hypocapnia with HFOV but did not specifically look for a statistical association between hypocapnia and PVL [84]. One study with high-frequency jet ventilation (HFJV) could not link PVL statistically to hypocarbia, only to HFJV [85], though the same group had just reported an association of PVL with hypocarbia with HFJV and previously with conventional ventilation [73,74]. A larger multicenter trial of HFJV did show an association between ventilator strategy, hypocapnia, and PVL [86]. However, the authors found a decreased risk of PVL with HFJV when used with a strategy that avoided hyperventilation.

There is also further evidence of hypocapnia being a risk for perinatal brain injury in the setting of hypoxic-ischemic injury. In a large Canadian cohort study of term infants meeting the rigorous definition of hypoxic-ischemic encephalopathy (HIE) [87], outcomes were analyzed for exposure to either high PaO_2 (>200 mmHg) or low $PaCO_2$ (<20 mmHg) during the first 2 hours of life. Multivariate analysis controlling for degree of illness showed a significant association of severe hypocapnia with adverse outcome (odds ration [OR] 2.34, 95% confidence interval [CI] 1.02–5.37). The strongest association with bad outcome was with both severe hyperoxemia and severe hypocapnia (OR 4.56, 95% CI 1.4–14.9). Lower levels of hyperoxemia or hypocapnia were not significant. Interestingly, in this study, the first available base deficit was not significant. Again, these authors postulate that an additive effect of hypocapnic alkalosis induced decreased cerebral blood flow on underlying hypoxic-ischemic injury. Higher PaO_2 levels, which occur not infrequently during resuscitation, may contribute to oxidative injury [88].

A review of hypocapnia [89] as a treatment for brain injury in adults and children concluded that this "can cause harm and should be strictly limited to the emergent management of life-threatening intracranial hypertension pending definitive measures." The same is very likely true for hypocapnia in neonates.

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Metabolic Alkalosis

Metabolic alkalosis occurs less commonly than respiratory alkalosis and often is related to treatment with an alkalinizing agent such as sodium bicarbonate. It may be associated with chloride depletion due to hyperemesis; the use of diuretics, primarily furosemide, and especially if there is inadequate replacement of potassium; severe dehydration resulting in a state of "contraction alkalosis"; and more rarely, a number of uncommon renal, endocrine, and gastrointestinal disorders [90]. Interestingly, though some of the hereditary renal causes of persistent metabolic alkalosis are associated with developmental delay and sensorineural deafness, not all are, and the mechanism of the CNS abnormality may be part of the overall genetic syndrome [91,92]. Congenital chloride diarrhea can result in metabolic alkalosis, but when treated, even with a mean age of diagnosis over 2 months, neurologic outcome is good [93,94]. These observations suggest that the neonatal brain can tolerate metabolic alkalosis fairly well, especially considering that these diagnoses also commonly add hypovolemia and other electrolyte abnormalities but generally not hypoxemia.

Because hyperventilatory alkalosis has been recommended for treatment of pulmonary hypertension (see earlier), metabolic alkalinization also has been proposed. Indeed, as recently as 1997, it was listed as part of the "basic therapy" in a European review [95]. However, a review of data from US multicenter trials actually showed that bicarbonate use resulted in a worse outcome, with an odds ratio for ECMO of 5.03 versus hyperventilatory alkalosis [68].

Given the current data on the use of sodium bicarbonate, there appear to be few, if any, indications, some significant concerns about risk, and virtually no documented benefits. Though it continues to be used to treat acidosis due to the lack of any readily available alternative, this does not necessarily mean that it is better than no treatment [96]. Thus, if used, it must be used minimally and cautiously, and not using it clearly should not be considered a breach of standard of care.

Conclusions

We have reviewed the literature on the impact of alkalosis and acidosis on the brain of the neonate. Though it is clear that much remains to be learned, it appears that the neonatal CNS has remarkable resilience. Respiratory alkalosis does seem to be associated with injury when prolonged or associated with hypoxia. Permissive hypercapnia may be well tolerated, too, if extremes and pronounced swings in pH are avoided. Careful monitoring to prevent this is warranted. Furthermore, the benefits of sodium bicarbonate treatment remain at best unproven, with reasons to be concerned about complications thereof. However, it appears that the newborn brain can tolerate acidosis, both respiratory and metabolic, better than one might have imagined.

References

1. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990; **16**: 372–7.
2. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics* 1999; **104**: 1082–8.
3. Ni Chonghaile M, Higgins B, Laffey JG. Permissive hypercapnia: role in protective lung ventilatory strategies. *Curr Opin Crit Care* 2005; **11**: 56–62.
4. Carlo WA. Permissive hypercapnia and permissive hypoxemia in neonates. *J Perinatol* 2007; **27**:S64–70.
5. Thome UH, Ambalavanan A. Permissive hypercapnia to decrease lung injury in ventilated preterm neonates. *Semin Fetal Neonatal Med* 2009; **14**: 21–7.
6. Hernandez MJ, Brennan RW, Vannucci RC, et al. Cerebral blood flow and oxygen consumption in the newborn dog. *Am J Physiol* 1978; **234**: R209–15.
7. Reivich M, Brann AW, Shapiro H. Reactivity of cerebral vessels to CO_2 in the newborn rhesus monkey. *Eur Neurol* 1971; **6**: 132–6.
8. Rosenberg AA, Jones MD, Traystman RJ, et al. Response of cerebral blood flow to changes in pCO_2 in fetal, newborn, and adult sheep. *Am J Physiol* 1982; **242**: H862–6.
9. Griesen G. Cerebral blood flow and energy metabolism in the newborn. *Clin Perinatol* 1997; **24**: 531–46.
10. Dietz V, Wolf M, Keel M, et al. CO_2 reactivity of the cerebral hemoglobin concentration in healthy term newborns measured by near infrared spectrophotometry. *Biol Neonate* 1999; **75**: 85–90.
11. Jayasinghe D, Gill AB, Levene MI. CBF reactivity in hypotensive and normotensive preterm infants. *Pediatr Res* 2003; **54**: 848–53.
12. Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatr Res* 2005; **58**: 931–5.

13. Kenny JD, Garcia-Prats JA, Hilliard JL, et al. Hypercarbia at birth:a possible role in the pathogenesis of intraventricular hemorrhage. *Pediatrics* 1978; **62**: 465–7.

14. Levene MI, Fawer, CL, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm neonate. *Arch Dis Child* 1982; **57**: 410–17.

15. Kaiser JR, Gauss CH, Pont MJ, et al. Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. *J Perinatol* 2006; **26**: 279–85.

16. Kaiser JR, Gauss CH, Williams DK. Surfactant administration acutely affects cerebral and systemic hemodynamics and gas exchange in very low birth weight infants. *J Pediatr* 2004; **144**: 809–14.

17. Lightbum MH, Gauss CH, Williams DK, Kaiser JR. Observational study of cerebral hemodynamics during dopamine treatment in hypotensive ELBW infants on the first day of life. *J Perinatol* 2013; **33**: 698–702.

18. Zayek MM, Alrifai W, Whitehurst RM Jr, et al. Acidemia versus hypercapnia and risk for severe intraventricular hemorrhage. *Am J Perinatol* 2014; **31**: 345–52.

19. Gleason CA, Short BL, Jones Jr MD. Cerebral blood flow and metabolism during and after prolonged hypocapnia in newborn lambs. *J Pediatr* 1989; **115**: 309–14.

20. Fabres J, Carlo WA, Phillips V, et al. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. *J Pediatr* 2007; **119**: 299–305.

21. Noori S, Anderson M, Soleymani S, Seri I. Effect of carbon dioxide on cerebral blood flow velocity in preterm infants during postnatal transition. *Acta Paediatr* 2014; **103**:e344–9.

22. Vannucci RC, Towfighi J, Heitjan DF, et al. Carbon dioxide protects the perinatal rat brain from hypoxic–ischemic damage. *Pediatrics* 1995; **95**: 868–74.

23. Vannucci RC, Towfighi J, Brucklacher RM, et al. Effect of extreme hypercapnia on hypoxic–ischemic brain damage in the immature rat. *Pediatr Res* 2001; **49**: 799–803.

24. Komori M, Takada K, Tomizawa Y, et al. Permissive range of hypercapnia for improved peripheral microcirculation and cardiac output in rabbits. *Crit Care Med* 2007; **35**: 2171–5.

25. Xu L, Glassford AJM, Giaccia AJ, et al. Acidosis reduces neuronal apoptosis. *NeuroReport* 1998; **9**: 875–9.

26. Laffey JG, Tanaka M, Engelberts D, et al. Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. *Am J Respir Crit Care Med* 2000; **162**: 2287–94.

27. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med* 2000; **161**: 141–6.

28. Fujita M, Asanuma H, Hirata A, et al. Prolonged transient acidosis during early reperfusion contributes to the cardioprotective effects of postconditioning. *Am J Physiol Heart Circ Physiol* 2007; **292**: H2004–8.

29. Carlo WA, Stark AR, Wright LL, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely low-birth-weight infants. *J Pediatr* 2002; **141**: 370–5.

30. Thome UH, Carroll W, Wu T-J, et al. Outcome of extremely preterm infants randomized at birth to different $PaCO_2$ targets during the first seven days of life. *Biol Neonate* 2006; **90**: 218–25.

31. Miller JD, Carlo WA. Safety and effectiveness of permissive hypercapnia in the preterm infant. *Curr Opin Pediatr* 2007; **19**: 142–4.

32. Ou X, Glasier CM, Ramakrishnaiah RH, et al. Diffusion tensor imaging in extremely low birth weight infants managed with hypercapnic vs. normocapnic ventilation. *Pediatr Radiol* 2014; **44**: 980–6.

33. van Kaam AH, De Jaegere AP, Rimensberger PC, et al. Incidence of hypo- and hypercapnia in a cross-sectional European cohort of ventilated newborn infants. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**:F323–6.

34. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. Umbilical cord blood gas and acid-base analysis. *Obstet Gynecol* 2006; **108**: 1319–22.

35. Evans OB. Lactic acidosis in childhood, part I. *Pediatr Neurol* 1985; **1**: 325–8.

36. Bar A, Riskin A, Iancu T, et al. A newborn infant with protracted diarrhea and metabolic acidosis. *J Pediatr* 2007; **150**: 198–201.

37. Debray FG, Lamber M, Chevalier I, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases. *Pediatrics* 2007; **119**: 722–33.

38. Bhati RS, Sheridan BC, Mill MR, et al. Heart transplantation for progressive cardiomyopathy as a manifestation of MELAS syndrome. *J Heart Lung Transplant* 2005; **24**: 2286–9.

39. Schurr A. Lactate: the ultimate cerebral oxidative energy substrate? *J Cerebral Blood Flow Metabol* 2006; **26**: 142–52.

40. Bergersen LH. Is lactate food for neurons? Comparison of monocarboxylate transporter subtypes in brain and muscle. *Neuroscience* 2007; **145**:11–19.

41. Boumezbeur F, Petersen KF, Cline GW, et al. The contribution of blood lactate to brain energy

metabolism in humans measured by dynamic ^{13}C nuclear magnetic resonance spectroscopy. *J Neurosci* 2010; **30**: 13983–191.

42. Overgaard M, Rasmussen P, Bohm AM, et al. Hypoxia and exercise provoke both lactate release and lactate oxidation by the human brain. *FASEB J* 2012; **26**: 3012–20.
43. Pirchl M, Marksteiner J, Humpel C. Effects of acidosis on brain capillary endothelial cells and cholinergic neurons: relevance to vascular dementia and Alzheimer's disease. *Neurol Res* 2006; **28**: 657–64.
44. Gilbert E, Tang JM, Ludvig N, et al. Elevated lactate suppresses neuronal firing in vivo and inhibits glucose metabolism in hippocampal slice cultures. *Brain Res* 2006; **1117**: 213–23.
45. Ammari AN, Schulze KF. Uses and abuses of sodium bicarbonate in the neonatal intensive care unit. *Curr Opin Pediatr* 2002; **14**: 151–6.
46. Murki S, Kumar P, Lingappa L, et al. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life. *J Perinatol* 2004; **24**: 696–9.
47. Lokesh L, Kumar P, Murki S, et al. A randomized, controlled trial of sodium bicarbonate in neonatal resuscitation: effect on immediate outcome. *Resuscitation* 2000; **60**: 219–23.
48. Beveridge CJE, Wilkinson AR. Sodium bicarbonate infusion during resuscitation of infants at birth. *Cochrane Database Syst Rev* 2006; **1**:CD004864.
49. Mintzer JP, Parvez B, Alpan G, LaGamma EF. Effects of sodium bicarbonate correction of metabolic acidosis on regional tissue oxygenation in very low birth weight neonates. *J Perinatol* 2015; **35**(8): 601–6.
50. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med* 2002; **347**:43–53.
51. Cassin S, Dawes GS, Mott JC, et al. The vascular resistance of the foetal and newly ventilated lung of the lamb. *J Physiol* 1964; **171**:61–79.
52. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and Hþ ion concentration changes. *J Clin Invest* 1966; **45**:399–411.
53. Peckham GJ, Fox WW. Physiologic factors affecting pulmonary artery pressure in infants with persistent pulmonary hypertension. *J Pediatr* 1978; **93**: 1005–10.
54. Fox WW, Duara S. Persistent pulmonary hypertension in the neonate: diagnosis and management. *J Pediatr* 1983; **103**: 505–14.
55. Marron MJ, Crisafi MA, Driscoll JM, et al. Hearing and neurodevelopmental outcome in survivors of persistent pulmonary hypertension of the newborn. *Pediatrics* 1992; **90**: 392–6.
56. Brett C, Dekle M, Leonard CH, et al. Developmental follow-up of hyperventilated neonates: preliminary observations. *Pediatrics* 1981; **68**: 588–91.
57. Ferrara B, Johnson DE, Chang PN, et al. Efficacy and neurologic outcome of profound hypocapneic alkalosis for the treatment of persistent pulmonary hypertension in infancy. *J Pediatr* 1984; **105**: 457–61.
58. Bernbaum JC, Russell P, Sheridan PH, et al. Long-term follow-up of newborns with persistent pulmonary hypertension. *Crit Care Med* 1984; **12**: 579–83.
59. Ballard RA, Leonard CH. Developmental follow-up of infants with persistent pulmonary hypertension of the newborn. *Clin Perinatol* 1984; **11**: 737–44.
60. Leavitt AM, Watchko JF, Bennett FC, et al. Neurodevelopmental outcome following persistent pulmonary hypertension of the neonate. *J Perinatol* 1987; **7**: 288–91.
61. Bifano EM, Pfannenstsiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. *Pediatrics* 1988; **81**: 657–61.
62. Cohen RS, Stevenson D, Malachowski N, et al. Late morbidity among survivors on respiratory failure treated with tolazoline. *J Pediatr* 1980; **97**: 644–7.
63. Graziani LJ, Baumgart S, Desai S, et al. Clinical antecedents of neurologic and audiologic abnormalities in survivors of extracorporeal membrane oxygenation. *J Child Neurol* 1997; **12**: 415–22.
64. Lyrene Rk, Welch KA, Godoy G, et al. Alkalosis attenuates hypoxic pulmonary vasoconstriction in neonatal lambs. *Pediatr Res* 1985; **19**: 1268–71.
65. Schreiber MD, Heymann MA, Soifer SJ. Increased arterial pH, not decreased PaCO2, attenuates hypoxia-induced pulmonary vasoconstriction in newborn lambs. *Pediatr Res* 1986; **20**: 113–17.
66. Chang AC, Zucker HA, Hickey PR, et al. Pulmonary vascular resistance in infants after cardiac surgery: role of carbon dioxide and hydrogen ion. *Crit Care Med* 1995; **23**: 568–74.
67. Lee KJ, Hernandez G, Gordon JB. Hypercapnic acidosis and compensated hypercapnia in control and pulmonary hypertensive piglets. *Pediatr Pulmonol* 2003; **36**:94–101.
68. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000; **105**:14–20.
69. Hansen NB, Nowicki PT, Miller RR, et al. Alterations in cerebral blood flow and oxygen consumption during prolonged hypocarbia. *Pediatr Res* 1986; **20**: 147–50.

70. Kusada S, Shisida N, Miyagi N, et al. Cerebral blood flow during treatment for pulmonary hypertension. *Arch Dis Child Fetal Neonatal Ed* 1999; **80**:F30–3.

71. Menke J, Michel E, Rabe H, et al. Simultaneous influence of blood pressure, PCO_2, and PO_2 on cerebral blood flow velocity in preterm infants of less than 33 weeks' gestation. *Pediatr Res* 1993; **24**: 173–7.

72. Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatr Res* 2005; **58**: 931–5.

73. Soul JS, Hammer PE, Tsuji P, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007; **61**: 467–73.

74. Kennedy C, Sakurada O, Shinohara M, et al. Local cerebral glucose utilization in the newborn macaque monkey. *Ann Neurol* 1982; **12**: 333–40.

75. Vannucci RC, Vannucci SJ. Perinatal brain metabolism. In Polin RA, Fox WW, Abman SH, eds., *Fetal and Neonatal Physiology*, 3rd edn. Philadelphia: Saunders, 2004: 1713–25.

76. Graham EM, Apostolou M, Mishra OP, et al. Modification of the *N*-methyl-D-aspartate (NMDA) receptor in the brain of newborn piglets following hyperventilation induced ischemia. *Neurosci Lett* 1996; **218**:29–32.

77. Fritz KI, Zubrow AB, Ashraf QM, et al. The effect of moderate hypocapnic ventilation on nuclear Ca^{2+}-ATPase activity, nuclear Ca^{2+} flux, and Ca^{2+}/calmodulin kinase IV activity in the cerebral cortex of newborn piglets. *Neurochem Res* 2004; **29**: 791–6.

78. Naulty CM, Weiss IP, Herer GR. Progressive sensorineural hearing loss in survivors of persistent fetal circulation. *Ear Hear* 1986; **7**: 74–7.

79. Hendricks-Munoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 1988; **81**: 650–6.

80. Calvert SA, Hoskins EM, Fong KW, et al. Etiological factors associated with the development of periventricular leukomalacia. *Acta Paediatr Scand* 1987; **76**: 254–9.

81. Graziani LJ, Spitzer AR, Mitchell DG, et al. Mechanical ventilation in preterm infants: neurosonographic and developmental studies. *Pediatrics* 1992; **90**: 515–22.

82. Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics* 1996; **98**: 918–24.

83. Shankaran S, Langer JC, Kazzi SN, et al. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. *Pediatrics* 2006; **118**: 1654–9.

84. HiFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. *J Pediatr* 1993; **122**: 609–19.

85. Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics* 1996; **98**: 1035–43.

86. Keszler M, Modanlou HD, Brudno DS, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics* 1997; **100**: 593–9.

87. Klinger G, Beyene J, Shah P, et al. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child Fetal Neonatal Ed* 2005; **90**:F49–52.

88. Vento M, Asensi M, Sastre J, et al. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr* 2003; **142**: 240–6.

89. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med* 2010; **38**: 1348–59.

90. Laski ME, Sabatini S. Metabolic alkalosis, bedside and bench. *Semin Nephrol* 2006; **26**: 404–21.

91. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. *Am J Med Sci* 2001; **322**: 316–32.

92. Naesens M, Steels P, Verberckmoes R, et al. Bartter's and Gitelman's syndromes: from gene to clinic. *Nephron Physiol* 2004; **96**:65–78.

93. Kagalwalla AF. Congenital chloride diarrhea:a study in Arab children. *J Clin Gastroenterol* 1994; **19**:36–40.

94. Hihnala S, Höglund P, Lammi L, et al. Long-term clinical outcome in patients with congenital chloride diarrhea. *J Pediatr Gastroenterol Nutr* 2006; **42**: 369–75.

95. Sasse S, Kribs A, Vierzig A, et al. A staged protocol for the treatment of persistent pulmonary hypertension of the newborn. *Klin Padiatr* 1997; **209**: 301–7.

96. Adeva-Andany MM, Fernandez-Fernandez C, Mourino-Bayolo D, et al. Sodium bicarbonate therapy in patients with metabolic acidosis. *Sci World J* 2014; available at http://dx.doi.org/10.1155/2014/627673.

Chapter

36

Persistent Pulmonary Hypertension of the Newborn

Robin H. Steinhorn

Introduction

At birth, the fetus switches from the placenta to the lung as the organ of gas exchange by rapidly decreasing pulmonary vascular resistance and increasing pulmonary blood flow. Pulmonary artery pressure and vascular resistance then progressively decrease through the first few weeks of life. The vasoconstrictive response to hypoxia is retained into adulthood, and pulmonary hypertension can be easily triggered in the newborn period by hypoxic lung disease, apnea, or other causes. Abnormalities of vascular development or function during this critical developmental period will result in persistent pulmonary hypertension of the newborn (PPHN), a syndrome of failed circulatory adaptation at birth.

Clinically significant PPHN occurs in about 2/1,000 live-born infants [1]. The PPHN syndrome is characterized by sustained elevation of pulmonary vascular resistance (PVR) and is often associated with normal or low systemic vascular resistance. The term PPHN is commonly used interchangeably with *hypoxemic respiratory failure* (HRF), although the latter refers only to respiratory failure associated with hypoxemia, with or without pulmonary hypertension. While mostly seen in term and late-preterm infants, PPHN is also recognized in up to 2% of premature infants presenting with early respiratory distress [2,3]. In term and near-term infants, PPHN can occur idiopathically, but it is more commonly associated with diverse lung pathologies including meconium aspiration syndrome (MAS), perinatal asphyxia, congenital diaphragmatic hernia (CDH), pneumonia, and respiratory distress syndrome (RDS). Pulmonary hypertension can also arise in early infancy due to lung diseases such as bronchopulmonary dysplasia and congenital diaphragmatic hernia and is a common complication of congenital heart disease.

Timely recognition of and appropriate therapy for PPHN are important because of high associated rates of neonatal mortality as well as short- and long-term morbidities, including significant neurodevelopmental sequelae. Because PPHN affects up to 10% of neonates that require neonatal intensive care unit (NICU) hospitalization, the clinician should always maintain a high index of suspicion, particularly when hypoxemia is out of proportion to the parenchymal lung disease.

Epidemiology and Classification of PPHN

The classification, genetic causes, and treatment of pulmonary hypertension are strikingly different in neonates versus older children and adults. This is largely because the developing lung is subject to genetic, pathologic, and/or environmental influences that affect lung adaptation, development, and growth, leading to a greater complexity of phenotypes (Figure 36.1) [4]. In recognition of these differences, the 2013 Nice classification of PAH was updated with an increased emphasis on pediatric disease [5]. Due to its unique anatomic and functional differences (Figure 36.2), PPHN is now classified as a separate subcategory in group 1 (pulmonary arterial hypertension). In group 3 PH, developmental lung diseases are listed due to growing recognition of the important role of abnormal lung structural and vascular growth in the pathogenesis of pulmonary hypertension in these disorders. Congenital diaphragmatic hernia, bronchopulmonary dysplasia (BPD), and several other developmental disorders, such as surfactant protein deficiencies and alveolar capillary dysplasia (ACD), are now included as relatively rare but important causes of pulmonary hypertension.

In clinical practice, neonatologists commonly classify PPHN based on its etiology. *Primary* or *idiopathic PPHN* is the least common and occurs in 10% of cases. Primary PPHN implies intrauterine pulmonary vascular remodeling and is suspected when there is an absence of parenchymal lung disease to explain elevated pulmonary arterial pressure. More commonly,

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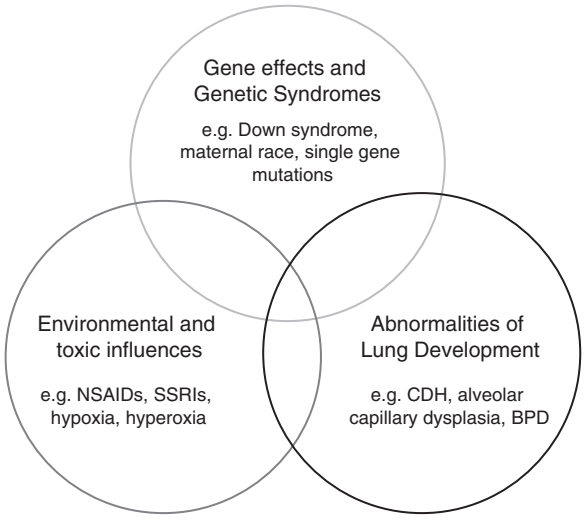


Figure 36.1 Remodeling of the pulmonary vasculature occurs during antenatal or postnatal life when risk factors interact with the early developing lung. Risk factors include environmental factors and toxic exposures, genetic risk factors, and abnormalities of lung development.

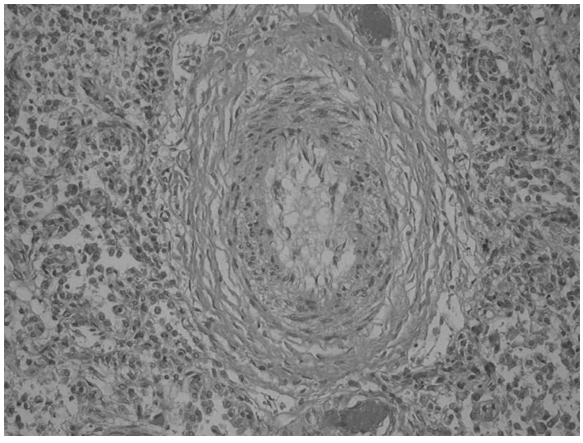


Figure 36.2 Histology of a pulmonary vessel from an infant who died of fatal PPHN illustrating the dramatic medial and adventitial remodeling that can occur in severe disease.

PPHN is associated with other acute respiratory conditions, such as MAS, RDS, or pneumonia, and is referred to as *maladaptive* or *secondary PPHN*. The third common etiology of PPHN is pulmonary vascular hypoplasia, which is usually associated with lung hypoplastic disorders such as congenital diaphragmatic hernia. While this etiologic classification approach is helpful, it is very difficult to separate chronic intrauterine vascular remodeling from acute pulmonary vasoconstriction due to parenchymal lung disease or lung hypoplasia. For example, neonates with severe, lethal meconium aspiration typically have excessive muscularization found at autopsy, consistent with antenatal vascular remodeling.

Pathogenesis of PPHN

During fetal life, the placenta is the organ of gas exchange. Placental vascular resistance is low, and fetal pulmonary vascular resistance (PVR) is high, such that blood flow is diverted from the pulmonary artery to the aorta and umbilical arteries toward the placenta. During early lung development (canalicular phase), the cross-sectional area of pulmonary vasculature is low and results in high PVR. As lung development progresses through the saccular phase, growth of pulmonary blood vessels produces a decrease in PVR and increased blood flow to the lungs. However, as gestation approaches term, pulmonary blood decreases in spite of increased pulmonary vascular capacity. This is largely because the pulmonary vasculature develops increased sensitivity to oxygen, leading to fetal hypoxic pulmonary vasoconstriction and elevated PVR.

At birth, a series of circulatory events ensures the transition from fetal to neonatal life. Clamping of the umbilical cord removes the low-resistance placental circulation and increases systemic vascular resistance. Simultaneously, several mechanisms facilitate a rapid reduction in pulmonary arterial pressure and increase in pulmonary blood flow. Of these, the most important stimuli are ventilation of the lungs and an increase in oxygen tension [6], which trigger release of vasoactive mediators from the vascular endothelium. Both oxygen and vascular shear stress stimulate a marked increase in pulmonary endothelial nitric oxide (NO) production. Nitric oxide exerts its action through activation of soluble guanylate cyclase (sGC), which increases cyclic guanosine monophosphate (cGMP) production [7]. Phosphodiesterase 5 (PDE5) catalyzes the inactivation of cGMP. Both sGC and PDE5 peak in the immediate newborn period in sheep and rats [8,9]. The pivotal role of NO in mediating pulmonary vascular transition at birth largely explains its success as a therapeutic agent for PPHN. The arachidonic acid–prostacyclin pathway operates in parallel to the NO-cGMP pathway and also plays an important role in the transition at birth. The cyclooxygenase enzyme acts on arachidonic acid to produce prostaglandin endoperoxides. Prostaglandins activate adenylate cyclase to increase cyclic adenosine monophosphate (cAMP) concentrations in vascular

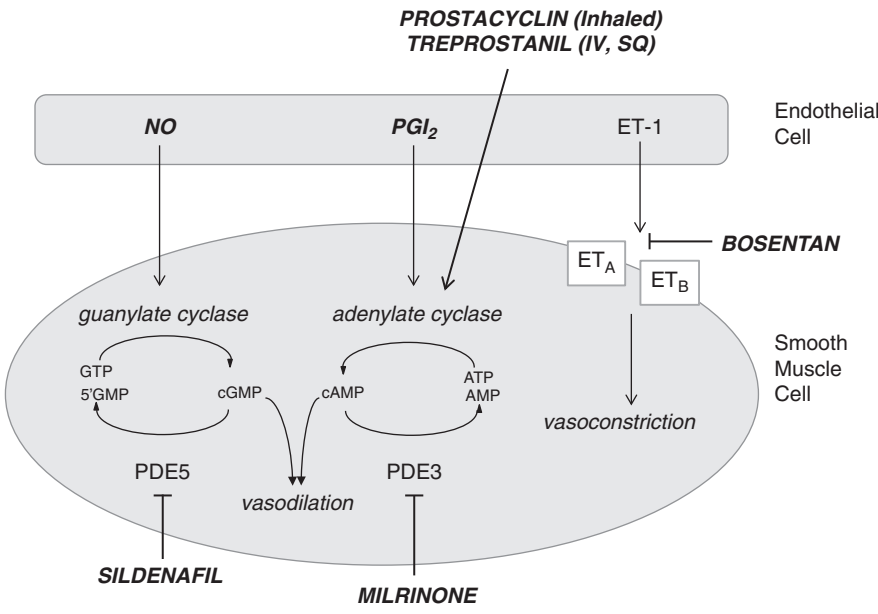


Figure 36.3 Schematic of the nitric oxide (NO), prostacyclin (PGI_2), and endothelin 1 (ET-1) signaling pathways and therapies taking advantage of the signaling abnormalities. NO stimulates soluble guanylate cyclase to increase intracellular cGMP, and PGI_2 stimulates adenylate cyclase to increase intracellular cAMP. Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. ET-1 produced by endothelial cells binds endothelin A (ETA) and endothelin B (ETB) receptors on smooth muscle cells. Sildenafil inhibits PDE5 in vascular smooth muscle, and milrinone inhibits PDE3 in cardiomyocytes and vascular smooth muscle. Prostanoids such as Flolan (prostacyclin) and treprostanil can be given by inhaled or intravenous routes. The ET-1 receptor antagonist Bosentan blocks ET-1 effects and reduces vasoconstriction.

smooth muscle cells. Phosphodiesterase 3A (PDE3A) catalyzes the breakdown of cAMP (Figure 36.3).

PPHN can result when the normal sequence of fetal pulmonary development is disrupted by environmental, toxic, or other influences. A recent case-control surveillance study reported maternal risk factors of black or Asian maternal race, elevated body mass index (BMI > 27), diabetes, and asthma. Neonatal risk factors included male gender, delivery by cesarean section, large-for-gestational-age infants, and delivery before 37 weeks' gestation or after 41 weeks [10]. Recent animal and epidemiologic studies also suggest that maternal therapy can alter fetal PVR. In particular, two classes of medications, selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory agents (NSAIDs), have been reported as potential triggers for PPHN.

Serotonin infusions increase PVR in fetal lambs [11,12], and exposure of pregnant rats to the SSRI fluoxetine produced pulmonary hypertension, hypoxia, and increased mortality in rat pups [13,14]. The use of SSRIs during the last half of pregnancy has been associated with an increased incidence of PPHN in several well-controlled human population studies [15–17]. While the mechanism by which SSRIs induce pulmonary hypertension in newborn is not known, it is speculated that higher drug-induced serotonin levels result in pulmonary vasoconstriction. It is important to note that this finding has not been consistently reported, and the severity of PPHN has not been well documented in any study [18,19]. Furthermore, a recent report observed no differences in right pulmonary artery Doppler pulsatility index (PI) in fetuses of mothers exposed to SSRI antidepressants [20]. At present, maternal physical and psychological well-being remains the primary factor guiding antidepressant therapy during pregnancy and the postpartum period.

The use of NSAIDs such as aspirin during late gestation may be associated with closure of the fetal ductus arteriosus and PPHN [21]. Prostaglandins maintain ductal patency in utero and are important mediators of pulmonary vasodilation in response to ventilation at birth. Experimental ligation or constriction of the ductus arteriosus in lambs during fetal life is associated with rapid development of pulmonary vascular remodeling and PPHN, suggesting that NSAID-mediated ductal constriction is a plausible mechanism [22]. Based on recent epidemiologic data, the NSAID association appears to depend on the specific agent and the timing of exposure [23], although aspirin use during late pregnancy remains a risk factor for PPHN.

Unlike pulmonary hypertension in older patients, few genetic risk factors for PPHN have been identified. Children with Down syndrome (trisomy 21) commonly develop pulmonary hypertension in association with structural heart defects, but the risk for idiopathic PPHN is also elevated nearly 10-fold [24,25]. In a Dutch cohort with excellent early ascertainment, PPHN was documented in 5.2% of Down syndrome infants [26], and other studies have shown that Down syndrome infants are overrepresented in neonates requiring ECMO support [27]. A recent single-center study reported the results of rigorous genotype analysis of 88 neonates with documented PPHN [28].No differences were noted in most candidate genes, including *BMPR2* and nitric oxide synthase. However, PPHN was significantly associated with genetic variants for corticotrophin-releasing hormone (CRH) receptor 1 (*CRHR1*) and CRH-binding protein, and the authors also found increased levels of 17-hydroxyprogesterone in PPHN infants. These data are supported by animal data indicating that antenatal and postnatal steroids reduce oxidant stress and normalize nitric oxide synthase and phosphodiesterase function in experimental PPHN [29,30].

Multiple events can affect the timing and overall success of pulmonary vascular adaptation at birth. Both cesarean section and delayed cord clamping will delay the drop in pulmonary arterial pressure in animal models, although the effect of delayed cord clamping in the clinical setting appears to be modest. However, perinatal asphyxia can significantly hamper the transition and is a major risk factor for PPHN [31]. Multiple mechanisms associated with asphyxia will cause respiratory failure and affect the transitional pulmonary circulation, including fetal hypoxemia, ischemia, meconium aspiration, ventricular dysfunction, and acidosis [31]. Acute asphyxia is associated with reversible pulmonary vasoconstriction [32], but chronic in utero asphyxia with or without meconium aspiration may be associated with more significant vasoconstriction and vascular remodeling [33].

The introduction of therapeutic hypothermia generated concern that it would increase the risk and severity of PPHN in asphyxiated infants. For instance, in neonatal lambs, induction of extreme hypothermia (temperature of 30°C) increased mean pulmonary arterial pressure from 29 to 40 mmHg [34]. However, randomized trials of selective head cooling and whole-body cooling have not reported that moderate hypothermia (33.5°C) increases the incidence of PPHN (25% versus 20%) [35,36]. However, a trial of deeper whole-body hypothermia (32°C) compared with conventional hypothermia at 33.5°C increased the rate of PPHN (34% versus 25%, p = NS), the need for iNO therapy (34% versus 24%, $p < 0.05$) and ECMO (9% versus 4%, $p < 0.05$) [37]. Thus, while standard hypothermia at 33.5°C does not appear to worsen PPHN, deeper hypothermia should be avoided.

The pathophysiology of PPHN includes changes in pulmonary vascular structure and function. The four patterns most commonly observed are (1) pulmonary vasoconstriction, (2) structural remodeling of the pulmonary vasculature during fetal or early postnatal life, (3) intravascular obstruction from increased viscosity of blood as in polycythemia, and (4) lung (alveolar and vascular) hypoplasia. When these forces elevate the pulmonary-to-systemic vascular resistance ratio (PVR/SVR), right to left shunting of blood across the fetal channels of the foramen ovale and ductus arteriosus occurs, which results in potentially severe hypoxemia.

Autopsy studies of fatal PPHN suggest that the most severe hypertensive structural remodeling with vessel wall thickening and smooth muscle hyperplasia develops in utero, likely as a result of chronic intrauterine stress. In addition to changes in the muscular medial layer, adventitial thickening is observed in PPHN [22] and contributes to pulmonary artery stiffness [38]. The adventitial cells (fibroblasts, pericytes, progenitor cells, etc.) are now recognized as a critical regulator of vascular wall function from the "outside in" [39,40]. In addition, the vascular smooth muscle extends to the level of the intraacinar arteries, which does not normally occur until much later in postnatal lung development.

In sheep, fetal hypoxia elevates pulmonary vascular resistance and pressures, induces pulmonary arterial remodeling, and accentuates vasoconstrictor responses [41]. However, pulmonary arterial pressures become subsystemic during normoxic ventilation, suggesting an element of reversibility. Occlusion of the ductus arteriosus prior to delivery in fetal lamb acutely increases pulmonary artery flow and pressure. However, within days, pulmonary vascular resistance and pulmonary artery pressure increase, along with increased muscularity of the pulmonary arteries, analogous to that observed in infants who die with PPHN.

Ductal ligation of late gestation fetal lambs was developed as a clinically relevant model based on these principles and is often used because of its many similarities to the human disease.

Postnatal influences that affect neonatal pulmonary vascular reactivity include parenchymal lung diseases such as MAS. Approximately 13% of all live births are associated with meconium-stained fluid, although only 5% of these infants will go on to develop MAS. Aspiration of meconium either before or during delivery can obstruct small airways, cause severe pneumonitis, and induce inflammatory changes in the lung. All these abnormalities can impair oxygenation after birth and acutely constrict the pulmonary vasculature. In the most severe cases of meconium aspiration, structural remodeling of small intraacinar arteries occurs in response to chronic intrauterine hypoxia or lung injury [33]. In support of this idea, depressed expression of endothelial nitric oxide synthase has been noted in umbilical venous endothelial cells in infants who have severe PPHN in association with meconium-stained amniotic fluid [42]. Meconium also induces postnatal release of pulmonary vasoconstrictors such as endothelin, thromboxane, and prostaglandin E2, all of which promote the development of pulmonary hypertension and proliferation of vascular smooth muscle that will lead to antenatal and postnatal vascular remodeling [43–45].

Perinatal asphyxia is another well-known predisposing factor for PPHN. Various mechanisms cause respiratory failure in asphyxia, including fetal hypoxemia, ischemia, meconium aspiration, ventricular dysfunction, and acidosis, all of which can increase PVR [31]. Even beyond perinatal asphyxia, many of the elements of PPHN physiology have the potential to increase the risk for neurodevelopmental impairment. Many infants have been exposed to a disrupted intrauterine environment for several days. Reduced arterial oxygen content, due to impaired placental function or increased arteriovenous admixture at the atrial level after premature constriction of the ductus, may impair cerebral oxygen delivery and increase the risk for intrauterine hypoxic-ischemic cerebral insults. Redistribution of cardiac output in a hypoxic fetus may reduce flow from the ductus into the descending aorta and impair renal perfusion, causing oligohydramnios and increasing the risk of cord compression events prior to and during labor and delivery [46]. These events may also reduce the capacity of the fetus to tolerate the stress of labor and delivery, either directly or by blunting the metabolic and endocrine responses to this stress.

Numerous signaling pathways in the pulmonary vascular endothelium and smooth muscle are involved in PPHN pathogenesis. The nitric oxide–cGMP pathway has been particularly well studied. Nitric oxide (NO) produced by the endothelium stimulates soluble guanylate cyclase (sGC) in the pulmonary arterial smooth muscle cells to produce cGMP. Impaired endothelial constitutive nitric oxide synthase (eNOS) and sGC activity has been reported in animal models of PPHN [47] and CDH [48], and additional reports have found evidence for oxidization of sGC that renders it NO insensitive [49]. Because NO and cGMP both vasodilate and inhibit vascular smooth muscle growth, a combination of diminished eNOS expression, inactivation of sGC, and reduced cGMP levels likely contributes to the abnormal vasoreactivity and remodeling of pulmonary vessels in PPHN.

Evaluation and Differential Diagnosis of PPHN

The clinical features of PPHN include labile oxygenation, differential saturation consistent with right-to-left ductal shunt (higher SpO_2 in the right upper extremity compared with a lower extremity), and profound hypoxemia despite oxygen and mechanical ventilation. The diagnosis of PPHN should be considered in any infant (term or preterm) who remains hypoxemic out of proportion to the degree of parenchymal lung disease.

Early evaluation with a chest x-ray (CXR) should be performed because the lung findings are important in guiding therapeutic choices. The CXR in classic idiopathic PPHN is oligemic, normally or slightly hyperinflated, and without parenchymal infiltrates. However, more commonly, the CXR identifies parenchymal lung diseases such as pneumonia, RDS, and MAS or other lung abnormalities such as congenital diaphragmatic hernia and cystic adenomatoid malformation.

Because infants with PPHN often present with cyanosis that is poorly responsive to oxygen therapy and/or mechanical ventilation, an early echocardiogram must be performed to rule out congenital heart disease as a cause of extrapulmonary shunting. The initial echocardiographic evaluation rules out structural heart disease causing hypoxemia or ductal shunting (e.g., coarctation of the aorta or total anomalous pulmonary venous return), determines the predominant

direction of shunting at the patent foramen ovale and patent ductus arteriosus (PDA), and assesses right and left ventricular function. Echocardiography also shows that left ventricular insufficiency is present, which produces pulmonary venous hypertension that would only be aggravated by a pulmonary vasodilator. Despite the importance of examining the pulmonary veins and aortic arch, their imaging is particularly challenging in the presence of severe right-to-left shunting across the ductus arteriosus.

Treatment of PPHN

General management principles for the newborn with PPHN include maintenance of normal body temperature, electrolytes (particularly calcium), glucose, and intravascular volume. Polycythemia should be corrected with a partial exchange transfusion. Other general principles include optimization of lung function and support of cardiac function and oxygen delivery. The importance of the hemoglobin level in blood oxygen-carrying capacity should be remembered: increasing the hematocrit from 30% to 40% would produce a substantial 33% increase in oxygen delivery. Systemic blood pressure should be maintained at normal levels for age with volume and cardiotonic therapy, with a primary goal of optimizing both left and right ventricular dysfunction and enhancing systemic O_2 transport. However, increasing blood pressure to supraphysiologic levels for the sole purpose of driving a left-to-right shunt across the PDA may transiently improve oxygenation but will not reduce pulmonary vascular resistance and should be avoided.

Pulmonary Management

Although neonates with clinically significant PPHN almost always require mechanical respiratory support, few guidelines have emerged to standardize ventilator management. High-frequency ventilation can facilitate lung expansion in infants with parenchymal lung disease and often improves oxygenation and/or amplifies the oxygenation response to inhaled NO [50]. Others have advocated a "gentle ventilation" approach to ventilation, with more modest blood gas goals such as a PaO_2 of 50–70 mmHg and a $PaCO_2$ of 40–60 mmHg, along with avoidance of paralysis. However, this strategy has only been reported in case series [51] and may most benefit infants still in the early phases of disease.

Surfactant deficiency (RDS) or inactivation (e.g., from MAS or pneumonia) is commonly associated with PPHN. A large prospective trial found that administration of surfactant reduced the need for ECMO by 30% relative to a control group [52]. More recently, a retrospective analysis of a large group of infants with moderate PPHN found that the use of surfactant was significantly associated with decreased risk of ECMO/death [53]. Similar to high-frequency ventilation, improving lung expansion via surfactant administration may be important in optimizing the effect of iNO. However, neither of these strategies is effective for idiopathic PPHN because the lungs are already well expanded.

Acidosis is a pulmonary vasoconstrictor and enhances hypoxic vasoconstriction and should be avoided. Alkalosis induced by hyperventilation or infusion of sodium bicarbonate was frequently employed prior to the availability of specific pulmonary vasodilators [54]. While transient improvements in PaO_2 may be observed, no long-term benefit has ever been documented. Furthermore, prolonged alkalosis may paradoxically worsen pulmonary vascular tone, reactivity, and permeability edema [55] and may cause cerebral constriction, reduced cerebral blood flow, and worse neurodevelopmental outcomes, including sensorineural hearing loss [56,57]. However, a retrospective cohort analysis suggested that modest respiratory alkalosis induced by hyperventilation reduced the need for ECMO, although this study was before widespread adoption of iNO [1].

Pulmonary Vasodilation

Oxygen

Oxygen is a mainstay of PPHN therapy as a pulmonary vasodilator and to provide adequate oxygen delivery to the brain and other tissues. Oxygen delivery depends on blood flow and arterial oxygen content. In turn, oxygen content is largely determined by the oxygen saturation of hemoglobin, highlighting the importance of maintaining adequate hemoglobin levels. Alveolar hypoxia and hypoxemia are pulmonary vasoconstrictors and contribute to the pathophysiology of PPHN and should be avoided. However, hyperoxic ventilation has traditionally been used during the acute phase of illness to promote pulmonary vasodilation. Recently, the degree of hyperoxia needed to maximize benefit has been studied in animal models. While oxygen is a pulmonary vasodilator, the use of concentrations

greater than 50% has not been shown to provide any additional benefit in pulmonary vasodilation. Nevertheless, hyperoxic ventilation increases oxidant stress and lung injury and may paradoxically impair the vasodilator response to iNO [58,59]. Therefore, the oxygen concentration and PaO_2 should be titrated to maximize pulmonary vasodilation. Studies in newborn lambs suggest that the lowest PVR can be maintained with a preductal SpO_2 in the 90–97% range with preductal PaO_2 between 60 and 80 mmHg. Overall, oxygen should be used like any other drug in the therapeutic context, taking into account potential benefits and side effects.

Inhaled NO

NO production is diminished in PPHN, so the therapeutic use of iNO was a logical advance. Inhaled NO reduces pulmonary vascular resistance and extrapulmonary right-to-left shunting and likely improves intrapulmonary ventilation perfusion matching. Based on the results of large randomized, controlled trials, iNO is currently the only pulmonary vasodilator therapy approved by the US Food and Drug Administration (FDA) specifically for PPHN. Inhaled NO acutely improves oxygenation and decreases the need for ECMO support in newborns with PPHN and an oxygenation index (defined as $FiO_2 \times$ mean airway pressure $\times$ 100/postductal PaO_2) of greater than 25. However, up to a third of infants fail to achieve a sustained improvement in oxygenation, and iNO has not reduced mortality or length of hospitalization in any study.

The optimal window for the introduction of therapy with iNO remains uncertain. The initial randomized trials studied infants with severe PPHN and an oxygenation index (OI) of 25–40 [60,61]. In another large randomized trial, earlier use of iNO in infants with moderate respiratory failure (median OI of ~20) did not reduce the primary outcome of ECMO/death relative to controls (16.7% versus 19.5%, respectively; p = NS). However, a post hoc analysis suggested that initiating iNO at an OI of less than 20 was associated with decreased use of ECMO compared with initiation at an OI of greater than 20, which could be a subject for future study.

Inhaled NO has potential risks, including methemoglobinemia and increased bleeding time, but over the last 15 years, it has proven to be an exceptionally safe therapy. Because iNO consistently reduces the need for ECMO, it was hoped that it would improve rates of neurodevelopmental impairment. However, follow-up to the pivotal studies used for FDA approval found similar rates of neurodevelopmental, behavioral, and medical abnormalities at 2 years of age for infants treated with iNO versus placebo [62,63]. This was surprising given the consistent improvements in oxygenation and ECMO reduction and suggests that neurodevelopmental impairment could be the result of antenatal or other factors prior to iNO initiation.

Phosphodiesterase Inhibitors

Phosphodiesterase 5 (PDE5) catalyzes the breakdown of cGMP (Figure 36.3) and is thus a key regulator of cGMP levels. Similar to eNOS and sGC, expression of PDE5 in the lungs peaks in the immediate newborn period in sheep and rats, indicating its importance in regulating pulmonary vascular tone at the time of transition [8,9].

Increased activity of PDE5 has been consistently reported in experimental models of PPHN [8,64]. More recently, in vitro and in vivo studies have shown that even brief periods of hyperoxia independently increase the activity of PDE5 by a mechanism that appears to involve reactive oxygen species (ROS) [64–66]. This finding could partially explain why some infants do not respond favorably to iNO.

Sildenafil is the best studied of the available phosphodiesterase inhibitors and can be administered by the enteral and intravenous routes. In initial studies, enteral sildenafil was found to improve oxygenation and survival in term and late-preterm neonates with PPHN [67]. In a subsequent dose-finding study, intravenous sildenafil improved oxygenation in neonates with and without concurrent iNO treatment [68], suggesting that sildenafil may be a useful adjunct in patients with partial or poorly sustained responses to iNO. Theoretically, sildenafil may be particularly effective in neonates with PPHN following prolonged hyperoxic ventilation because PDE5 expression and activity are increased following ventilation with high concentrations of oxygen and exposure to ROS (Figure 36.3). Sildenafil is generally well tolerated, although hypotension can occur, particularly if a loading dose is given too rapidly [68]. The availability of sildenafil as an enteral preparation also makes it feasible for long-term therapy for infants with chronic pulmonary hypertension associated with congenital diaphragmatic hernia [69], although this aspect of treatment needs more study. A multicenter randomized, controlled trial is underway to test the efficacy of sildenafil in iNO-resistant PPHN (NCT01720524). Other PDE inhibitors include tadalafil and vidalafil, but their use in PPHN has not yet been reported.

Other Pulmonary Vasodilators

Prostanoids

A complementary vasodilatory pathway in the perinatal lung is mediated by prostacyclin (PGI_2), a metabolite of arachidonic acid that is endogenously produced by the vascular endothelium (Figure 36.3). Similar to NO, prostacyclin production increases in late gestation and early postnatal life [70,71], indicating its importance in the pulmonary vascular transition. Neonatal pulmonary hypertension is associated with decreased prostacyclin levels accompanied by increased synthesis of the vasoconstrictor thromboxane A_2 [72,73].

Prostacyclin (epoprostanol) was approved by the FDA in 1995 for the treatment of adult pulmonary arterial hypertension. While intravenous PGI_2 remains a mainstay of therapy for treatment of pulmonary hypertension in adults, rapid dosage escalation is often necessary for acute disease and can produce systemic hypotension. Its utility in the NICU setting is also limited by the need for a dedicated central venous catheter, the potential to worsen ventilation-perfusion matching, and other systemic side effects including pain.

Aerosolized PGI_2 has been widely adopted in adult critical care units [74]. There are fewer reports of its use in infants [75–77], although case series indicate that continuous inhaled PGI_2 (50–100 ng/kg/min) is well tolerated and improves oxygenation in infants with severe PPHN and inadequate response to iNO [78,79]. Risks include airway irritation from the alkaline solution needed to maintain drug stability, rebound pulmonary hypertension if the drug is abruptly discontinued, and inconsistent drug delivery due to loss into the circuit. New, more stable preparations are emerging that are specifically designed for intermittent nebulization, such as iloprost or treprostinil. Treprostanil is also suitable for systemic administration, including by the subcutaneous route [80].

Endothelin Receptor Antagonists

Endothelin 1 (ET-1) is a potent vasoconstrictor synthesized by vascular endothelial cells [81] that acts through two receptors: ET_A and ET_B (Figure 36.3). The ET_A receptor plays a critical role in vasoconstriction, whereas the ET_B receptor promotes vasodilation mediated by endothelium-derived NO [82,83]. Selective blockade of the ET_A receptor causes fetal pulmonary vasodilation [84]. ET-1 gene expression and levels are increased in the lungs and pulmonary arterial endothelial cells in the fetal lamb model of PPHN [85,86], and chronic intrauterine ET_A receptor blockade following ductal ligation decreases pulmonary arterial pressure and distal muscularization of small pulmonary arteries in utero, decreases right ventricular hypertrophy, and increases the fall in PVR at delivery in newborn lambs with PPHN [87]. Thus ET-1 acting through the ET_A receptor might contribute to the pathogenesis and pathophysiology of PPHN. Bosentan, a nonspecific ET-1 receptor blocker, has been used mainly to treat pulmonary hypertension (PH) in adults. Two recent trials show that bosentan is well tolerated in neonates with PPHN, although its efficacy is variable, possibly due to inconsistent intestinal absorption [88,89].

Cardiac Support

PPHN is frequently associated with low systemic pressure and low cardiac output, in part, because of increased right ventricular afterload, bowing of the intraventricular septum and restriction of left-side filling, and myocardial dysfunction. Infants with PPHN typically have right-to-left shunting at the atrial and ductal levels. Because this extrapulmonary shunting can produce severe hypoxemia, it is often tempting to elevate systemic vascular resistance to reverse the ductal shunt and improve pulmonary blood flow and oxygenation. While this may be temporarily effective, it should be remembered that the neonatal right ventricle is poorly adapted to handle an acute elevation in afterload [90], so using pressors to raise systemic blood pressure may induce right ventricular (RV) failure if PVR does not also fall. It is also important to remember that an open ductus can also protect the right ventricle by providing a "pop-off" that relieves some of the RV afterload.

Some infants may develop the worrisome finding of left-to-right shunt at the foramen ovale despite predominant right-to-left shunting at the ductus. When this occurs, left ventricular dysfunction is contributing to the underlying pathophysiology, which increases left atrial and pulmonary venous pressure, elevates pulmonary arterial pressure, and causes right-to-left shunting with little vasoconstriction. In such cases, pulmonary vasodilators will not improve oxygenation and may cause or aggravate pulmonary edema, so they must be accompanied by therapies targeted to increase cardiac performance and decrease left ventricular afterload.

Dopamine is the most commonly used first-line agent: it stimulates dopaminergic α1, α2, and β1 receptors and reliably increases systemic blood pressure in

neonates. However, some animal studies show that high doses of dopamine will elevate both systemic and pulmonary vascular resistances, particularly if pulmonary vascular remodeling is present [91]. Milrinone, which inhibits PDE3 activity in cardiomyocytes and pulmonary arterial smooth muscle, may be particularly effective in improving left ventricular function and reducing pulmonary venous hypertension (Figure 36.3) [92]. In newborn lambs with PPHN, intravenous milrinone reduced PVR by 22% and increased pulmonary blood flow by 18%. Milrinone may also enhance the effect of iNO, as reported in both translational and clinical studies [93,94]. The successful use of vasopressin was recently reported as a potential adjunctive therapy for improving both oxygenation and systemic hypotension in infants with PPHN [95].

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is heart-lung bypass adapted to provide cardiorespiratory support for days to weeks and is available at approximately 225 centers worldwide. All infants who fail to respond to medical management with sustained improvement in oxygenation and good hemodynamic function should receive prompt evaluation for ECMO treatment. An OI (i.e., $FiO_2 \times$ mean airway pressure $\times$ 100/postductal PaO_2) greater than 40 is often used as the threshold for transfer for evaluation for ECMO, although other factors such as hemodynamic stability and need for high-frequency support should also be considered. Because ECMO is centralized in so few centers, most patients will need to be transferred to an ECMO center, and both the receiving and referring hospitals share the responsibility to facilitate safe and timely transfers.

Although ECMO can be lifesaving, it is also costly, labor-intensive, and associated with many potential adverse effects, such as intracranial hemorrhage and ligation of the right common carotid artery. ECMO programs should belong to the registry maintained by the Extracorporeal Life Support Organization to facilitate sharing of data and to support decision making for individual patients.

Neonatal ECMO use fell significantly in the 1990s due to improved obstetric practices (e.g., group B *Streptococcus* prophylaxis and avoiding postdate deliveries) and neonatal practices (introduction of iNO) but has remained steady at approximately 800 cases per year since 1998 [96]. MAS, congenital diaphragmatic hernia, and PPHN are the three most common indications for neonatal respiratory ECMO according to the registry kept by the Extracorporeal Life Support Organization (Table 36.1). Venoarterial (VA) bypass is used most commonly because it can provide both respiratory and cardiac support. Venovenous (VV) ECMO, usually performed via a double-lumen catheter placed into right atrium, oxygenates the venous blood but relies on the native cardiac function. Both modalities require systemic heparinization to prevent circuit clotting, which increases the risk for intracranial hemorrhage and other bleeding complications. VA bypass includes ligation of the right common carotid artery, which leads to collateral flow to the right side of the brain. Some centers perform post-ECMO carotid artery repair, but subsequent stenosis often occurs, and there are no data to date demonstrating improved neurobehavioral outcomes.

Table 36.1 Outcomes for Neonatal ECMO Diagnoses, Modes of Support, and Complications

	No. of cases	Survival
Diagnosis		
MAS	8,423	94%
CDH	6,845	51%
PPHN	4,526	77%
Sepsis	2,809	73%
RDS	1,541	84%
Other	2,318	61%
Mode of support		
VA	19,377	71%
VV	5,973	84%
Complications		
Cannula problems	6%	33%
Oxygenator failure	7.1%	25%
Intracranial hemorrhage	11.2%	23%
Clinical seizures	7.1%	31%

Note: MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; VA, venoarterial; VV, venovenous.

Outcomes of PPHN

Infants with PPHN are among the most critically ill patients cared for in the NICU. These infants often have a perinatal history that includes low Apgar scores or fetal compromise that place them at high risk for abnormal outcomes. The treatment of PPHN involves the use of therapies, including high-frequency ventilation, ECMO, hyperoxia, and iNO, that may also adversely affect outcome.

Outcomes after Medical Therapy

Early reports before the introduction of modern therapies began to establish the high risk for mortality and abnormal neurodevelopmental outcomes for survivors of PPHN [97]. At least one report showed that oxygenation (measured by the alveolar-arterial oxygen difference) correlated well with survival but not with long-term outcome [98]. Some reports further indicated that low Apgar scores and prolonged hypocarbia were predictive of adverse neurodevelopmental outcomes [56,97].

iNO has become the standard treatment for term and near-term infants with hypoxemic respiratory failure and PPHN. The long-term outcome data for the largest iNO trials are summarized in Table 36.2, which also provides the most comprehensive, standardized assessment for PPHN infants treated with and without iNO. Overall, these results highlight that neurodevelopmental impairment is high in this population (14–30%) and not improved by iNO [62,63,99,100]. In each of these trials, a trend toward higher motor impairment was observed in the iNO group, and in the early iNO trial reported by Konduri et al., the difference in the Bayley psychomotor development index (PDI) was statistically significant [100]. The NINOS trial reported that the rate of disability was not affected by the need for ECMO [62], leading the authors to speculate that the timing of injury was most likely before ECMO.

Neurodevelopmental impairment is high even for infants presenting with moderate PPHN. Konduri et al. reported on the 18- to 24-month outcomes of infants enrolled in a randomized multicenter clinical trial of early initiation of iNO therapy for infants presenting with respiratory failure at an OI of 15–25 [100]. Earlier initiation of iNO did not reduce the combined incidence of ECMO/mortality but did limit the progression of respiratory failure to an OI greater than 25. Overall rates of neurodevelopmental impairment were similar to those of other trials that enrolled patients with more advanced disease (Table 36.2), and early iNO did not translate into improved outcomes. The proportion of infants with medical problems, such as the need for home medications, oxygen, and gastrostomy feedings, also tended to be higher in the early iNO group, although these differences were not statistically significant.

Outcomes after ECMO

ECMO is the only PPHN therapy that has been proven to be lifesaving, but it remains a technically complex and invasive therapy with many potential complications. More than 27,000 newborns have been treated with ECMO for respiratory failure, with a cumulative overall survival to discharge of 75% [96]. The introduction of iNO, surfactant, and high-frequency ventilation has been effective in decreasing the use of ECMO [101], but infants who currently receive treatment have longer, more complicated ECMO runs [96]. Mechanical complications such as cannula problems and oxygenator failure are common, along with patient complications such as bleeding and seizures, and these complications worsen chances for survival (Table 36.1).

Ultrasound monitoring to detect intracranial hemorrhage is standard during ECMO, and MRI neuroimaging is routine after ECMO to document injury and help to predict outcome. The predictive value of neuroimaging has not been well established [102], although in one large cohort of ECMO-eligible survivors, moderate to severe neuroimaging abnormalities were independent predictors of abnormal neurologic outcome and cerebral palsy (odds ratio [OR] 5.1, $p < 0.01$) [103]. However, no standard approach for neuromonitoring for severe PPHN has emerged. In a large cohort of ECMO-treated infants, the combination of a normal bedside head ultrasound (HUS) and an electroencephalogram (EEG) without marked abnormalities was highly predictive of normal post-ECMO neuroimaging [104]. In another series, abnormal serial amplitude-integrated electroencephalography (aEEG) was associated with death or moderate to severe intracranial neuropathology [105]. These findings are encouraging, but more data are needed before recommending routine aEEG monitoring. While the use of near-infrared spectroscopy (NIRS) has been reported during neonatal ECMO, little information has emerged regarding its clinical or predictive value.

Mild to major neurodevelopmental impairment is described in 15–25% of neonatal ECMO survivors [106]. However, determining the role of ECMO versus other disease factors in the neurodevelopmental outcomes for

Table 36.2 Neurodevelopmental Outcomes for the Major iNO Clinical Trials

Study	*N*	Initial OI	Age at follow-up (mos.)	% NDI		Bayley mental developmental index		Bayley physical developmental index		% Cerebral palsy	
				Control	iNO	Control	iNO	Control	iNO	Control	iNO
NINOS [62]	235	44	18–24	30	35	87	85	93.6	85.7	10.3	11.8
Clark [63]	248	39	12	14	19	95	95	85	92	1.4	4
Davidson [99]	155	24.7	12	20	18	[a]	[a]	[b]	[b]	6	8
Konduri [100]	299	19.2	18–24	25	28	86.1	83.3	98	89	6.3	8.2

Note: OI, oxygenation index; NDI, neurodevelopmental impairment.

[a] 71% of control group and 69% of iNO group reported as normal (MDI ≥ 85).

[b] 82% of control group and 76% of iNO group reported as normal (PDI ≥ 85).

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ECMO survivors is difficult. While from the pre-iNO era, the UK Collaborative Randomized Trial of ECMO provides the most direct comparison of outcomes after ECMO versus conventional treatment and included neurodevelopmental assessments at ages 1, 4, and 7 years. At age 1, a significant survival benefit was observed in the ECMO-treated versus conventionally treated group (68% versus 41%) [107], and survivors demonstrated similar rates of impairment or disability. At the 4-year follow-up, there continued to be a higher proportion of survivors without disability in the ECMO-treated versus conventionally treated group (50% versus 37%) [108]. At the 7-year follow-up, cognitive function and rate of survival without disability were similar between the groups (55% versus 50%) [109]. The authors concluded that ECMO therapy improves survival and does not increase disability in neonates with severe respiratory failure up to 7 years of age. The high rate of neurodevelopmental impairment in both groups suggests that the underlying disease process, rather than the treatment, is the major influence on neurodevelopmental outcome. Several more recent studies also indicate that ECMO survivors may be at risk for academic problems [110], so these children benefit from detailed assessment as they reach school age.

Other clinical events may help to predict long-term outcomes for ECMO and severe PPHN survivors. In one small cohort, infants who required a feeding tube at discharge were 12 times more likely to have moderate to severe neurodevelopmental impairment compared with those discharged on full oral feedings [103]. Neonatal seizures occur in 9.3% of neonatal ECMO patients [111] and appear to be a strong predictor for poor neurodevelopmental outcomes at 2 and 4–6 years of age [112,113]. Finally, at least two studies indicate that the presence of chronic lung disease is associated with lower Bayley scores and higher rates of cerebral palsy and speech-language delays [114,115]. It will be interesting to learn whether long-term ECMO outcomes have improved or worsened after the introduction of iNO.

The effect of right carotid artery ligation on ECMO outcomes has also been studied. Early reports were inconclusive whether short- or long-term outcomes were associated with injury in the distribution of the middle cerebral artery. Van Meurs et al. reported that Bayley scores and neuroimaging results were similar after VA versus VV ECMO, suggesting that carotid artery ligation did not directly affect neurodevelopmental outcome or neuroimaging [116]. For infants who underwent ligation versus reconstruction of the right common carotid artery following ECMO, reconstruction was successful (defined as <50% occlusion) in 76% of cases and was associated with fewer neuroimaging abnormalities and less cerebral palsy at 18 months [117]. However, no differences in neurodevelopmental outcomes were found at 30 months and 5–6 years, and the long-term risks and benefits of carotid repair remain unclear.

Other Morbidities after PPHN

Hearing Loss

An increased risk of hearing loss associated with PPHN was recognized more than 30 years ago. An important feature of the sensorineural hearing loss (SNHL) seen in PPHN survivors is that it frequently has delayed onset after a normal neonatal hearing screen [118], indicating the importance of long-term monitoring. A strong association with hyperventilation/alkalosis and pancuronium has been suggested in several retrospective cohorts. Numerous studies published over the last 30 years report a consistent rate of SNHL in ECMO survivors of 7.5% (range 3–21%) [119], although a UK randomized trial found rates in ECMO survivors to be similar to those in conventionally treated infants [108]. In the iNO follow-up studies, rates of SNHL were in a similar range (7.3–12.7%) and were not different with and without iNO [62,100]. Although the 2007 position statement from the Joint Committee on Infant Hearing did not discuss PPHN as an independent risk indicator for delayed SNHL, it was recommended that all infants who received assisted ventilation or ECMO therapy undergo close monitoring because of the risk of delayed-onset hearing loss [120].

Respiratory Morbidity and Rehospitalization

Survivors of PPHN are at increased risk of long-term respiratory morbidity, including chronic lung disease, asthma, and susceptibility to respiratory tract infections. The degree of respiratory morbidity also affects somatic growth. However, the effect of various therapeutic strategies on the risk for these morbidities remains unclear. Follow-up from the UK Randomized ECMO trial indicates that a larger proportion of the medically managed infants reported wheezing and other respiratory symptoms and received respiratory medication at 1, 4, and 7 years of age [108,109,121], possibly due to subtle impairment of small-airway function relative to those assigned to ECMO [121]. Other cohort studies in the United

States have reported a similar protective effect of ECMO [114]. A western Canada outcome study found abnormal childhood lung function in more than half of survivors after severe neonatal respiratory failure: CDH, need for ECMO, and fetal growth restriction were most associated with poorer pulmonary outcome at 8 years of age [122]. Anecdotal reports suggest that hyperventilation leads to higher rates of chronic lung disease relative to "gentle ventilation" approaches, although no direct comparisons have been made. However, none of the large multicenter iNO trials reported any effect of iNO on long-term respiratory outcomes [62,63,100].

Hospitalization after discharge is common in survivors of PPHN, particularly in the first year and mostly as a consequence of respiratory illness. In the follow-up studies of the major iNO trials, 25–36% of infants required rehospitalization, and iNO had no effect on these rates [62,63,100]. Few data are available to determine whether ECMO affects rates of rehospitalization.

Conclusions

An increased understanding over the last two decades of pulmonary pathophysiology and vascular signaling changes that trigger PPHN has led to improved management and a substantial decrease in the number of neonatal respiratory patients requiring ECMO. Animal models have contributed significantly to the understanding of fetal circulation, pulmonary vascular transition at birth, and the hemodynamic and biochemical abnormalities associated with PPHN. However, continued basic, translational, and clinical research into pulmonary vasodilator therapy, reversal of remodeling in pulmonary vasculature, and right ventricular failure will be needed to improve long-term respiratory and neurodevelopmental outcomes. The overall lack of ECMO or iNO effect on neurodevelopmental outcomes also suggests that a better understanding of the fetal and placental abnormalities associated with PPHN will be needed to attain optimal neurodevelopmental outcomes. Other ongoing challenges will be congenital diaphragmatic hernia and the premature infant with early pulmonary hypertension or pulmonary hypertension associated with BPD.

References

1. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000; **105**: 14–20
2. Kumar VH, Hutchison AA, Lakshminrusimha S, et al. Characteristics of pulmonary hypertension in preterm neonates. *J Perinatol* 2007; **27**: 214–9.
3. Aikio O, Metsola J, Vuolteenaho R, et al. Transient defect in nitric oxide generation after rupture of fetal membranes and responsiveness to inhaled nitric oxide in very preterm infants with hypoxic respiratory failure. *J Pediatr* 2012; **161**: 397–403.
4. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ* 2011; **1**: 286–98.
5. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**: D117–26.
6. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. *Pediatr Res* 1990; **27**: 372–8.
7. Bloch KD, Filippov G, Sanchez LS, et al. Pulmonary soluble guanylate cyclase, a nitric oxide receptor, is increased during the perinatal period. *Am J Physiol* 1997; **272**: L400–6.
8. Hanson KA, Ziegler JW, Rybalkin SD, et al. Chronic pulmonary hypertension increases fetal lung cGMP phosphodiesterase activity. *Am J Physiol* 1998; **275**: L931–41.
9. Sanchez LS, de la Monte SM, Filippov G, et al. Cyclic-GMP-binding, cyclic-GMP-specific phosphodiesterase (PDE5) gene expression is regulated during rat pulmonary development. *Pediatr Res* 1998; **43**: 163–8.
10. Hernandez-Diaz S, Van Marter LJ, Werler MM, et al. Risk factors for persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **120**: e272–82.
11. Delaney C, Gien J, Grover TR, et al. Pulmonary vascular effects of serotonin and selective serotonin reuptake inhibitors in the late-gestation ovine fetus. *Am J Physiol Lung Cell Mol Physiol* 2011; **301**: L937–44.
12. Delaney C, Gien J, Roe G, et al. Serotonin contributes to high pulmonary vascular tone in a sheep model of persistent pulmonary hypertension of the newborn. *Am J Physiol Lung Cell Mol Physiol* 2013; **304**: L894–901.
13. Belik J. Fetal and neonatal effects of maternal drug treatment for depression. *Semin Perinatol* 2008; **32**: 350–4.
14. Fornaro E, Li D, Pan J, Belik J. Prenatal exposure to fluoxetine induces fetal pulmonary hypertension in the rat. *Am J Respir Crit Care Med* 2007; **176**: 1035–40.
15. Hybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 2015; **313**: 2142–51.
16. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the

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.037

newborn: population based cohort study from the five Nordic countries. *BMJ* 2012; **344**: d8012.

17. Grigoriadis S, Vonderporten EH, Mamisashvili L, et al. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. *BMJ (Clin Res Ed)* 2014; **348**: f6932.
18. Wilson KL, Zelig CM, Harvey JP, et al. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol* 2011; **28**: 19–24.
19. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 2009; **18**: 246–52.
20. Lim K, Sanders A, Brain U, et al. Third trimester fetal pulmonary artery Doppler blood flow velocity characteristics following prenatal selective serotonin reuptake inhibitor (SSRI) exposure. *Early Hum Dev* 2012; **88**: 609–15.
21. Talati AJ, Salim MA, Korones SB. Persistent pulmonary hypertension after maternal naproxen ingestion in a term newborn: a case report. *Am J Physiol* 2000; **17**: 69–71.
22. Wild LM, Nickerson PA, Morin FC 3rd. Ligating the ductus arteriosus before birth remodels the pulmonary vasculature of the lamb. *Pediatr Res* 1989; **25**: 251–7.
23. Van Marter LJ, Hernandez-Diaz S, Werler MM, et al. Nonsteroidal antiinflammatory drugs in late pregnancy and persistent pulmonary hypertension of the newborn. *Pediatrics* 2013; **131**: 79–87.
24. Shah PS, Hellmann J, Adatia I. Clinical characteristics and follow up of Down syndrome infants without congenital heart disease who presented with persistent pulmonary hypertension of newborn. *J Perinat Med* 2004; **32**: 168–70.
25. Cua CL, Blankenship A, North AL, et al. Increased incidence of idiopathic persistent pulmonary hypertension in Down syndrome neonates. *Pediatr Cardiol* 2007; **28**: 250–4.
26. Weijerman ME, van Furth AM, van der Mooren MD, et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. *Eur J Pediatr* 2010; **169**: 1195–9.
27. Southgate WM, Annibale DJ, Hulsey TC, Purohit DM. International experience with trisomy 21 infants placed on extracorporeal membrane oxygenation. *Pediatrics* 2001; **107**: 549–52.
28. Byers HM, Dagle JM, Klein JM, et al. Variations in CRHR1 are associated with persistent pulmonary hypertension of the newborn. *Pediatr Res* 2012; **71**: 162–7.
29. Chandrasekar I, Eis A, Konduri GG. Betamethasone attenuates oxidant stress in endothelial cells from fetal lambs with persistent pulmonary hypertension. *Pediatr Res* 2008; **63**: 67–72.
30. Perez M, Lakshminrusimha S, Wedgwood S, et al. Hydrocortisone normalizes oxygenation and cGMP regulation in lambs with persistent pulmonary hypertension of the newborn. *Am J Physiol Lung Cell Mol Physiol* 2011; **302**(6): L595–603.
31. Lapointe A, Barrington KJ. Pulmonary hypertension and the asphyxiated newborn. *J Pediatr* 2011; **158**: e19–24.
32. Cornish JD, Dreyer GL, Snyder GE, et al. Failure of acute perinatal asphyxia or meconium aspiration to produce persistent pulmonary hypertension in a neonatal baboon model. *Am J Obstet Gynecol* 1994; **171**: 43–9.
33. Murphy JD, Vawter GF, Reid LM. Pulmonary vascular disease in fatal meconium aspiration. *J Pediatr* 1984; **104**: 758–62.
34. Toubas PL, Hof RP, Heymann MA, Rudolph AM. Effects of hypothermia and rewarming on the neonatal circulation. *Arch Fr Pediatr* 1978; **35**: 84–92.
35. Thoresen M. Hypothermia after perinatal asphyxia: selection for treatment and cooling protocol. *J Pediatr* 2011; **158**: e45–9.
36. Sarkar S, Barks JD, Bhagat I, et al. Pulmonary dysfunction and therapeutic hypothermia in asphyxiated newborns: whole body versus selective head cooling. *Am J Perinatol* 2009; **26**: 265–70.
37. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *JAMA* 2014; **312**: 2629–39.
38. Dodson RB, Morgan M, Galambos C, et al. Chronic intrauterine pulmonary hypertension increases main pulmonary artery stiffness and adventitial remodeling in fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2014; **307**(11): L822–8.
39. Stenmark KR, Davie N, Frid M, et al. Role of the adventitia in pulmonary vascular remodeling. *Physiology* 2006; **21**: 134–45.
40. Stenmark KR, Yeager ME, El Kasmi KC, et al. The adventitia: essential regulator of vascular wall structure and function. *Annu Rev Physiol* 2013; **75**: 23–47.
41. Soifer SJ, Kaslow D, Roman C, Heymann MA. Umbilical cord compression produces pulmonary hypertension in newborn lambs: a model to study the pathophysiology of persistent pulmonary hypertension in the newborn. *J Dev Physiol* 1987; **9**: 239–52.
42. Villaneuva ME, Zaher FM, Svinarich DM, Konduri GG. Decreased gene expression of endothelial nitric oxide synthase in newborns with persistent pulmonary hypertension. *Pediatr Res* 1998; **44**: 338–43.

43. Zagariya A, Doherty J, Bhat R, et al. Elevated immunoreactive endothelin-1 levels in newborn rabbit lungs after meconium aspiration. *Pediatr Crit Care Med* 2002; **3**: 297–302.

44. Soukka H, Jalonen J, Kero P, Kaapa P. Endothelin-1, atrial natriuretic peptide and pathophysiology of pulmonary hypertension in porcine meconium aspiration. *Acta Paediatr* 1998; **87**: 424–8.

45. Soukka H, Viinikka L, Kaapa P. Involvement of thromboxane A2 and prostacyclin in the early pulmonary hypertension after porcine meconium aspiration. *Pediatr Res* 1998; **44**: 838–42.

46. Davis AS, D. RW, Van Meurs KP. Persistent pulmonary hypertension of the newborn. In Stevenson DK, Benitz WE, Sunshine P, et al., eds., *Fetal and Neonatal Brain Injury*, 4th edn. Cambridge University Press, 2009: 419–42.

47. Steinhorn RH, Russell JA, Morin FC 3rd. Disruption of cGMP production in pulmonary arteries isolated from fetal lambs with pulmonary hypertension. *Am J Physiol* 1995; **268**: H1483–9.

48. de Buys Roessingh A, Fouquet V, Aigrain Y, et al. Nitric oxide activity through guanylate cyclase and phosphodiesterase modulation is impaired in fetal lambs with congenital diaphragmatic hernia. *J Pediatr Surg* 2011; **46**: 1516–22.

49. Chester M, Seedorf G, Tourneux P, et al. Cinaciguat, a soluble guanylate cyclase activator, augments cGMP after oxidative stress and causes pulmonary vasodilation in neonatal pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2011; **301**: L755–64.

50. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr* 1997; **131**: 55–62.

51. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985; **76**: 488–94.

52. Lotze A, Mitchell BR, Bulas DI, et al. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. *J Pediatr* 1998; **132**: 40–7.

53. Konduri GG, Sokol GM, Van Meurs KP, et al. Impact of early surfactant and inhaled nitric oxide therapies on outcomes in term/late preterm neonates with moderate hypoxic respiratory failure. *J Perinatol* 2013; **33**: 944–9.

54. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000; **105**: 14–20.

55. Laffey JG, Engelberts D, Kavanaugh BP. Inurious effects of hypocapnic alkalosis in the isolated lung. *Am J Respir Crit Care Med* 2000; **162**: 399–405.

56. Marron MJ, Crisafi MA, Driscoll JM Jr, et al. Hearing and neurodevelopmental outcome in survivors of persistent pulmonary hypertension of the newborn. *Pediatrics* 1992; **90**: 392–6.

57. Hendricks-Munoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 1988; **81**: 650–6.

58. Lakshminrusimha S, Russell JA, Steinhorn RH, et al. Pulmonary hemodynamics in neonatal lambs resuscitated with 21%, 50%, and 100% oxygen. *Pediatr Res* 2007; **62**: 313–8.

59. Lakshminrusimha S, Swartz DD, Gugino SF, et al. Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension. *Pediatr Res* 2009; **66**: 539–44.

60. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. *N Engl J Med* 2000; **342**: 469–74.

61. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med* 1997; **336**: 597–604.

62. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). *J Pediatr* 2000; **136**: 611–7.

63. Clark RH, Huckaby JL, Kueser TJ, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension: 1-year follow-up. *J Perinatol* 2003; **23**: 300–3.

64. Farrow KN, Lakshminrusimha S, Czech L, et al. SOD and inhaled nitric oxide normalize phosphodiesterase 5 expression and activity in neonatal lambs with persistent pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2010; **299**: L109–16.

65. Farrow KN, Groh BS, Schumacker PT, et al. Hyperoxia increases phosphodiesterase 5 expression and activity in ovine fetal pulmonary artery smooth muscle cells. *Circ Res* 2008; **102**: 226–33.

66. Farrow KN, Lee KJ, Perez M, et al. Brief hyperoxia increases mitochondrial oxidation and increases phosphodiesterase 5 activity in fetal pulmonary artery smooth muscle cells. *Antioxid Redox Signal* 2012; **17**: 460–70.

67. Baquero H, Soliz A, Neira F, et al. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. *Pediatrics* 2006; **117**: 1077–83.

68. Steinhorn RH, Kinsella JP, Pierce C, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr* 2009; **155**: 841–7.
69. Keller RL, Moore P, Teitel D, et al. Abnormal vascular tone in infants and children with lung hypoplasia: findings from cardiac catheterization and the response to chronic therapy. *Pediatr Crit Care Med* 2006; **7**: 589–94.
70. Brannon TS, MacRitchie AN, Jaramillo MA, et al. Ontogeny of cyclooxygenase-1 and cyclooxygenase-2 gene expression in ovine lung. *Am J Physiol* 1998; **274**: L66–71.
71. Brannon TS, North AJ, Wells LB, Shaul PW. Prostacyclin synthesis in ovine pulmonary artery is developmentally regulated by changes in cyclooxygenase-1 gene expression. *J Clin Invest* 1994; **93**: 2230–5.
72. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992; **327**: 70–5.
73. Lakshminrusimha S, Porta NF, Farrow KN, et al. Milrinone enhances relaxation to prostacyclin and iloprost in pulmonary arteries isolated from lambs with persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2009; **10**: 106–12.
74. Walmrath D, Schneider T, Schermuly R, et al. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153**: 991–6.
75. Bindl L, Fahnenstich H, Peukert U. Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994; **71**: F214–6.
76. Soditt V, Aring C, Groneck P. Improvement of oxygenation induced by aerosolized prostacyclin in a preterm infant with persistent pulmonary hypertension of the newborn. *Intensive Care Med* 1997; **23**: 1275–8.
77. Olmsted K, Oluola O, Parthiban A, Raghuveer T. Can inhaled prostacyclin stimulate surfactant in ELBW infants? *J Perinatol* 2007; **27**: 724–6.
78. Kelly LK, Porta NF, Goodman DM, et al. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141**: 830–2.
79. Porta NF, Steinhorn RH. Pulmonary vasodilator therapy in the NICU: inhaled nitric oxide, sildenafil, and other pulmonary vasodilating agents. *Clin Perinatol* 2012; **39**: 149–64.
80. Ferdman DJ, Rosenzweig EB, Zuckerman WA, Krishnan U. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. *Pediatrics* 2014; **134**: e274–8.
81. Luscher TF. Endothelin: systemic arterial and pulmonary effects of a new peptide with potent biologic properties. *Am Rev Respir Dis* 1992; **146**: S56–60.
82. Perreault T, Coceani F. Endothelin in the perinatal circulation. *Can J Physiol Pharmacol* 2003; **81**: 644–53.
83. Mann J, Farrukh IS, Michael JR. Mechanisms by which endothelin 1 induces pulmonary vasoconstriction in the rabbit. *J Appl Physiol* 1991; **71**: 410–6.
84. Ivy DD, Kinsella JP, Abman SH. Physiologic characterization of endothelin A and B receptor activity in the ovine fetal pulmonary circulation. *J Clin Invest* 1994; **93**: 2141–8.
85. Ivy DD, Le Cras TD, Horan MP, Abman SH. Chronic intrauterine pulmonary hypertension increases preproendothelin-1 and decreases endothelin B receptor mRNA expression in the ovine fetal lung. *Chest* 1998; **114**: 65S.
86. Gien J, Tseng N, Seedorf G, et al. Endothelin-1 impairs angiogenesis in vitro through Rho-kinase activation after chronic intrauterine pulmonary hypertension in fetal sheep. *Pediatr Res* 2013; **73**: 252–62.
87. Ivy DD, Parker TA, Ziegler JW, et al. Prolonged endothelin A receptor blockade attenuates chronic pulmonary hypertension in the ovine fetus. *J Clin Invest* 1997; **99**: 1179–86.
88. Mohamed WA, Ismail M. A randomized, double-blind, placebo-controlled, prospective study of bosentan for the treatment of persistent pulmonary hypertension of the newborn. *J Perinatol* 2012; **32**(8): 608–13.
89. Steinhorn RH, Fineman J, Kusic-Pajic A, et al. Bosentan as adjunctive therapy for persistent pulmonary hypertension of the newborn: results of the FUTURE-4 study. *Circulation* 2014; **130**: A13503.
90. Reller MD, Morton MJ, Reid DL, Thornburg KL. Fetal lamb ventricles respond differently to filling and arterial pressures and to in utero ventilation. *Pediatr Res* 1987; **22**: 621–6.
91. Cheung PY, Barrington KJ. The effects of dopamine and epinephrine on hemodynamics and oxygen metabolism in hypoxic anesthetized piglets. *Crit Care* 2001; **5**: 158–66.
92. James AT, Corcoran JD, McNamara PJ, et al. The effect of milrinone on right and left ventricular function when used as a rescue therapy for term infants with pulmonary hypertension. *Cardiol Young* 2015:**1**–10.
93. McNamara PJ, Shivananda SP, Sahni M, et al. Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. *Pediatr Crit Care Med* 2013; **14**: 74–84.
94. Chen B, Lakshminrusimha S, Czech L, et al. Regulation of phosphodiesterase 3 in the pulmonary arteries during the perinatal period in sheep. *Pediatr Res* 2009; **66**: 682–7.
95. Mohamed A, Nasef N, Shah V, McNamara PJ. Vasopressin as a rescue therapy for refractory

pulmonary hypertension in neonates: case series. *Pediatr Crit Care Med* 2014; **15**: 148–54.

96. Paden ML, Rycus PT, Thiagarajan RR. Update and outcomes in extracorporeal life support. *Semin Perinatol* 2014; **38**: 65–70.
97. Bifano EM, Pfannenstiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. *Pediatrics* 1988; **81**: 657–61.
98. Hageman JR, Dusik J, Keuler H, et al. Outcome of persistent pulmonary hypertension in relation to severity of presentation. *Am J Dis Child* 1988; **142**: 293–6.
99. Lipkin PH, Davidson D, Spivak L, et al. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. *J Pediatr* 2002; **140**: 306–10.
100. Konduri GG, Vohr B, Robertson C, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr* 2007; **150**: 235–40.
101. Fliman PJ, deRegnier RA, Kinsella JP, et al. Neonatal extracorporeal life support: impact of new therapies on survival. *J Pediatr* 2006; **148**: 595–9.
102. Massaro AN. MRI for neurodevelopmental prognostication in the high-risk term infant. *Semin Perinatol* 2015; **39**: 159–67.
103. Rollins MD, Yoder BA, Moore KR, et al. Utility of neuroradiographic imaging in predicting outcomes after neonatal extracorporeal membrane oxygenation. *J Pediatr Surg* 2012; **47**: 76–80.
104. Gannon CM, Kornhauser MS, Gross GW, et al. When combined, early bedside head ultrasound and electroencephalography predict abnormal computerized tomography or magnetic resonance brain images obtained after extracorporeal membrane oxygenation treatment. *J Perinatol* 2001; **21**: 451–5.
105. Pappas A, Shankaran S, Stockmann PT, Bara R. Changes in amplitude-integrated electroencephalography in neonates treated with extracorporeal membrane oxygenation: a pilot study. *J Pediatr* 2006; **148**: 125–7.
106. van Heijst AF, de Mol AC, Ijsselstijn H. ECMO in neonates: neuroimaging findings and outcome. *Semin Perinatol* 2014; **38**: 104–13.
107. UK Collaborative ECMO Trial Group. The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial: follow-up to 1 year of age. *Pediatrics* 1998; **101**: E1.
108. Bennett CC, Johnson A, Field DJ, Elbourne D. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. *Lancet* 2001; **357**: 1094–6.
109. McNally H, Bennett CC, Elbourne D, Field DJ. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. *Pediatrics* 2006; **117**: e845–54.
110. Ijsselstijn H, van Heijst AF. Long-term outcome of children treated with neonatal extracorporeal membrane oxygenation: increasing problems with increasing age. *Semin Perinatol* 2014; **38**: 114–21.
111. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR. Extracorporeal life support organization registry report 2012. *ASAIO J* 2013; **59**: 202–10.
112. Parish AP, Bunyapen C, Cohen MJ, et al. Seizures as a predictor of long-term neurodevelopmental outcome in survivors of neonatal extracorporeal membrane oxygenation (ECMO). *J Child Neurol* 2004; **19**: 930–4.
113. Campbell LR, Bunyapen C, Gangarosa ME, et al. Significance of seizures associated with extracorporeal membrane oxygenation. *J Pediatr* 1991; **119**: 789–92.
114. Vaucher YE, Dudell GG, Bejar R, Gist K. Predictors of early childhood outcome in candidates for extracorporeal membrane oxygenation. *J Pediatr* 1996; **128**: 109–17.
115. Kornhauser MS, Baumgart S, Desai SA, et al. Adverse neurodevelopmental outcome after extracorporeal membrane oxygenation among neonates with bronchopulmonary dysplasia. *J Pediatr* 1998; **132**: 307–11.
116. Van Meurs KP, Nguyen HT, Rhine WD, et al. Intracranial abnormalities and neurodevelopmental status after venovenous extracorporeal membrane oxygenation. *J Pediatr* 1994; **125**: 304–7.
117. Desai SA, Stanley C, Gringlas M, et al. Five-year follow-up of neonates with reconstructed right common carotid arteries after extracorporeal membrane oxygenation. *J Pediatr* 1999; **134**: 428–33.
118. Desai S, Kollros PR, Graziani LJ, et al. Sensitivity and specificity of the neonatal brain-stem auditory evoked potential for hearing and language deficits in survivors of extracorporeal membrane oxygenation. *J Pediatr* 1997; **131**: 233–9.
119. Cheung PY, Robertson CM. Sensorineural hearing loss in survivors of neonatal extracorporeal membrane oxygenation. *Pediatr Rehabil* 1997; **1**: 127–30.
120. Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics* 2007; **120**: 898–921.
121. Beardsmore C, Dundas I, Poole K, et al. Respiratory function in survivors of the UK Extracorporeal Membrane Oxygenation Trial. *Am J Respir Crit Care Med* 2000; **161**: 1129–35.
122. Majaesic CM, Jones R, Dinu IA, et al. Clinical correlations and pulmonary function at 8 years of age after severe neonatal respiratory failure. *Pediatr Pulmonol* 2007; **42**: 829–37.

Chapter 37

Pediatric Cardiac Surgery

Relevance to Fetal and Neonatal Brain Injury

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Introduction

This chapter discusses the impact of congenital heart disease and its surgical treatment on the neonatal brain. Babies may have congenital cardiac disease as an isolated malformation or may have a heart defect as part of a larger spectrum of abnormalities, which may, in turn, be associated with a syndrome. In addition, these babies are often profoundly ill, presenting to medical attention on the verge of cardiac arrest with severe hypoxia, hypotension, or both. Treatment of the condition usually involves a trip to the catheterization laboratory or operating room (or both). We therefore have great potential for neurologic morbidity, with a combination of possible underlying abnormality of the brain and preoperative, perioperative, and postoperative insults all conspiring to injure the cardiac surgery patient's brain. Despite these problems, the majority of babies do extremely well following heart surgery in the newborn period, although it is important to recognize that many of them will have a subtle neurologic deficit if they are compared with the normal population. These are evidenced as cognitive and intellectual impairments, behavioral difficulties, speech delays, and so on [1–3]. The incidence of major neurologic insult postoperatively as manifest by seizures, stroke, coma, or choreoathetoid movements has fallen to around 2–11% in the current era [4,5].

Congenital Heart Disease and Common Genetic Associations

Fortunately, congenital heart disease (CHD) is rare, affecting 2.8/1,000 live births [6]. It does not have a clear, solely genetic causation because the risk of ostium secundum atrial septal defect (ASD) in sisters of patients with secundum ASD is 33%, and the chances of a mother of a child with secundum ASD having the same defect is only 22.5% [7]. The incidence of CHD in dizygotic twins is only 13.6%, but in one series they all had the same type of defect, pointing to a shared environmental risk during pregnancy [8]. Nevertheless, there are clearly familial clusters of congenital heart defects [9], especially in consanguineous families, so there are definite genetic components involved [10]. Approximately one-third of children with CHD have an associated non-cardiac abnormality [11]. There are also certain genetic syndromes that are associated with specific cardiac defects.

DiGeorge Syndrome/Velocardiofacial Syndrome (VCFS)

This is caused by microdeletion of chromosome 22q11. It occurs in 1 out of 4,000 live births. This entity is now more appropriately referred to as *22q11.2 deletion* because the presentation encompasses a broad phenotypic spectrum including thymic aplasia, hypocalcemia, facial dysmorphism, velopharyngeal dysfunction, impairment in neurodevelopmental outcome, and conotruncal abnormalities such as interrupted aortic arch and truncus arteriosus. The deletion can be inherited in an autosomal dominant fashion, but most cases are thought to be new deletions. It has been estimated that 77% of these babies have a deficit of cell-mediated immunity [12]. All blood for transfusion to these patients must be irradiated to prevent graft-versus-host disease from live leukocytes in the transfused blood, although this procedure is standard practice in many institutions. Although clinical variability is marked, 40–50% of patients with 22q11.2 deletion have cognitive or learning difficulties. The neurodevelopmental prognosis for children with 22q11.2 deletion and CHD requiring surgery in the neonatal period appears to be even more guarded (see "Neurodevelopmental Outcomes" below). These children also have been reported to be at significantly

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higher risk for schizophrenia and other behavioral disorders than the general population [13].

Down Syndrome

Caused by trisomy 21, this well-known syndrome is the most common chromosomal anomaly, affecting approximately 1/700 to 1/1,000 live births. It is associated with congenital heart disease in 40% of cases, nearly half of which are atrioventricular septal defects (AVSD) [14]. Indeed, 40–60% of children with AVSD have a chromosomal abnormality, usually Down syndrome [15]. It is unusual for a newborn with Down syndrome and AVSD to require surgery, most patients being operated on electively at around the age of 6 months. If there is severe left AV valve regurgitation and heart failure in the newborn period requiring surgery, the prognosis is usually guarded.

Other Syndromes

Polymorphism for apolipoprotein E, which is involved in neuronal repair, can cause susceptibility to neurologic injury following heart surgery [16]. Williams syndrome, a microdeletion of chromosome 7q11.23 (elastin gene) affecting 1/20,000 live births, is associated with valvar and supravalvar aortic stenosis, pulmonary artery stenosis, developmental impairments, and elfin facies. There is also a clear association between congenital heart disease and congenital malformation of the brain [3].

Presurgical Neurologic Injury

We have seen in the preceding section how some babies have congenital anomalies that can contribute to their ultimate neurologic outcome. However, even children who have anatomically normal brains can suffer injury from hypoxia and ischemia as a result of their cardiac malformation, and this can occur in 15–30% of patients preoperatively [17,18]. Congenital heart disease often presents in the first few days of life when the ductus arteriosus closes. Patients can then be largely divided into those with cyanotic lesions, where the duct had been supplying the pulmonary blood flow (i.e., pulmonary atresia with intact ventricular septum [PAIVS]), and those with obstructive lesions, where the duct had been supplying the systemic blood flow (i.e., coarctation of the aorta). Babies with transposition of the great arteries (TGA) do not fit neatly into this categorization because their duct acts to increase mixing of oxygenated blood between the pulmonary and systemic circulations, nor do children with obstructed total anomalous pulmonary venous connections (TAPVC), but since both may present with cyanosis and collapse in the first few days of life, this is largely an academic issue. Patients may present with profound desaturation, collapse, cardiogenic shock, or cardiac failure. Obviously, any condition that reduces oxygen delivery to the brain by reducing the oxygen content of the blood and the cardiac output can cause neurologic injury. Thus, as in preterm infants, the white matter of term infants with CHD is exquisitely vulnerable to injury [19]. Hypoxic-ischemic insults as well as pro-inflammatory mediators may injure the developing oligodendrocytes in the term infant with CHD, causing periventricular leukomalacia (PVL), which is detectable by MRI in as many as 50% of neonates following cardiac surgery [20,21]. Oligodendrocytes may also be damaged by inflammatory cytokines and therefore can be injured by cardiopulmonary bypass (CPB) itself, as well as by other inflammatory states such as meningitis [22]. While previous literature has addressed possible brain damage that occurs intraoperatively, in a cohort study from 2010, investigators performed MRIs on newborns with hypoplastic left heart syndrome (HLHS) and transposition of the great vessels prior to surgery and found that mean head circumference was 1 standard deviation below normal and that mean total maturation score for the cohort was significantly below normative data in newborns with no CHD. These findings suggest that the presence of complex cardiac disease itself contributes to the inherent vulnerability these newborn brains have to neurologic insults such as PVL even prior to surgery [23].

Recognition of the possibility of duct-dependent congenital heart disease in a collapsed newborn and early resuscitation with prostaglandin infusion to reopen the duct restores oxygenation of the tissues and limits brain injury in most cases. The exception to this is obstructed TAPVC: these babies have severe consolidation of the lungs and may present in the first few hours of life with apparent respiratory failure, which may be refractory to ventilation and nitric oxide. Prostaglandin infusion does not help and may be detrimental, and many of these babies are referred for extracorporeal membrane oxygenation (ECMO) as cases of persistent fetal circulation. Sometimes the correct diagnosis is not made until after they have

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been cannulated for ECMO. Because ECMO is a good way to restore oxygenation, this allows for resuscitation before surgery.

Aside from presurgical brain injury, there is likely a high rate of unrecognized structural brain abnormality in children with CHD. For example, in a postmortem series of 41 babies with HLHS, 29% had a major structural brain abnormality, including absent corpus callosum, holoprosencephaly, and immature cortical mantle [24]. In a more recent study, Hinton et al. examined the fetal brains of electively aborted fetuses with known HLHS and found that all fetuses demonstrated varying degrees of white matter injury, according to the fetal CNS white matter injury classification scheme. And more specifically, both GFAP and CD68 expression was substantially higher when compared with age-matched controls, which is consistent with chronic white matter injury [25]. Carefully performed cranial ultrasound (CUS) may be sufficient to reveal significant preoperative structural abnormalities. In a retrospective series, te Pas et al. reported that 42% of term and near-term infants with CHD had preoperative brain abnormalities detected by CUS [26]. These included ventriculomegaly, wide subarachnoid spaces, lenticulostriate vasculopathy, and acute ischemic changes and were most likely to occur in those with HLHS. More recently, MRI and diffusion tensor imaging (DTI) have been employed to delineate both macro- and microstructural preoperative brain abnormalities among term infants with HLHS and TGA compared with control infants without CHD [27]. On preoperative imaging, 41% of those with TGA and 17% of those with HLHS had brain injury; none of the control infants had white matter injury on MRI. Using more advanced microstructural interrogation with DTI, white matter fractional anisotropy (a measure of directionality of water movement, which should increase with maturation) was significantly lower among those with CHD than among control infants. Average diffusivity (a measure of overall diffusion of water, which should decrease with maturation) was significantly higher among infants with CHD. These concerning findings indicate that the pattern of brain microstructural development in term infants with HLHS and TGA is similar to that of premature infants. Furthermore, because observations were made soon after birth, the DTI results suggest that impaired fetal brain development is likely to be associated with these congenital cardiac anomalies. In light of these important findings, advanced neuroimaging prior to surgical intervention may become increasingly important to clinical management and decision making. Significant attention has been paid to developing neuroprotective perioperative strategies, with much of the focus on modifying perfusion strategies, which is discussed later in this chapter. However, substantial opportunities remain for further investigation into preoperative neuroprotective strategies.

In some cases, the standard treatment for TGA is balloon atrial septostomy (BAS) as a resuscitative measure to improve mixing across the atrial septum and then a switch operation at some point a week or more later. Recently, neurologic morbidity has been associated with the septostomy itself [28] In a series of 29 patients with TGA studied with brain MRI prior to definitive switch repair, 12 of the 19 patients who required BAS as a resuscitative measure had focal or multifocal stroke; none of the patients without BAS had such injury. In a larger series of patients with a range of congenital cardiac defects, 39% had preoperative brain injury by MRI, most commonly stroke, and this was independently associated with BAS [29]. On the basis of this evidence, some centers appear to be moving toward immediate surgery in more TGA cases because septostomy itself appears to be a risk factor for neurologic injury.

Preoperative Injury: Timing of Surgery

All babies who have had a significant hypoxic or ischemic neurologic insult should undergo neuroimaging after resuscitation. If intracranial hemorrhage (ICH) is detected, surgery should be deferred for as long as practicable to reduce the risk of extension of the ICH when the patient undergoes cardiopulmonary bypass. It can take several weeks for an ICH to organize sufficiently to make CPB "safe," but a delay of as little as 1 week can reduce the risk of ICH substantially.

Limitation of Perioperative Neurologic Injury

Unfortunately, the process of surgical correction of congenital heart defects causes neurologic injury when surgical patients are compared with the general population [30]. This is inherent in the technology that is available and the diseases being treated. Fortunately, however, modern surgical and anesthetic

techniques have evolved so that this damage is limited. It requires a neurophysiologist armed with sophisticated psychomotor tests and an MRI scanner to detect. Most children who undergo cardiac surgery probably will function within the normal range during childhood and beyond. It is likely that if these children had been born without a heart defect, they would have had higher IQs and better psychomotor function. However, comparing these children with the ideal situation is futile; in the majority of cases, these infants with CHD would not have survived or at the very least would have had a far more guarded neurologic prognosis without surgical intervention. Thus we must focus on optimizing operative and perioperative management and techniques to ensure the best possible outcomes.

Anesthesia

In a baby with duct-dependent CHD, the usual anesthetic technique of pre-oxygenation prior to intubation causes pulmonary vasodilation resulting in steal from the systemic circulation. This can paradoxically cause a massive reduction in tissue oxygen delivery with systemic hypotension. Ventilation is therefore tailored to avoid this. Animal studies have shown neuroprotective effects of various different anesthetic agents including the volatiles, which have calcium channel-blocking effects, and the barbiturates [11,31,32], but these have not been borne out in clinical practice, and so the anesthesiologist's focus is to maintain cardiovascular stability and tissue oxygen delivery by use of a variety of techniques. Barbiturates may have a protective effect against air embolism in the warm brain and are sometimes used following catastrophic air embolism [33]. Surface cooling in the anesthetic room is a useful adjunct to cooling on CPB.

Cardiopulmonary Bypass

CPB is what makes surgery possible, but it is an abnormal nonpulsatile circulation and requires full anticoagulation with heparin to the extent that the blood will not clot at all. This is achieved with a heparin dose of 3 mg/kg and is necessary to prevent the patient's blood clotting in the extracorporeal circuit. CPB causes dilution and consumption of clotting proteins and activation and consumption of platelets, resulting in a typical coagulopathy [34]. There is also a panendothelial injury caused by activation of inflammatory cytokines such as complement factors, interleukins, and tumor necrosis factor (TNF), although there is no clear correlation between the degree of inflammation and the clinical outcome [35]. Blood into the surgical field is aspirated back to the CPB machine and reinfused into the patient. This blood can contain particulate debris such as pieces of bone, bone wax, small clots, fat, and microbubbles. The addition of arterial line filters and avoidance of embolism have reduced the neurologic injury that was attendant on the reinfusion of these particles into the aorta [36,37]. Children with cyanotic heart disease often have many collateral vessels between the systemic and pulmonary circulations; these may be anatomic structures such as major aortopulmonary collateral arteries (MAPCAs) or smaller vessels that open up as a result of the chronic hypoxia. When CPB is established, these vessels can result in a huge amount of blood returning to the heart despite the diversion of all the venacaval blood to the machine. This open-heart return can obscure the surgical field and make repair impossible. The use of systemic hypothermia reduces the metabolic rate by a factor of approximately 2.5 for every 10°C and thus allows lower CPB flows, which reduce the collateral return and makes surgery possible [38]. Hypothermia, in turn, causes increased viscosity in the blood, and historically it was routine to hemodilute patients to offset this because it was thought that a lower viscosity would result in higher tissue oxygen delivery. In addition, this reduced blood transfusion requirements [39]. Modern practice has moved away from this concept because it has been shown that a relatively normal hematocrit of 30% is preferable on bypass to optimize tissue oxygen delivery and improve neurologic outcome [40–42]. During open-heart surgery, air enters the heart and great vessels, but this must not enter the cerebral circulation and must be removed at the end of the procedure because it is a potent cause of neurologic injury; even if a blood vessel is not blocked, the mere passage of an air bubble can cause injury [22]. In addition to these factors, the newborn brain appears more susceptible to neurologic injury following CPB, in that MRI evidence of PVL can be seen in 50% of newborns following CPB, whereas in older babies only 5% are affected [19]. The clinician has little influence over most of these factors because they are inherent in the use of the technology [22], but there are some aspects that the clinician can influence to affect the

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outcome and limit neurologic injury. These factors are discussed below.

Cooling Strategy

Cooling is the main neuroprotective tool used during CPB. It is important to ensure that the brain cools evenly. To this end, cooling (and warming) should be relatively slow, to allow thorough equilibration of temperature throughout the tissues. In complex congenital cardiac surgery, deep hypothermic cardiac arrest (DHCA) is used for neuroprotection when the heart is stopped during portions of the procedure where a bloodless field is required. It is agreed that cooling prior to deep hypothermic circulatory arrest should take at least 20 minutes [22]. Also, barbiturates (if used) should not be given until the desired temperature is reached because they can cause cerebral vasoconstriction and prevent even cooling. The blood gas management during cooling is also important. CPB was run using an alpha-stat profile for many years because this was felt to provide the best perfusion conditions as well as being easy to manage. During alpha-stat management, the blood gas machine is not adjusted for temperature; in other words, the pH is measured at 37°C, even though the patient may be at 25°C. The upshot of this is that the patient becomes more alkalotic during cooling, and this, in turn, leads to cerebral vasoconstriction, reduced oxygen delivery to boundary areas, and uneven cooling. The alternative method is pH-stat, where the blood gas machine is adjusted for temperature, and CO_2 is added to the bypass oxygenator sweep gas to offset the alkalosis. The relative acidosis keeps the brain vasodilated and maintains cerebral blood flow, especially once cerebral autoregulation is abolished as the patient becomes poikilothermic during cooling [11,43]. There is substantial evidence that neurologic outcomes are better when pH-stat is used during cooling; in addition, and some clinicians support the use of alpha-stat during rewarming [44–47]. A typical protocol employs pH-stat during cooling, switching to alpha-stat prior to circulatory arrest, and using alpha-stat during warming. Most units also employ some form of topical brain cooling.

Perfusion Strategies

Numerous variables affect the neurologic outcomes of pediatric patients undergoing surgical repair of complex congenital cardiac disorders. A particular point of interest is the implementation of different perfusion strategies, specifically regarding methods that avoid or minimize the need for DHCA, because hypothermia is associated with altered glucose and oxygen uptake in the brain [48] and insufficient brain perfusion [49, 50].

DHCA versus Low-Flow CPB versus Head Perfusion

When the brain temperature is sufficiently low (~15° C), the circulation can be stopped for a period of time and restarted with few sequelae. This process is termed *deep hypothermic circulatory arrest* (DHCA). There is much discussion about how long that period of time is, but less than 25 minutes is indistinguishable from low-flow CPB and therefore relatively safe [51,52]. All children in the Boston DHCA study whose arrest time exceeded 35 minutes had postoperative seizure activity [53], and there was an incremental decrease in intellectual ability that correlated closely with duration of DHCA beyond the very short "safe period" [52,54]. In addition, the children in the Boston study whose DHCA time exceeded 41 minutes had worse late neurodevelopmental outcome than the children in the low-flow continuous bypass group. DHCA is useful because it allows the bypass cannulas to be removed and provides excellent operative conditions with a bloodless field [55]. It is therefore helpful for some operations in very small patients and for some parts of operations around the arch of the aorta (e.g., Damus-Kaye-Stansell procedure). Some surgeons use DHCA routinely, but most prefer to limit its use [51]. There is currently much controversy regarding this issue because surgeons have realized that they can perform most of the operation on CPB and that long periods of DHCA are no longer mandatory [51]. The use of low-flow CPB at around 50 mL/kg per minute, with a cerebral perfusion pressure of 13 mmHg and isolated anterograde head perfusion at flows of 20–30 mL/kg per minute, has meant that periods of circulatory arrest can often be reduced to just a few minutes [56]. In addition, periods of reperfusion during DHCA may also reduce the neurologic insult [11]. Although anterograde cerebral perfusion (ACP) was thought to be a promising alternative to DHCA, it was unknown whether the former offered superior neurologic outcomes. In a 2013 randomized, controlled trial, investigators randomized neonates undergoing aortic reconstruction to ACP

or DHCA, the primary outcome being new postoperative neurologic insult. The results of the study demonstrated no difference in the total number of new postoperative neurologic injuries between the two arms. Furthermore, cerebral infarction occurred exclusively in the ACP arm [57]. Most surgeons adopt a combination of techniques, which they adapt to the individual patient's condition.

Hypothermia versus Normothermia in ACP

While the differences in neurologic outcomes between ACP and DHCA are unremarkable, there has been interest in using regional perfusion at normal temperatures, the idea being that the brain can be perfused while avoiding the potential dangers of DHCA, such as an increased risk of perioperative bleeding and hyperthermia to peripheral regions of the brain during rewarming, In a retrospective study, investigators analyzed outcomes of patients who underwent cardiac surgery for congenital disease when ACP was used in hypothermic or normothermic conditions and found that in the normothermic group there were lower CPB and aortic clamp times. The study found no differences in immediate postoperative complications, including neurologic insults; however, postoperative MRIs were not routinely performed [58]. Therefore, this warrants further investigation.

NIRS Intraoperative Monitoring of Cerebral Oxygen Delivery

Near-infrared spectroscopy (NIRS) is now available commercially as transcutaneous devices that can continually monitor cerebral oxygen delivery (Somanetics, Hamamatsu). It has been shown in a retrospective study that the use of NIRS during heart surgery improves the general condition of the patient as well as the short-term neurologic outcome, reducing length of stay [59]. This is likely due to the ability of this device to identify periods of occult cerebral hypoxia. Such periods can occur when the cerebral perfusion pressure decreases below 13 mmHg without being noticed [11], which, in turn, can occur when a child has bicaval venous cannulation with a transiently obstructed superior vena cava cannula causing intracranial venous hypertension [60]. It can also occur when the perfusion pressure decreases because of vasodilation, runoff via aortopulmonary collaterals or a shunt, or reduced CPB flow to allow improved visualization of the surgical field. By immediately identifying cerebral hypoxia and correcting it, brain injury is limited, and neurologic outcome may be improved. Most CPB circuits have a continuous display of the venous line oxygen saturation using devices such as the CDI500 (Terumo). Maintaining the SvO_2 at more than 65% ensures global tissue oxygen delivery but does not identify regional tissue hypoxia. Because the brain has the fastest metabolic rate of any organ, it will be the first to suffer from a global decrease in oxygen delivery during CPB, and using NIRS in addition to SvO_2 monitoring acts to prevent cerebral hypoxia. In a 2010 study, Kussman et al. investigated the relationship between low regional cerebral oxygen saturation (rSO_2) and neurodevelopmental outcomes at 1 year post-surgery in infants undergoing biventricular repair without aortic reconstruction. The authors found that intraoperative periods of diminished rSO_2 were associated with 1-year psychomotor development index and brain MRI abnormalities among newborns undergoing surgery for CHD [61].

CO_2 Flooding

Open-heart surgery inevitably allows air to enter the heart, and this must be removed at the end of the procedure before the heart is allowed to beat. This is an imperfect process and can result in air embolus to the brain, with disastrous consequences. By flooding the surgical field with CO_2, any gas left in the heart at the end of the procedure will be soluble and theoretically less dangerous if not completely removed [62].

Corticosteroids

Intravenous steroids are used routinely in a number of centers preoperatively (dexamethasone 1 mg/kg or methylprednisolone 30 mg/kg) to reduce the inflammatory activation associated with CPB, but there is little consensus on dosing protocols [63,64]. There is good evidence that this is effective in limiting postoperative inflammatory markers and that this translates into improved pulmonary, renal, and general clinical outcome, but specific neurologic outcome was not studied [63].

Modified Ultrafiltration

Modified ultrafiltration (MUF) also can act to remove inflammatory mediators and can result in improved myocardial function. MUF may reduce brain injury associated with DHCA [22,65]. However, use of arteriovenous MUF can result in

hypotension, and this may contribute to a reduction in cerebral oxygen delivery [66].

Postoperative Management

Once patients have undergone successful surgery, they are taken to the pediatric intensive care unit (PICU), where their organ functions are further optimized as they recover from the operation. Hypotension and hypoxia are both predictive of PVL postoperatively [20]. A full discussion of PICU management is beyond the scope of this chapter, but three specific treatments that could help to improve neurologic outcome are discussed.

NOMO-VAD

In some cases, cardiac output is marginal following a successful corrective operation. Some of these patients will deteriorate and die, and some will survive. It has been suggested that early or even elective mechanical support of cardiac output can improve survival as well as improve the neurologic outcome in these borderline cases [67]. NOMO-VAD uses an ECMO circuit without an oxygenator (hence NOMO) to provide ventricular assist (ventricular assist device [VAD]) via venoarterial cannulation to children with arteriopulmonary shunts. The flow in the circuit is set at around 200 mL/kg per minute, approximately double that used for VA ECMO. Pulmonary blood flow comes from the shunt flow, augmented by the flow from the circuit. Children with biventricular circulations and normal pulmonary blood flow anatomy can be supported with VA ECMO in the event of low cardiac output postoperatively [68]. Larger children can be supported with VADs such as the Berlin heart [69].

Cooling

Cooling has been used as a neuroprotective treatment in many different arenas following cardiac arrest in adults and children, birth asphyxia, and head trauma [70, 71]. There are two potential mechanisms by which cooling could help to improve neurologic outcome following cardiac surgery. First, by reducing the metabolic rate of the brain, the balance between oxygen supply and demand can be restored in the presence of a limited cardiac output, and further improvement of this equation occurs because of a reduction in excitotoxic neurotransmitters in the cooled brain [72]. Second, many children suffer tachycardia after heart surgery, which can impair cardiac output, and many of these tachycardias (e.g., junctional ectopic tachycardia [JET]) respond well to cooling, which boosts cardiac output and improves cerebral oxygen delivery

Tight Glycemic Control

There is evidence that tight glycemic control with prevention of hyperglycemia can improve outcome after head injury in children [73,74]. A recent study that randomized PICU patients to either tight glycemic control, with a target range of 72–126 mg/dL, or conventional glycemic control, with a target glucose of under 216 mg/dL, found no significant difference in clinical outcomes between the groups but did find that there was a higher incidence of hypoglycemic episodes in the tight glycemic control group [75]. It is important to avoid hypoglycemia because it is associated with seizures [76].

Neurodevelopmental Outcomes

With substantial advances in intraoperative and perioperative management and remarkable improvements in surgical technique and approach allowing for better short-term outcomes, the focus of attention both for families and for further research turns to long-term neurodevelopmental outcomes [77]. Studies reporting neurodevelopmental follow-up assessments in children after complex congenital heart surgery have been challenging to interpret for several reasons. Given the rapidly changing and improving strategies for operative and perioperative management, the outcomes of infants born years ago may not be generalizable to the present. The morbidities associated with approaches used in the past may be related to adverse neurocognitive outcomes reported now; similarly, the potential modifying effects of newer techniques may not be fully understood for several years. Specific CHD lesions and numerous other intrinsic and extrinsic patient variables may be associated with differing outcomes. Thus, if a small but very diverse cohort of CHD survivors is examined, such predictors may be difficult to assess. In addition, most of these studies do not include contemporaneous control groups.

Intrinsic Genetic Variables

As discussed previously, several genetic syndromes known to be associated with CHD are also known to be associated with increased risk for developmental impairment [78,77]. These include trisomy 21,

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Williams syndrome, and CHARGE (coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities) association. More subtle genetic variables also have been recognized as potentially important determinant factors for adverse outcomes after complex congenital heart surgery.

Polymorphisms of the apolipoprotein E (*APOE*) gene are associated with impaired recovery after brain ischemic injury and with neurologic decline after surgery for CHD [16]. In a recent neurodevelopmental follow-up study by Gaynor et al., 188 patients who had undergone two-ventricle repair for a range of CHD lesions were assessed at 1 year of age using the Bayley Scales of Infant Development II (BSID) Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) (population normed mean = 100, standard deviation = 15), as well as neurologic examination [79]. For the entire cohort, mean scores were within or slight lower than those expected for the general population (MDI 90.6 ± 14.9, PDI 81.6 ± 17.2). Although numerous potentially important pre-, intra-, and postoperative variables were evaluated, only preoperative factors were independently associated with worse MDI scores on multivariate analyses. These intrinsic factors included low birth weight, presence of a genetic syndrome, and presence of the *APOE* ε2 polymorphism.

The outcomes of children with CHD affected by 22q11.2 deletion spectrum have also recently been evaluated. The Western Canadian Complex Pediatric Therapies Project Follow-up Group reported on the 18-month outcomes of a regional cohort of 85 patients who had undergone a range of interventions including arterial switch, Norwood, and TAPVC repairs, as well as other procedures [80]. For the entire cohort, BSID scores were lower than would be expected for the population (MDI 84 ± 17, PDI 80 ± 22). However, for the subgroup with genetic abnormalities, the majority of whom had 22q11.2 deletion, mean BSID scores were substantially lower (mean MDI and PDI scores < 70). Another study from this group compared 2-year outcomes of a small group of CHD patients with 22q11.2 deletion with patients without deletion [81] matched on cardiac lesion, socioeconomic status, and hospital and year of operation. There were significant differences between the groups. Of the group with the 22q11.2 deletion, 61.5% had an MDI of less than 70, 84.6% had a PDI of less than 70, and 69% were in a developmental intervention program. Of the group without deletion, only 13.8% had an MDI of less than 70, 6.7% had a PDI of less than 70, and 20% were in developmental intervention. Forbess et al. reported on the 5-year outcomes of children who had had definitive repair or palliative surgery for a range of CHD lesions in the neonatal period [82]. In this analysis, the presence of 22q11.2 deletion was significantly associated with lower full-scale IQ, performance IQ, and verbal IQ independent of numerous other variables. Taken together, these data suggest the critical importance of making the diagnosis of 22q11.2 deletion as soon as possible – preferably in the prenatal period – to allow appropriate and better-informed counseling as to long-term outcomes. The diagnosis is now easy to make with the use of fluorescent in situ hybridization (FISH).

Socioeconomic Factors

The association of socioeconomic status (SES) with cognitive and developmental outcomes has been demonstrated in numerous neurodevelopmental follow-up studies of high-risk neonatal groups, including extremely low-birth-weight and extremely preterm infants [83,84]. This association is also true for children followed after congenital cardiac surgery [77]. Forbess et al. reported that lower SES was independently correlated with lower full-scale IQ and verbal IQ at 5 years of age in a cohort with a range of CHD lesions [82]. After Fontan operation specifically, Wernovsky et al. found that SES was also significantly independently associated with cognitive outcome [85].

Congenital Heart Lesion Type

Robust assessment of neurodevelopmental outcomes by CHD lesion has been challenging, given the limitation of patient numbers of any single diagnostic category in any single institution. However, special interest has been given to HLHS because of improved survival, the severity of the lesion and complexity of the intervention needed, early reports of extremely poor neurodevelopmental outcomes, and recognition that cerebral blood flow is impaired among infants with HLHS [8,37,77,86,87]. More recent investigations of early development and school-age outcomes of patients with HLHS after either staged palliation or transplant have reported low to low-normal IQ [6,38,88,89]. In young children who had undergone transplantation for HLHS, Ilke et al. found mean full-scale IQ to be 88.5, verbal IQ 89.9, and performance

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IQ 90 [88]. Mahle et al. compared school-age outcomes of patients who had undergone transplant (n = 21) with those who had undergone the Norwood procedure (n = 26) for HLHS [86]. They found no significant differences between the groups in IQ, expressive or receptive language, motor function, or behavior. For the overall cohort, mean full-scale IQ was 86, mean expressive and receptive language scores and mean math, reading, and spelling achievement scores were all approximately one standard deviation below the population-expected mean. In multivariate analyses, only prolonged length of stay was associated with lower full-scale IQ.

The Western Canadian Complex Pediatric Therapies Project Follow-up Group reported that among patients who had undergone Norwood procedures (n = 16), 18-month mean BSID MDI was 84, and mean PDI was 68; 25% had an MDI of less than 70, and 56% had a PDI of less than 70 [80]. However, very early childhood BSID scores may not be predictive of later outcome [90,91]. This group also reported on early childhood outcomes after TAPVC repair in the neonatal period [92]. Mean BSID scores were also in the low-normal range, with a mean MDI of 87 and a mean PDI of 89. Comparing developmental outcomes as a function of single-ventricle or biventricular repairs, Forbess et al. found significant differences between the patients at 5 years of age [82]. Mean full-scale IQ was 89.9 and performance IQ was 88.4 in the single-ventricle group compared with 98.2 and 97.8, respectively, in the biventricular repair group. Results of visual-motor tests were significantly worse for single-ventricle patients, although mean scores were still within the low-normal range.

Intraoperative Factors

One of the most comprehensive trials of intraoperative interventions is the Boston Circulatory Arrest Study (BCAS), in which infants with dextro transposition of the great arteries (d-TGA) were randomized to DHCA or continuous low-flow CPB and received neurodevelopmental follow-up at several points during childhood [1,30,35]. At 4 years of age, there were no differences between the DHCA and CPB groups in terms of IQ, although the DHCA group was more likely to have gross and fine motor impairment and speech and language delay. The mean full-scale IQ (92.6) and performance IQ (91.6) scores for the cohort as a whole were in the low-normal range. Assessment at 8 years of age revealed impaired outcomes for the overall cohort in areas including cognitive and executive function, fine motor skills, and speech and language. Although there were no differences between the DHCA and CPB groups in full-scale, verbal, or performance IQ, the length of time under DHCA was significantly correlated with lower full-scale and performance IQ scores. Of note, at 1-year follow-up, significantly lower BSID PDI scores and a trend toward lower MDI scores were observed in the DHCA group; this disparity between 1- and 8-year findings underscores the poor predictive validity of very early neurodevelopmental testing and the importance of long-term follow-up [90,91]. Forbess et al. also found an independent correlation of length of time under DHCA with lower performance IQ scores at 5 years of age, and this correlation approached significance in other IQ domains [81].

Hematocrit strategy during CPB has also been investigated [40,93] Combined results at 1 year of age from two trials (n = 271) suggest that hematocrit at the initiation of CPB is linearly associated with increasing BSID PDI score to a threshold hematocrit level of 23.5%; beyond this point, the effect plateaus, and no apparent improvement is achieved. There was no significant association between pre-CPB hematocrit level and BSID MDI scores at 1 year. These are very early childhood results; extended follow-up to school age will be valuable.

Length of Hospital Stay

In the BCAS, in which infants with TGA were randomized to DHCA or continuous low-flow CPB, follow-up at 8 years of age revealed impaired outcomes for the overall study group in areas including executive function, fine motor skills, and speech and language [1,30,55]. Although treatment group and other variables were associated with some outcomes, longer postoperative stay in the intensive care unit was an independent risk factor for lower IQ [94]. Others have also found significant or nearly significant independent correlations of length of stay with lower IQ in middle childhood [82,86]. This finding suggests that immeasurable or unmeasured variables may influence hospital course and are associated with adverse long-term outcomes. Events and findings that traditionally keep a child in the hospital longer, such as infection and significant feeding issues, may portend larger and more complex issues. Data on variables such as these should be collected and reported meticulously

in future studies. A continued search to define significant modifiable clinical factors will be critical for the development of protective strategies.

Conclusions

Congenital heart disease may be associated with intrinsic brain malformations, especially when part of a dysgenetic syndrome. Hypoxia and hypotension can then cause preoperative brain injury that can be minimized by appropriate resuscitation. Definitive or palliative repair is then performed, usually with the aid of cardiopulmonary bypass using hypothermia as neuroprotection and avoiding DHCA except where absolutely necessary or minimizing the length of exposure to this maneuver. A range of neurodevelopmental outcomes has been reported for patients after surgery for CHD. Patients with CHD requiring surgery in the neonatal period are at risk for cognitive, academic, and neurologic impairment compared with the general population. Meticulous attention to preoperative and intraoperative management strategies that protect the patient from ischemic or hemorrhagic injury is critical. However, factors such as socioeconomic status also influence developmental progress. Genetic variables, such as the presence of 22q11.2 deletion, are extremely significant predictors of adverse neurocognitive outcomes. CHD is more manageable and its treatment much safer today than at any time in history, but there is still much more to be learned and understood to improve the ultimate outcome for these high-risk infants. Continued vigorous research on the short- and long-term neurologic progress of patients with CHD and identification of factors linked with improved outcomes will allow us to better care for these vulnerable patients and their families.

References

1. Bellinger DC, Wypij D, Kuban KC, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 1999; **100**: 526–32.
2. Majnemer A, Limperopoulos C. Developmental progress of children with congenital heart defects requiring open heart surgery. *Semin Pediatr Neurol* 1999; **6**:12–19.
3. Mahle WT, Wernovsky G. Neurodevelopmental outcomes in hypoplastic left heart syndrome. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2004; **7**:39–47.
4. Trittenwein G, Nardi A, Pansi H, et al. Early postoperative prediction of cerebral damage after pediatric cardiac surgery. *Ann Thorac Surg* 2003; **76**: 576–80.
5. Menache CC, du Plessis AJ, Wessel DL, et al. Current incidence of acute neurologic complications after open heart operations in children. *Ann Thorac Surg* 2002; **73**: 1752–8.
6. Pradat P. Epidemiology of major congenital heart defects in Sweden, 1981–1986. *J Epidemiol Community Health* 1992; **46**: 211–15.
7. Caputo S, Capozzi G, Russo MG, et al. Familial recurrence of congenital heart disease in patients with ostium secundum atrial septal defect. *Eur Heart J* 2005; **26**: 2179–84.
8. Caputo S, Russo MG, Capozzi G, et al. Congenital heart disease in a population of dizygotic twins: an echocardiographic study. *Int J Cardiol* 2005; **102**: 293–6.
9. Cymbron T, Anjos R, Cabral R, et al. Epidemiological characterization of congenital heart disease in Sao Miguel Island, Azores, Portugal. *Community Genet* 2006; **9**: 107–12.
10. Stollenberg C, Magnus P, Skrondal A, et al. Consanguinity and recurrence risk of birth defects: a population-based study. *Am J Med Genet* 1999; **82**: 423–8.
11. Williams GD, Ramamoorthy C. Brain monitoring and protection during pediatric cardiac surgery. *Semin Cardiothorac Vasc Anesth* 2007; **11**:23.
12. Sullivan KE, Jawad KF, Randall P, et al. Lack of correlation between impaired T cell production, immunodeficiency, and other phenotypic features in chromosome 22q11.2 deletion syndromes. *Clin Immunol Immunopathol* 1998; **86**: 141–6.
13. Gothelf D. Velocardiofacial syndrome. *Child Adolesc Psychiatr Clin North Am* 2007; **16**: 677–93.
14. Mokhtar MM, Abdel-Fattah M. Major birth defects amongst infants with Down syndrome in Alexandria, Egypt (1995–2000): trends and risk factors. *East Mediterr Health J* 2001; **7**: 441–51.
15. Ashok M, Thangavel G, Indrani S, et al. Atrioventricular septal defect: associated anomalies and aneuploidy in prenatal life. *Indian Pediatr* 2003; **40**: 659–64.
16. Gaynor JW, Gerdes M, Zackai EH, et al. Apolipoprotein E genotype and neurodevelopment sequelae on infant cardiac surgery. *J Thorac Cardiovasc Surg* 2003; **126**: 1736–45.
17. Mahle WT, Tavani F, Zimmerman RA, et al. An MRI study of neurological injury before and after congenital heart surgery. *Circulation* 2002; **106**: I109–14.

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.038

18. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr* 2002; **141**: 51–8.
19. Miller SP, McQuillen PS. Neurology of congenital heart disease: insight from brain imaging. *Arch Dis Child Fetal Neonatal Ed* 2007; **92**:F435–7.
20. Gaynor JW. Periventricular leukomalacia following neonatal and infant cardiac surgery. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2004; **7**: 133–40.
21. Galli KK, Zimmerman RA, Jarvik GP, et al. Periventricular leukomalacia is common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg* 2004; **127**:692–704.
22. Hsia TY, Gruber PJ. Factors influencing neurological outcome after neonatal cardiopulmonary bypass: what we can and cannot control. *Ann Thorac Surg* 2006; **81**: S2381–8.
23. Licht, DJ, Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg*. 2009; **137**(3): 529–37.
24. Glauser TA, Rorke LB, Weinberg PM, et al. Congenital brain anomalies associated with the hypoplastic left heart syndrome. *Pediatrics* 1990; **85**: 984–90.
25. Hinton RB, et al. Prenatal head growth and white matter injury in hypoplastic left heart syndrome. *Pediatr Res* 2008; **64**(4): 364–9
26. Te Pas AB, van Wezel-Meijler G, Bokenkamp-Gramann R, et al. Preoperative cranial ultrasound findings in infants with major congenital heart disease. *Acta Paediatr* 2005; **94**: 1597–603.
27. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 2007; **357**: 1928–38.
28. McQuillen PS, Hamrick SEG, Perez MJ, et al. Balloon atrial septostomy is associated with preoperative stroke in neonates with transposition of the great arteries. *Circulation* 2006; **113**: 280–5.
29. McQuillen PS, Barkovic AJ, Hamrick SEG, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. *Stroke* 2007; **38**: 736–41.
30. Bellinger DC, Wypij D, duPlessis AJ, et al. Neurodevelopmental status at eight years in children with Dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 2003; **126**: 1385–96.
31. Kurth CD, Priestley M, Watzman HM, et al. Desflurane confers neurologic protection for deep hypothermic circulatory arrest in newborn pigs. *Anesthesiology* 2001; **95**: 959–64.
32. Kawaguchi M, Furuya H, Patel PM. Neuroprotective effects of anesthetic agents. *J Anesth* 2005; **19**: 150–6.
33. Reid RW, Warner DS. Pro: arguments for use of barbiturates in infants and children undergoing deep hypothermic circulatory arrest. *J Cardiovasc Anesth* 1998; **12**: 591–4.
34. Peek GJ, Firmin RK. The inflammatory and coagulative response to prolonged extracorporeal membrane oxygenation, a review. *ASAIO J* 1999; **45**: 250–63.
35. Westaby S, Saatvedt K, White S, et al. Is there a relationship between cognitive dysfunction and systemic inflammatory response after cardiopulmonary bypass? *Ann Thorac Surg* 2001; **71**: 667–72.
36. Stump DA. Embolic factors associated with cardiac surgery. *Semin Cardiothorac Vasc Anesth* 2005; **9**: 151–2.
37. Prasongsukarn K, Borger MA. Reducing cerebral emboli during cardiopulmonary bypass. *Semin Cardiothorac Vasc Anesth* 2005; **9**: 153–8.
38. Ehrlich MP, McCullough JN, Zhang N, et al. Effect of hypothermia on cerebral blood flow and metabolism in the pig. *Ann Thorac Surg* 2002; **73**: 191–7.
39. Neptune WB, Bougas JA, Panico FG. Open-heart surgery without the need for donor-blood priming in the pump oxygenator. *N Engl J Med* 1960; **263**: 111–15.
40. Jonas RA, Wypij D, Roth SJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. *J Thorac Cardiovasc Surg* 2003; **126**: 1765–74.
41. Jaggers JJ, Ungerleider RM. Cardiopulmonary bypass in infants and children. In Mavroudis C, Backer CL, eds., *Pediatric Cardiac Surgery*. St. Louis: Mosby, 2003: 171–93.
42. del Nido PJ, McGowan FX. Surgical approaches, cardiopulmonary bypass in pediatric cardiac surgery. In Sellke FW, Swanson SCJ, del Nido P, eds., *Surgery of the Chest*. Philadelphia: Elsevier Saunders, 2005: 1821–58.
43. du Plessis AJ, Jonas RA, Wypij D, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. *J Thorac Cardiovasc Surg* 1997; **114**:991–1001.
44. Hiramatsu T, Miura T, Forbess JM, et al. pH strategies and cerebral energetics before and after circulatory arrest. *J Thorac Cardiovasc Surg* 1995; **109**: 948–57.
45. Jonas RA. Optimal pH strategy for CPB in neonates, infants and children. *Perfusion* 1998; **13**: 377–87.
46. Scallan MJH. Cerebral injury during pediatric heart surgery: perfusion issues. *Perfusion* 2004; **19**: 221–8.
47. Gravlee GP, Davis RF, Kurusz M, et al. *Cardiopulmonary Bypass: Principles and Practice*,

2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2000:chap. 30.

48. Pigula FA, Siewers RD, Nemoto EM. Hypothermic cardio-pulmonary bypass alters oxygen/glucose uptake in the pediatric brain. *J Thorac Cardiovasc Surg* 2001; **121**: 366 –73
49. Schmid FX, Phillip A, Foltan M, et al. Adequacy of perfusion during hypothermia: regional distribution of cardiopulmonary bypass flow, mixed venous and regional venous oxygen saturation-hypothermia and distribution of flow and oxygen. *Thorac Cardiovasc Surg* 2003; **51**: 306 –11.
50. Kurth CD, Steven JM, Nicolson SC, Jacobs ML. Cerebral oxygenation during cardiopulmonary bypass in children. *J Thorac Cardiovasc Surg* 1997; **113**: 71–9
51. Hanley FL. Religion, politics . . . deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 2005; **130**:1236.
52. Gaynor JW, Nicholson SC, Jarvik GP, et al. Increasing duration of deep hypothermic circulatory arrest is associated with an increased incidence of postoperative electroencephalographicseizures. *J Thorac Cardiovasc Surg* 2005; **130**: 1278–86.
53. Newburger JW, Jonas RA, Wernozsky G, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med* 1993; **329**: 1057–64.
54. Ungerleider RM, Gaynor JW. The Boston Circulatory Arrest Study: an analysis. *J Thorac Cardiovasc Surg* 2004; **127**: 1256–61.
55. Wypij D, Newburger JW, Rappaport LA, et al. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 2003; **126**: 1397–403.
56. Amir G, Ramamoorthy C, Riemer RK, et al. Neonatal brain protection and deep hypothermic circulatory arrest: pathophysiology of ischemic neuronal injury and protective strategies. *Ann Thorac Surg* 2005; **80**: 1955–64.
57. Algra S, et al. Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. *Pediatr Cardiol* 2014; **129**: 224–33
58. Ly M. et al. Continuous cerebral perfusion for aortic arch repair: hypothermia versus normothermia. *Ann Thorac Surg* 2011; **92**: 942–8
59. Austin EH, Edmonds HL, Auden SM, et al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 1997; **114**: 707–16.
60. Sakamoto T, Duebener LF, Laussen PC, et al. Cerebral ischemia caused by obstructed superior vena cava cannula is detected by near-infrared spectroscopy. *J Cardiothorac Vasc Anesth* 2004; **18**:293–303.
61. Kussman BD, Wypij D, Laussen PC, et al. Relationship of intraoperative cerebral oxygen saturation to neurodevelopmental outcome and brain magnetic resonance imaging at 1 year of age in infants undergoing biventricular repair. *Circulation*. 2010; **122**(3): 245–54.
62. Svenarud P, Persson M, van der Linden J. Effect of CO_2 insufflation on the number and behaviour of air microemboli in open-heart surgery: a randomized clinical trial. *Circulation* 2004; **109**: 1127–32.
63. Bronicki RA, Backer CL, Baden HP, et al. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg* 2000; **69**: 1490–5.
64. Checchia PA, Bronicki RA, Costello JM, et al. Steroid use before pediatric cardiac operations using cardiopulmonary bypass: an international survey of 36 centers. *Pediatr Crit Care Med* 2005; **6**: 441–4.
65. Elliott M. Modified ultrafiltration and open heart surgery in children. *Pediatr Anaesth* 1999; **9**:1–5.
66. Rodriguez RA, Ruel M, Broecker L, et al. High flow rates during modified ultrafiltration decrease cerebral blood flow velocity and venous oxygen saturation in infants. *Ann Thorac Surg* 2005; **80**: 22–8.
67. Ungerleider RM, Shen I, Yeh T, et al. Routine mechanical ventricular assist following the Norwood procedure improved neurologic outcome and excellent hospital survival. *Ann Thorac Surg* 2004; **77**:18–22.
68. Peek GJ, Firmin RK. Extracorporeal membrane oxygenation for pediatric cardiac support. *Coron Artery Dis* 1997; **8**: 371–89.
69. Hetzer R, Loebe M, Potapov EV, et al. Circulatory support with pneumatic paracorporeal ventricular assist device in infants and children. *Ann Thorac Surg* 1998; **66**: 1498–506.
70. Edwards AD, Azzopardi D. Hypothermic neural rescue treatment: from laboratory to cotside? *Arch Dis Child Fetal Neonatal Ed* 1998; **78**:F88–91.
71. Liu WG, Qiu WS, Zhang Y, et al. Effects of selective brain cooling in patients with severe traumatic brain injury: a preliminary study. *J Int Med Res* 2006; **34**:58–64.
72. Gunn AJ, Gunn TR, de Haan HH, et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997; **99**: 248–56.
73. Paret G, Tirosh R, Lotan D, et al. Early prediction of neurological outcome after falls in children: metabolic and clinical markers. *J Accid Emerg Med* 1999; **16**: 186–8.

74. Chiaretti A, De Benedictis R, Langer A, et al. Prognostic implications of hyperglycaemia in paediatric head injury. *Childs Nerv Syst* 1998; **14**: 455–9.

75. Macrae D. A randomized trial of hyperglycemic control in the pediatric intensive care unit. *N Engl J Med* 2014; **370**(2): 107–18

76. Steward DJ, DaSilva CA, Flegel T. Elevated blood glucose levels may increase the danger of neurological deficit following profound hypothermic cardiac arrest. *Anesthesiology* 1998; **68**:653.

77. Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. *Pediatr Cardiol* 2007; **28**: 126–33.

78. Mahle WT. Neurologic and cognitive outcomes in children with congenital heart disease. *Curr Opin Pediatr* 2001; **13**: 482–6.

79. Gaynor JW, Wernovsky G, Jarvik GP, et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *J Thorac Cardiovasc Surg* 2007; **133**: 1344–53.

80. Robertson CMT, Joffe AR, Sauve RS, et al. Outcomes from an interprovincial program of newborn open heart surgery. *J Pediatr* 2004; **144**:86–92.

81. Atallah J, Joffe AR, Robertson CMT, et al. Two-year general and neurodevelopmental outcomes after neonatal complex cardiac surgery in patients with deletion 22q11.2: a comparative study. *J Thorac Cardiovasc Surg* 2007; **134**: 772–9.

82. Forbess JM, Visconti KJ, Hancock-Friesen C, et al. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. *Circulation* 2002; **106**:195–202.

83. Hack M, Wilson-Costello D, Friedman H, et al. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g:1992–1995. *Arch Pediatr Adolesc Med* 2000; **154**: 725–31.

84. Hintz SR, Kendrick DE, Vohr BR, et al. Changes in neurodevelopmental outcomes at 18–22 months corrected age among infants born at less than 25 weeks' gestation 1993–1999. *Pediatrics* 2005; **115**: 1645–51.

85. Wernovsky G, Stiles KM, Gauvreau K, et al. Cognitive development after Fontan operation. *Circulation* 2000; **102**: 883–9.

86. Mahle WT, Viconti KJ, Freier C, et al. Relationship of surgical approach to neurodevelopmental outcomes in hypoplastic left heart syndrome. *Pediatrics* 2006; **117**: e90–7.

87. Licht DJ, Wang J, Silvestre DW, et al. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J Thorac Cardiovasc Surg* 2004; **128**: 841–9.

88. Ilke L, Hale K, Fashaw L, et al. Developmental outcome of patients with hypoplastic left heart syndrome treated with heart transplantation. *J Pediatr* 2003; **142**: 20–5.

89. Mahle WT, Clancy RR, Moss EM, et al. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatrics* 2000; **105**: 1082–9.

90. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics* 2005; **116**: 333–41.

91. McGrath E, Wypij D, Rappaport LA, et al. Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D-transposition of the great arteries. *Pediatrics* 2004; **114**:e572–6.

92. Alton GY, Robertson CMT, Sauve R, et al. Early childhood health, growth, and neurodevelopmental outcomes after complete repair of total anomalous pulmonary venous connection at 6 weeks or younger. *J Thorac Cardiovasc Surg* 2007; **133**: 905–11.

93. Wypij D, Jonas RA, Bellinger DC, et al. The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: results from the combined Boston hematocrit trials. *J Thorac Cardiovasc Surg* 2008; **135**: 355–60.

94. Newburger JW, Wypij D, Bellinger DC, et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. *J Pediatr* 2003; **143**:67–73.

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Chapter 38

Neonatal Resuscitation
Immediate Management

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Introduction

Despite the fact that recent studies suggest that postpartum events account for only a fraction of untoward outcomes such as cerebral palsy, mental retardation, and chronic seizure disorders, management of the newborn during the immediate postpartum period is often subject to rigorous scrutiny by malpractice attorneys and their medical consultants. Because the potential for cerebral injury during the intrapartum period is real, it is critical that evidence-based principles of neonatal resuscitation as described in the Neonatal Resuscitation Program (NRP) of the American Academy of Pediatrics (AAP) be applied in an effort to attenuate or even reverse pathologic processes originating in utero.

Adequate maternal cardiac output and arterial oxygen content, in addition to a functioning placenta, serve to support the metabolic needs of the fetus. Disruption of oxygen supply to the fetus may have consequences after birth depending on the severity and duration of decreased oxygen delivery. Anything that affects the health of the pregnant woman may also have adverse effects on the fetus. Fetal oxygen delivery may be impaired by poor maternal cardiopulmonary function such as that seen in cystic fibrosis and cardiomyopathy, altered uterine blood flow as in maternal hemorrhage, chronically or acutely diminished placental perfusion due to pregnancy-induced hypertension and uterine hyperstimulation, or umbilical cord dysfunction as in umbilical cord prolapse. Detection of fetal stress during the intrapartum period relies mainly on monitoring of the fetal heart rate. When a nonreassuring fetal heart rate is present, maneuvers to restore adequate oxygen delivery to the fetus are indicated. These attempts at intrauterine resuscitation include maternal repositioning, intravenous fluid administration, and delivery of oxygen to the mother.

When maternal conditions exist that have the potential to negatively affect the fetus or in fact fetal stress has been detected, communication of this information to the neonatal resuscitation team is mandatory. Of particular importance is the transfer of information concerning events that clearly affect the fetus, such as the presence of severe blood loss at the time of delivery; because the source of the blood loss often cannot be prospectively determined to be maternal or fetal in origin, the team caring for the neonate must be prepared to replace large amounts of volume rapidly in order to successfully resuscitate the potentially hypovolemic newborn. Lack of clear communication and coordination of efforts between obstetric and neonatal healthcare professionals (HCPS) places the stressed newborn in a dangerous situation. In July 2004, the Joint Commission (JC) issued a Sentinel Event Alert detailing 47 cases of neonatal mortality or severe neonatal morbidity reported since 1996 [1]. This alert was updated at the end of 2005 to include a total of 109 cases. Root-cause analyses performed in these cases revealed that inadequate communication played a significant role in the outcome of more than 70% of the cases. In response to these findings the JC recommended that healthcare facilities where newborns are delivered conduct team training and debriefings such as those pioneered at the Center for Advanced Pediatric and Perinatal Education at Stanford (CAPE, www.cape.stanford.edu).

This chapter first outlines the appropriate steps and current evidence behind cardiopulmonary resuscitation of the newborn. Stabilization after cardiopulmonary resuscitation will also be reviewed. Finally, the principles guiding delivery room decision making, focused on decreasing neurologic morbidities in the perinatal period, will be discussed.

Evidence-Based Resuscitation Medicine

Over the past several decades, a concerted effort has been made to improve the care of the newborn infant

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by basing all treatment guidelines on the best evidence available in the medical literature. Spearheading this effort is the International Liaison Committee on Resuscitation (ILCOR). ILCOR is composed of representatives from the American Heart Association (AHA), the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Resuscitation Council of Southern Africa, the Australian and New Zealand Committee on Resuscitation, the Inter-American Heart Foundation, and the Resuscitation Council of Asia. The mission of ILCOR is to provide a regular international forum for review and discussion of resuscitation practices and the evidence (or lack thereof) supporting them. Task forces composed of ILCOR members are assigned to review the scientific literature on specific issues in resuscitation and to prepare both written and verbal reports on their findings. The task forces meet with other scientists and clinicians over a period of 5 years; their work culminates in a meeting of the ILCOR group at large, where consensus is reached as to the quality of the science behind current clinical practices. This review of the science is published as a document called the *International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science and Treatment Recommendations* (CoSTR). Once the review of the science is available, each national or regional resuscitation council then uses this review to determine its own treatment recommendations. The most recent review of evidence occurred in 2015, and those recommendations have been incorporated into the NRP [2–4].

Cardiopulmonary Resuscitation of the Newborn

Anticipation and Planning

Most newborns will not require resuscitation in the delivery room. Prenatal findings that are consistent with a smooth transition to extrauterine life include full-term gestation, no history or evidence of fetal infection, clear amniotic fluid, and no evidence of fetal stress on fetal heart rate monitoring. In circumstances where these conditions are present, the newborn should be dried and stimulated, the airway should be cleared if necessary, heart rate and respiratory effort should be assessed, and the infant should be placed on the mother's chest to maintain normothermia if her condition allows [2–4]. Because it is impossible to predict with absolute certainty which fetuses will present as neonates in distress, those responsible for caring for the newborn in the delivery room must always be prepared to deliver whatever level of care is required. Approximately 10% of newborns will require support of breathing efforts in the delivery room, and 1% will require more extensive resuscitation [5]. Anticipation of the infant who will require resuscitation will be facilitated by clear communication with the obstetric team. Essential information that needs to be obtained prior to or immediately on entry into the delivery room by the neonatal resuscitation team includes the gestational age of the fetus and the number of fetuses being delivered. This information allows the neonatal team to begin preparations for resuscitation. Other information specific to the condition of the mother or fetus(es), including chronic conditions such as intrauterine growth restriction and acute emergencies such as uterine rupture, will also prove helpful to the neonatal team.

Appropriately Trained Personnel

Professionals trained in neonatal resuscitation must be readily available 24 hours a day in any hospital that offers obstetric services [6]. According to the *Textbook of Neonatal Resuscitation*:

> Every birth should be attended by at least one qualified individual skilled in the initial steps of newborn care and PPV, whose only responsibility is management of the newborn baby. If risk factors are present, at least two qualified people should be present solely to manage the baby. The number and qualifications of personnel will vary depending on the anticipated risk, the number of babies and the hospital setting. A qualified team with full resuscitation skills, including endotracheal intubation, chest compressions, emergency vascular access and medication administration, should be identified and immediately available for every resuscitation. The resuscitation team should be present at the time of birth if the need for extensive resuscitation measures is anticipated. It is not sufficient to have the team with these advanced skills on call at home or in a remote area of the hospital. When resuscitation is needed, it must begin without delay [5].

When delivery of a stressed infant is anticipated, responsibility for various aspects of the resuscitation should be delegated to each team member prior to delivery. These tasks depend on the problems anticipated. One team member should attend to the airway and assist breathing, if necessary. Another team member should palpate the umbilical cord or ausculate the chest to assess the heart rate, provide this information

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to the team, and initiate chest compressions if required. A third professional should assume responsibility for other procedures such as umbilical venous cannulation or thoracentesis. If necessary, other team members should prepare and administer drugs and record the progress of the resuscitation. Ideally, the team member directing the resuscitation should not be responsible for any of these tasks so that he or she can focus full attention on the overall condition of the neonate and the performance of the entire team. Also, in an ideal situation, documentation of the techniques used, timing of interventions, the use and dosage of medications, and the response of the newborn to these procedures should be delegated to an individual who is not directly involved in the resuscitation. Documentation of the events of a resuscitation in a post hoc manner via recall is suboptimal at best and creates a situation that is ripe for misrepresentation and misunderstanding, potentially leading to serious legal consequences.

Equipment

In any situation where resuscitation may be needed, appropriate equipment must be readily available (Table 38.1). Equipment should be located in a clearly identified clean and warm environment in close proximity to the location of birth. This equipment must be checked periodically to ensure that all items are readily accessible and are in working order. If the newborn nursery is not adjacent to the delivery room, additional equipment may need to be located in the delivery room to allow more thorough stabilization of the newborn prior to transfer to the nursery. Ready access to equipment allowing blood gas, hematocrit, and glucose determinations is also important. Other equipment, supplies, and items may also be required. For example, blood products should be available for infants with severe isoimmune hemolytic disease or blood loss due to placental abnormalities such as vasa previa, large-bore intravenous catheters should be available to drain large pleural or pericardial effusions, and other items may be mandated by unique clinical situations. Finally, universal precautions should be observed by all professionals in the delivery room. Every team member should wear gloves and other protective devices as necessary.

Delayed Cord Clamping

Until recently, it was common practice to clamp the umbilical cord of a newborn immediately after birth. However, evidence now exists that a delay in cord clamping actually facilitates a smoother transition for the neonate, particularly if additional resuscitation is not required. Current evidence suggests that delayed cord clamping decreases the overall incidence of intraventricular hemorrhage (IVH), although there has been no decrease in severe IVH or neonatal death [2–4,7]. Studies indicate that delayed cord clamping produces an increased mean blood pressure at 4 hours of life, less need for postnatal blood transfusion, and a lower incidence of necrotizing enterocolitis. While neonates have been shown to have a higher peak bilirubin concentration following delayed cord clamping, there is no evidence for an increase in pathologic hyperbilirubinemia requiring treatment [8]. There also has been no statistically significant difference in neonatal admission temperatures. Importantly, at the time the evidence was reviewed by ILCOR members in 2015, there were no studies that examined the impact of delayed cord clamping on future neurodevelopment. Following the review of this evidence, it was recommended that cord clamping be delayed for 30–60 seconds for most vigorous term and preterm newborns. Insufficient evidence currently exists to recommend delayed cord clamping for newborns requiring resuscitation at birth. In the case of nonintact placental circulation (i.e., placental abruption, bleeding vasa previa, cord avulsion), the cord should be immediately clamped after birth regardless of the status of the newborn.

Cord milking or the process of stripping the umbilical cord from the placental side toward the newborn has also been recently evaluated. This method is of particular interest for preterm neonates or those needing resuscitation due to the presumed rapid transfer of fetal blood to the placenta. In light of absent long-term neurologic outcome data, as well as the imprecision present in studies to date, cord milking is not recommended on infants born at 28 weeks' gestation or less [9–10]. Several large randomized, controlled trials are currently underway to investigate the benefits and risks of delayed cord clamping and cord milking.

Rapid Cardiopulmonary Assessment in the Delivery Room

Immediate assessment of the stressed neonate by experienced HCPs is critically important. This should begin with immediate assessment of the neonate's heart rate, respiratory effort, color, tone, and response to stimulation immediately after birth. Reevaluation

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Table 38.1 Equipment for Neonatal Resuscitation

Suction equipment	Bulb syringe
	Wall/mechanical suction and tubing
	Suction catheters: 5–6F, 8F, 10F, 12–14F
	Feeding tube 8F, syringe (20 mL)
	Meconium aspirator
Positive-pressure ventilation equipment	Device for delivering positive-pressure ventilation (PPV): self-inflating or flow-inflating bag or T-piece resuscitator
	Face masks (premature and newborn): cushioned rims
	Oxygen/compressed air source
	Oxygen blender with flowmeter (target 10 L/min) with tubing
	Pulse oximeter with sensor and cover
	Target oxygen saturation table
Intubation equipment	Laryngoscope handle, batteries
	Laryngoscope blades (00, 0, 1), bulbs
	Endotracheal tubes: 2.5, 3.0, 3.5
	Laryngeal mask airway
	Oropharyngeal airways
	Scissors
	Device to secure endotracheal tube or tape
	Alcohol wipes
	CO_2 detector or capnography
Medications	Epinephrine 1:10,000 (1.0 mg/mL)
	100–250 mL isotonic crystalloid
	Normal saline flushes
	Umbilical vessel catheterization kit
	Syringes: 1, 3, 5, 10, 20, 50 mL
	Needles: 25, 21, 18 gauge
Miscellaneous	Personal protection gear
	Radiant warmer or heat source
	Resuscitation area: firm, padded
	Apgar timer or timer with second hand
	Warm blankets or towels
	Stethescope (neonatal)
	Tape
	Cardiac monitor/electrodes
	Pulse oximeter and probes
	Laryngoscope blade 00
Umbilical vessel catheterization supplies	Sterile gloves
	Antiseptic prep solution
	Umbilical tape
	Hemostat

Table 38.1 (cont.)

	Scalpel
	Umbilical catheters, single lumen (3.5F or 5F)
	Three-way stopcock
	Syringes (3–5 mL)
	Normal saline for flushes
	Clear adhesive dressing to temporarily secure umbilical venous catheter to abdomen (optional)
Very premature babies	Plastic wrap
	Warming pad (chemical activated)
	Transport incubator to maintain baby's temperature during move to the nursery

Source: Adapted from Weiner, *Neonatal Resuscitation Textbook*, 7th edn [5].

of heart rate, respirations, and color during the resuscitation provides an assessment of the efficacy of the resuscitative measures and the need for continued or more aggressive interventions. Apgar scores should be assigned and recorded at 1 minute, 5 minutes, and every 5 minutes thereafter until a score of 7 or more is attained.

The NRP algorithm for neonatal resuscitation has been developed to guide HCPs in caring for the newborn regardless of the setting or cause of distress (Figure 38.1) [5]. After the initial rapid cardiopulmonary assessment is complete, during which time drying, wiping, and placing the infant on prewarmed dry linens in a warm environment is taking place, the ABCD (airway, breathing, circulation, drugs) approach to resuscitation should be carried out.

Maintaining Neonatal Temperature

It has been well established that hypo- and hyperthermia contribute significantly to neonatal morbidity and mortality. Premature neonates are especially vulnerable to excessive heat loss due to their relatively large surface-area-to-volume ratio and evaporative skin losses. In fact, preterm neonates who experience hypothermia following birth have a higher mortality than those remaining normothermic. This increased mortality risk is related to the degree of hypothermia (28% increased risk of mortality for each 1°C below 36.5°C) and the size of the neonate (increased mortality risk in smaller infants) [11,12]. Therefore, it is recommended that in nonasphyxiated neonates normothermia (36.5–37.5°C axillary) be achieved and maintained. Because admission temperature is a strong predictor of morbidity and mortality, it has been recommended that it be routinely recorded as a quality-of-care indicator [2–4].

In an effort to decrease inadvertent hypothermia during neonatal resuscitation, ILCOR recommends that neonates who are less than 32 weeks of gestational age (GA) be resuscitated under a radiant warmer and in a temperature-controlled environment (23–25°C [74–77°F]). Additionally, they should be placed on a thermal mattress, covered in plastic wrap without drying, and provided with a thermal cap to reduce heat loss.

Airway

Several techniques may be used to clear the upper airway. Secretions near the surface can be wiped away with a towel or gauze pad. A bulb syringe can be used to clear the mouth and nose after delivery, if necessary. Suction catheters can be used to reach deeper into the airway, but team members must be aware that vigorous and aggressive suctioning of the pharyngeal region can cause laryngeal spasm and vagally mediated bradycardia and should be reserved for infants in whom bulb suctioning was unsuccessful in clearing the airway [13]. If required, the newborn can also be intubated and a meconium aspirator used to remove additional material from the airway.

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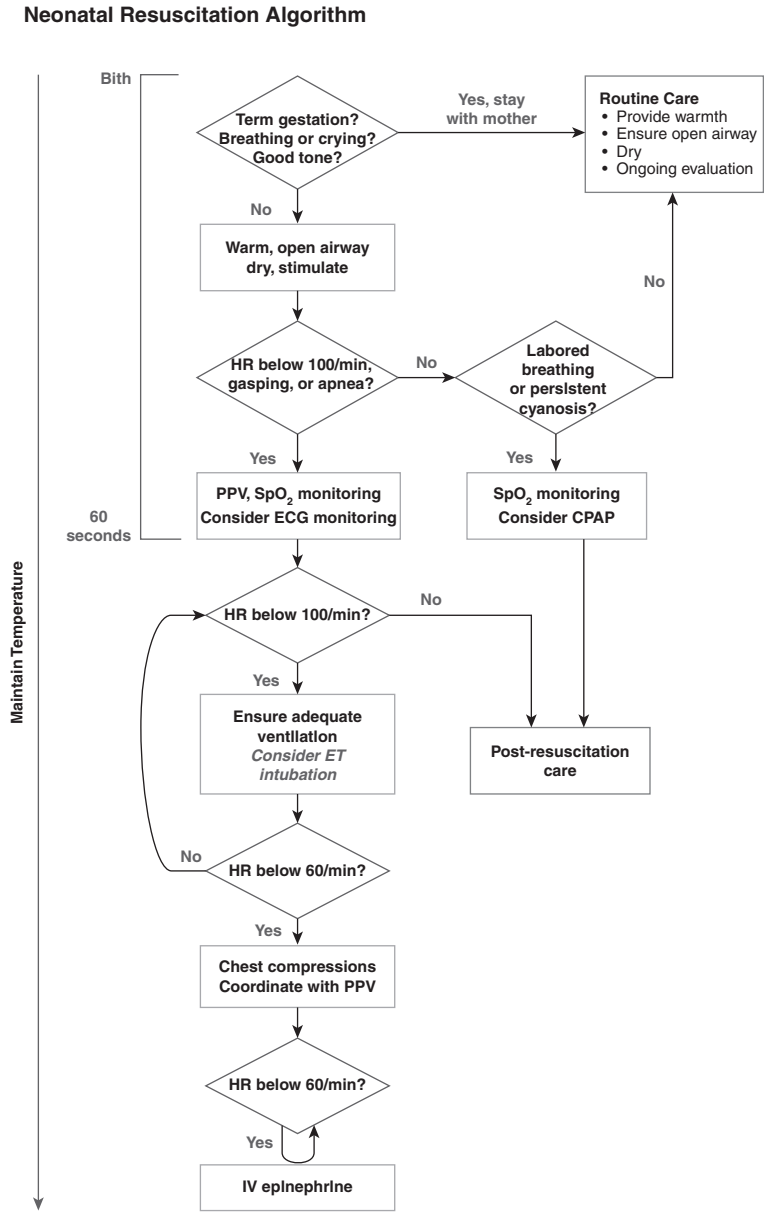


Figure 38.1 Neonatal resuscitation algorithm (pediatrics) [2–4].

Management of the Infant with Meconium Staining of the Amniotic Fluid

The presence of meconium in the amniotic fluid places the newborn at risk for meconium aspiration. Meconium aspiration is a potentially life-threatening pulmonary disease and is discussed at length in Chapter 36. Obstetric and neonatal management of the infant with meconium-stained fluid at delivery has changed dramatically in the past decade as more evidence regarding the efficacy of traditional therapies has been generated. A large prospective multicenter randomized controlled international trial did not show a reduction in meconium aspiration syndrome with perineal suctioning; thus suctioning of the naso- and oropharynx while the fetal head is on the perineum is no longer routinely recommended [14]. Another large prospective multicenter randomized

controlled international trial revealed that neonates with meconium-stained fluid who are *vigorous* at birth (i.e., demonstrating adequate respirations, heart rate above 100 beats/minute, and good muscle tone) do not benefit from endotracheal intubation and suctioning immediately after birth, and this once-routine practice is no longer indicated [15,16]. One of the most significant changes to the 2015 guidelines is that immediate intubation of nonvigorous and apneic neonates is no longer recommended. Following review of the literature, it was determined that there is not sufficient evidence to suggest that intubating and suctioning nonvigorous neonates born through meconium-stained amniotic fluid is beneficial [17]. In fact, it has been speculated that these intubation attempts may delay appropriate ventilation and resuscitation of these infants.

Breathing (Ventilation)

Newborns should be placed supine with the head and neck in a "sniffing" position to open the airway. Effective stimulation may be all that is required to elicit an appropriate response in an infant who is cyanotic and/or bradycardic. For those requiring additional support, positive-pressure ventilation (PPV) with a facemask may be used. The facemask should have a cushioned rim and provide a seal around the mouth and nose to prevent leakage of air. Creating and maintaining a good seal on the newborn's face are critical components of ventilation with a facemask, and acquisition and maintenance of this technical skill require practice. A small dead space of 5 mL or less is desired. The pressure required to establish effective ventilation varies with each patient, but the peak inspiratory pressure (PIP) and duration of inspiration (inspiratory time) should be sufficient to achieve chest excursion, audible breath sounds, and improvement in heart rate. Initial ventilation pressures should start with a PIP of 20–25 cm H_20, a respiratory rate of 40–60 breaths/min, and gas flow of 10 L/min [18]. Regardless of the device delivering PPV, positive end-expiratory pressure (PEEP) at a level of 5 cm H_20 should be provided in order to maintain lung inflation between breaths. However, current evidence recommends *against* the use of sustained lung inflation (>5 seconds) for newborns without spontaneous respirations immediately following delivery [1].

The types of resuscitation devices used to provide PPV with a facemask include the self-inflating bag, the flow-inflating bag, and the T-piece resuscitator. Bennett et al. compared these three devices and found that while the T-piece increased the PIP over a longer period of time, the maximum pressure delivered decreased with each ventilation. The T-piece and the flow-inflating bag were better able to maintain a more sustained inflation pressure than the self-inflating bag. The technical skill necessary to use the flow-inflating bag effectively requires more practice than either the self-inflating bag or the T-piece resuscitator [19].

The 2015 guidelines also indicate that the placement of a three-lead electrocardiographic (ECG) monitor should be considered when PPV is initiated for improved and continuous monitoring of the neonate's heart rate. However, as leads are being placed, an assistant should also listen for an increasing heart rate for at least the first 15 seconds of PPV [2–4].

Effective PPV should be established prior to proceeding to chest compressions or medication administration. The markers of effective PPV include an increase in heart rate, bilateral chest rise, bilateral breath sounds, and detection of CO_2 by capnography or change in color of a colorimetric device.

If successful PPV has not been established, additional corrective steps to optimize PPV include adjusting the position of the mask, repositioning of the airway, suctioning of the mouth and nose, opening of the mouth, increasing the pressure, and using an alternative airway. The mnemonic MRSOPA is useful in remembering the sequence of these steps (Table 38.2). Failure to respond to PPV via facemask indicates that an alternative airway is necessary. This can include an endotracheal tube or laryngeal mask airway (LMA) placed by a HCP experienced with these techniques. Other indications for endotracheal intubation include medication administration when other routes are unavailable, conditions where gastrointestinal obstruction complicates ventilation, and when chest compressions are being conducted [2–4]. Endotracheal intubation provides control of the airway even during chest compressions. It is recommended that newborns weighing 2 kg or more should be intubated with a size 3.5 endotracheal tube (ETT) rather than a size 4.0 ETT. The correct insertion depth of an ETT should be approximated by a tip-to-lip or nasal-tragus length measurement rather than the vocal cord guide on the tube [18]. Proper positioning of the ETT is best ascertained by the auscultation of equal bilateral breath sounds

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Table 38.2 Technique for Improving PPV by Mask

	Corrective steps	Actions
M	Mask adjustment	Reapply mask. Consider the 2-hand technique.
R	Reposition airway	Place head neutral or slightly extended
Try PPV and reassess chest movement		
S	Suction mouth and nose	Use a bulb syringe or suction catheter
O	Open mouth	Open the mouth and lift the jaw forward
Try PPV and reassess chest movement		
P	Pressure increase	Increase pressure in 5 to 0 cmH_20 increments (Maximum 40 cmH_20)
Try PPV and reassess chest movement		
A	Alternative airway	Place and endotracheal tube or laryngeal mask
Try PPV and reassess chest movement and breath sounds		

Source: Adapted from Weiner, *Neonatal Resuscitation Textbook*, 7th edn [5].

in the axillae and improvement in heart rate and color. Equal chest wall excursion, absence of air entry into the stomach, and the presence of mist in the ETT are other indirect markers of proper placement. Devices that indicate the presence of CO_2 in exhaled breaths by a change in color should be used to confirm proper tube placement. However, caution must be exercised because false-negative readings may occur during poor pulmonary perfusion, cardiac arrest, congenital heart disease, incomplete exhalation, and excessive air leak around the tube [20,21].

In circumstances where the infant (>34 weeks' GA) cannot be adequately ventilated with a facemask and intubation has not been successful or is outside the skill set of the resuscitation team members present, placement of a laryngeal mask airway (LMA) may be considered in order to provide a temporary airway. Based on evidence from three randomized controlled trials, ventilation via LMA is equivalent to ventilation via facemask [22]. Furthermore, in a separate randomized concurrent control study of 40 term newborns who received either endotracheal intubation or LMA following delivery by cesarean section, Esmail et al. compared insertion time, attempts at successful insertion, duration of PPV and continuous positive airway pressure (CPAP), hemoglobin oxygen saturation, Apgar scores, and trauma related to insertion and concluded that the LMA is an easy and effective means of managing a neonatal airway [23].

CPAP is recommended as a way to support ventilation in newborns who are spontaneously breathing but who continue to display increased work of breathing or suboptimal oxygenation as in preterm infants with respiratory distress syndrome (RDS). CPAP delivers oxygen to the lungs under sustained pressure and has been found to be effective at establishing functional residual capacity (FRC), reducing the work of breathing, and facilitating exchange of oxygen and carbon dioxide. Maintaining patency of the upper airway and establishing FRC can be problematic for preterm infants due to surfactant deficiency and inadequate inspiratory pressure [24–27]. CPAP effectively expands the lung, establishes FRC, and improves gas exchange [28–31]. Excessive CPAP, however, can increase pressure in the chest, reducing cardiac output and increasing the work of breathing for the newborn; it has also been associated with pneumothorax.

Use of Oxygen

Oxygen is a drug, and like all drugs, it possesses potentially toxic as well as therapeutic actions. Inappropriate use of oxygen has been associated with the development of acute lung injury (acute respiratory distress syndrome [ARDS]), chronic lung injury (bronchopulmonary dysplasia [BPD]), and retinopathy of prematurity (ROP). While historically most centers in the United States used 100% oxygen in neonatal resuscitation, studies indicate

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concentrations as low as room air (21%) for term newborns are equal to or more effective than 100% oxygen [32–35]. Saugstad et al. conducted a prospective multicenter international (both developed and developing countries) controlled trial of 21% versus 100% oxygen in 609 newborns weighing more than 999 g at birth. The study involved 288 neonates in the 21% oxygen group and 321 in the 100% oxygen group. The incidence of hypoxic-ischemic encephalopathy (HIE) did not differ between the groups, but the newborns resuscitated with 21% oxygen recovered more quickly than those resuscitated with 100% oxygen. Neurologic follow-up of 213 infants at 18 and 24 months of age revealed no significant differences in the incidence of neurodevelopmental handicap or rate of growth between the two groups [33,35]. Vento et al. confirmed these results in another study involving fewer patients and also showed that oxidative stress (as measured by the ratio of reduced to oxidized glutathione) was significantly higher in patients resuscitated with 100% oxygen [36]. In a follow-up study, the same authors confirmed their earlier findings of increased oxidative stress in 106 full-term asphyxiated infants randomized to resuscitation with either 21% or 100% oxygen [37].

Research has demonstrated that starting resuscitation with 21% oxygen for neonates more at than 35 weeks' GA does not increase their morbidity and mortality. Guidelines recommend subsequent oxygen concentration titration for infants requiring additional resuscitation who do not meet target saturations (Table 38.3). Specifically, 100% supplemental oxygen should be used when chest compressions are required. In 2015, ILCOR reviewed evidence from five randomized, controlled trials that enrolled 468 subjects comparing the outcomes of neonates in whom resuscitation was initiated with high oxygen concentrations (50–100%) versus low oxygen concentration (21–30%); high oxygen concentrations did not reduce mortality, BPD, IVH, or ROP [38–42]. In light of the lack of evidence supporting high oxygen concentrations, resuscitation in neonates at less than 35 weeks should be initiated with low oxygen concentrations (21–30%) [2–4].

In 2010, the guidelines included the recommendation to place a preductal SpO_2 monitor in the delivery room. Oxygen saturation targets were established (Table 38.3) indicating that approximately 10 minutes is required to reach normal levels following the transition from the hypoxic in utero environment. The fraction of inspired oxygen delivered to the patient should be titrated based on the saturation goals listed in Table 38.3.

Table 38.3 Target Preductal Oxygen Saturations Following Delivery

1 min	60–65%
2 min	65–70%
3 min	70–75%
4 min	75–80%
5 min	80–85%
10 min	85–95%

Source: Adapted from Kattwinkel, *Neonatal Resuscitation Textbook*, 6th edn [5].

Cardiac Output

If the heart rate remains less than 60 beats/minute despite effective PPV for at least 30 seconds, cardiac compressions should be initiated [5]. To ensure effective PPV prior to starting chest compression, an alternative airway should be placed (ETT or LMA). Chest compressions should be performed with the hands encircling the thorax and the thumbs placed on the lower third of the sternum. The compression depth varies depending on the size of the infant but should be one-third of the anteroposterior diameter of the chest. Compressions and breaths should be coordinated in a compression-to-breath ratio of 3:1, with 90 compressions and 30 breaths occurring each minute. Compressions should be continued until a heart rate greater than 60 beats/minute is achieved. An electronic cardiac monitor is the preferred method for assessing heart rate rapidly, accurately, and continuously while resuscitation is being performed.

In most situations, ventilation and chest compressions will be sufficient to stimulate an improvement in heart rate and restore adequate cardiac output. Should the heart rate remain less than 60 beats/min even with chest compressions, the use of inotropic and chronotropic medications is indicated. The endotracheal tube may serve as an initial route of delivery of epinephrine, but endotracheal administration of medication should not delay securing intravascular access via the umbilical vein. Vascular access is usually achievable within minutes by cannulation of the umbilical vein or by

intraosseous line placement [43,44]. Under emergency conditions, an umbilical venous catheter is inserted to a depth of 2–4 cm below the skin surface until blood can be withdrawn freely; once in this position, medications and volume can be given in a manner identical to that used with a central venous line. The catheter should not be advanced beyond this point because in the absence of radiologic conformation of its position, it could cause injury to the liver, intestine, or heart. Any umbilical venous catheter placed emergently should be removed once the patient has been resuscitated and a new catheter placed under sterile conditions and confirmed by x-ray to be in good position if central venous access continues to be required. The umbilical artery is a less than an ideal site for the administration of vasoactive medications due to the risk of vasospasm, and cannulation of the artery typically requires more time than cannulation of the vein; thus the umbilical vein is the recommended route for delivery of medications to the newborn in distress in the delivery room. An umbilical venous catheter also provides a portal for sampling venous blood gases; this is a useful adjunct to physical examination during extended resuscitations.

Special attention should be paid to the positioning of the resuscitation team, especially when chest compressions have been initiated. To make room for umbilical venous catheter placement, the compressor should move to the head of the bed, while the person responsible for ventilating though an alternative airway should move to the patient's side.

When intravascular access is warranted but the HCPs in attendance in the delivery room are unable to place an umbilical venous catheter, the team should consider placement of an intraosseous catheter. These catheters should be readily available on IV access and code carts and can be quickly placed into the marrow space of the tibia when emergent conditions dictate. Any medication or fluid that can be delivered into a central venous catheter can be delivered into the marrow. Physicians in hospital emergency departments should be very familiar with the placement and use of these devices and should be called on to assist with or perform the procedure if needed [45–47]. This technique is not recommended in small preterm neonates, who have fragile bones and relatively small intraosseus spaces. As a caveat, medications should never be given directly into the heart because the risk of coronary artery laceration, myocardial infarction, and pneumo- or hemopericardium with resulting cardiac tamponade is too great.

Epinephrine

Epinephrine has both α-adrenergic and β-adrenergic effects and is the medication used during resuscitation when the heart rate remains below 60 beats/min despite adequate PPV for 30 seconds and chest compressions for an additional 60 seconds. It should be delivered intravenously but also can be given via an endotracheal tube while intravenous access is being secured. The intravenous dose is 0.1–0.3 mL/kg of the 1/10,000 solution, and this dose may be repeated every 3–5 minutes until the heart rate improves to above 60 beats/minute. When delivered by the endotracheal tube, a higher dose (0.5–1.0 mL/kg) is required [48]. If an endotracheal dose is not effective, a dose of intravascular epinephrine should be given immediately when access is achieved, even if it has been less than 3–5 minutes between doses. The efficacy of epinephrine is reduced when the systemic pH is less than 7.1. Side effects include tachycardia, vasospasm, and tissue necrosis should extravasation occur.

Volume Resuscitation

The cardiac ventricles of neonates are less compliant than those of adults, and additional expansion of an already adequate vascular volume does not produce significantly increased cardiac output [49]. Nonetheless, inadequate end-diastolic pressure due to decreased intravascular volume is one of the most common correctable causes of decreased cardiac output in neonates, and hypovolemia should be suspected in a newborn who appears to be poorly perfused despite an adequate heart rate and PPV. This condition should be expected in several clinical conditions such as abruptio placentae, vasa previa, and hydrops fetalis. Hypovolemia may manifest as respiratory distress in the absence of readily apparent pulmonary disease or refractory hypoxemia in a newborn who is easily ventilated. If hypovolemia is suspected, the best diagnostic procedure is also therapeutic: administration of 10 mL/kg of isotonic saline. In a delivery room resuscitation situation, clinical indicators of efficacy include improved perfusion, better color, and correction of tachycardia. When possible, invasive measurement of central venous pressure is a useful guide to assess the adequacy of intravascular volume and any need for replacement.

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Crystalloid and Colloid Solutions

Isotonic saline solution should always be readily available because it has the advantage of being both inexpensive and an effective treatment for hypotension. Isotonic crystalloid is effective in the treatment of hypotension, as demonstrated in several randomized, controlled trials [50–52]. Of note, lactated Ringers solution is no longer recommended for use in the delivery room [2–4]. Colloid, in the form of cytomegalovirus-negative, type-specific or type O, Rh-negative blood crossmatched against the mother's blood, should be made available when acute blood loss or anemia is anticipated. Uncrossmatched type O, Rh-negative blood can also be used in emergencies, although transfusion reactions may occur. The hematocrit level should be measured approximately 4 hours after the last transfusion to determine whether additional transfusions are required.

Stabilization after Cardiopulmonary Resuscitation

Glucose

The cessation of glucose delivery via the placenta at the time of birth predisposes the neonate to hypoglycemia, yet under normal circumstances the term neonate is able to initiate gluconeogenesis and mobilize hepatic glycogen to maintain blood glucose levels in the normal range (40–60 mg/dL). Blood glucose levels do fall after birth, often to less than 30 mg/dL, typically achieving a nadir at about 1 hour of age; this decrease in glucose level acts as a stimulus to glycogen breakdown and gluconeogenesis, resulting in normal glucose levels by 2 hours of age in healthy term newborns even without feeding or other intervention [53]. Neonates who are small for gestational age or premature are at much higher risk of hypoglycemia secondary to diminished glycogen stores and impaired gluconeogenesis. Infants of diabetic mothers are another at-risk group because they have increased glucose utilization, impaired gluconeogenesis, and a relative inability to mobilize hepatic glycogen stores. Fetal exposure to β-mimetic drugs (such as tocolytics) results in increased insulin secretion and exhaustion of hepatic glycogen. Hypoxia, hypothermia, hyperthermia, and infection also predispose the newborn to hypoglycemia. When hypoglycemia is documented, intravenous administration of glucose (200–300 mg/kg or 2–3 mL/kg of 10% dextrose solution in water) should be followed by a continuous infusion of glucose at 6–8 mg/kg per minute. Management of hypoglycemia in the neonate is discussed in more detail in Chapter 26.

Sodium Bicarbonate

Oxidative metabolism depends on maintaining a balance between oxygen delivery and oxygen consumption. As the delivery-to-consumption ratio approaches 2:1, tissues begin to shift to anaerobic metabolism and generate lactic acid. When the oxygen delivery-to-consumption ratio remains unbalanced for a sustained period of time because of inadequate oxygen content in the blood (e.g., anemia, hypoxia), low oxygen delivery (e.g., bradycardia, hypotension), or increased oxygen consumption (e.g., sepsis, hyperthermia), diminished myocardial function, increased systemic and pulmonary vascular resistance, impaired response to catecholamines, inhibition of oxidative glucose metabolism, and impairment of other cellular functions result. Correction of acidemia can result in improved cardiac output, tissue perfusion, and substrate utilization.

Metabolic acidosis caused by the accumulation of lactic acid after a short period of either decreased oxygen delivery or increased oxygen consumption usually corrects spontaneously once oxidative metabolism is reestablished and the lactate is converted to pyruvate. Because of this fact, emphasis during neonatal resuscitation is placed on achieving and maintaining adequate ventilation and oxygenation rather than on pharmacologic treatment of metabolic acidosis with sodium bicarbonate. Sodium bicarbonate is eventually converted to CO_2, which must be exhaled from the lungs before it, too, adds to the acid load in the body; therefore, adequate ventilation must be established prior to administering sodium bicarbonate [54]. In fact, the blood pH does not increase and the CSF pH decreases after bicarbonate administration unless adequate alveolar ventilation ensures excretion of the carbon dioxide generated by the buffer reaction [55]. Overcorrection of the pH early in resuscitation may be detrimental because significant metabolic alkalosis impairs the dissociation of oxygen from hemoglobin and may actually impede oxygen delivery. Rapid infusion of hypertonic solutions such

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as sodium bicarbonate have been associated with altered blood flow and subsequent organ injury [56,57]. Sodium bicarbonate administration only "buys time" in providing a temporary correction in pH, and ultimately, the underlying cause of the acidosis must be treated for the patient to survive. For all these reasons, the use of sodium bicarbonate during resuscitation is no longer routinely recommended [58].

Naloxone

Naloxone is a pure opiate antagonist that had been recommended previously for the reversal of respiratory depression resulting from narcotic administration. Administration of naloxone to a neonate whose mother is a narcotic or methadone user may precipitate seizures, pulmonary edema, or cardiac arrest. Naloxone should *not* be given in the delivery room. The most appropriate management of the neonate with respiratory depression suspected to be secondary to maternal narcotic administration usually is to support the patient's respirations as needed and transfer him or her to the nursery, where the patient can be monitored continuously and more information can be obtained from the obstetric team and from ongoing examination of the newborn. Naloxone has not been shown in human neonates to affect respiratory depression due to asphyxia and is not recommended for use in that circumstance [59].

Cerebral Resuscitation

While the focus during neonatal resuscitation historically has been on restoring cardiac and pulmonary function, protecting the brain is now receiving increasing attention because a burgeoning body of evidence suggests that it is possible to ameliorate, if not reverse, the cerebral dysfunction and injury caused by inadequate oxygen delivery. An established therapy that specifically addresses cerebral injury is the use of hypothermia. In randomized, controlled trials, cooling of the head or the entire body was accomplished in infants at greater than 35 weeks' GA with indicators of hypoxic-ischemic injury including encephalopathy, need for respiratory support beyond 10 minutes of age, an Apgar score of less than 5 at 10 minutes, pH less than 7.0 or base deficit greater than 16 mmol/L on initial blood gas, or seizures consistent with a diagnosis of hypoxic-ischemic encephalopathy (HIE). Hypothermia following an acute perinatal event was found to be most effective in those infants (>35 weeks) with moderate to severe encephalopathy and additional criteria for hypothermia who underwent 72 hours of cooling to a temperature range of 33–34°C [22]. While the safety and efficacy of cooling in neonates at less than 36 weeks' GA is unknown at the time of this publication, trials examining this issue are ongoing.

Delivery Room Decision Making

The delivery room is the scene of many emotionally laden and ethically challenging situations that potentially carry lifelong consequences for newborns and their families. However, it should not be a place where difficult and irrevocable decisions are made without the availability of important objective data and the knowledge of parental desires. Deciding whether to initiate, forgo, or terminate resuscitation is often both intellectually challenging and emotionally draining. Situations where the presumed gestational age is at the borderline of viability or where the presence of malformations or other conditions clouds potential long-term outcome can be particularly challenging. Wishes of the parents should be considered but sometimes are unknown, discordant, or at odds with those of the HCPs charged with caring for the newborn [60,61]. An editorial by Saigal on the limits of viability points out the fact that predicting survival based on outcomes of groups of patients is intrinsically inaccurate when applied to an individual patient [62]. Furthermore, the likelihood of impairment in individual patients is even less predictable [63–67]. The same critical issues apply to all infants who have birth injuries and uncertain prognoses. In all these instances, parental input becomes of paramount importance [68–70].

Stevenson and Goldworth point out that the decision to withhold or withdraw life support in the early transitional period after birth is common but should never be routine [71]. The potential for development of functional status in the fetus or newborn is the single most important factor affecting immediate intervention and long-term outcome. The dilemma is that although there is a threshold of maturity or extent of brain injury beyond which survival, or

survival without devastating sequelae, is not possible, the exact threshold for a particular individual is typically not known prior to the attempt to assist the newborn to survive. Although the proportion of individuals who must face this threshold increases dramatically below 25 weeks' gestation, there is considerable variation in functioning by neonates provided with appropriate resuscitation interventions. Thus it is usually impossible at the onset of resuscitative efforts to know with certainty whether such efforts will result in intact survival, survival with devastating neurologic injury, or prolonged dying with gradually worsening organ failure.

So what recommendations can be made to assist those faced with this significant responsibility? While there are no simple answers, the most important component of this process is to establish and maintain effective communication. Discussion between the obstetric and neonatal teams regarding the best available information concerning gestational age, fetal condition, and other important factors is critical; without this, the neonatal team will not be able to deliver optimal care. A dialog among neonatal members is necessary so that the plan of care, regardless of degree of intervention, can be carried out in a coordinated and professional manner. Finally, all the obstetric and neonatal HCPs involved in the care of the pregnant woman and her newborn must establish open lines of communication with the mother and any significant other who is involved in the decision-making process. Clear communication of medical facts, likely clinical outcomes (ideally, based on objective, relevant, valid, institution-specific data), and medically acceptable options for care is an integral component of any counseling process and mandatory for establishing an atmosphere of trust and mutual respect between family members and the healthcare team.

Many times in caring for sick full-term neonates who, despite their current illness, have a high likelihood of recovery and good outcome, there is a clear consensus as to the medical choices to be made on behalf of the patient. A similar circumstance exists at the other end of the spectrum of care when death is determined to be inevitable, and relief of pain and discomfort coupled with emotional support of the patient and family is of paramount importance. There are clinical situations where the medically acceptable choices include options ranging from comfort care to initiation/continuation of aggressive intensive care – this is where the decision making is most complex and the consequences of the decisions made arguably carry the most potential for serious long-term physical, emotional, psychological, and financial harm. It is in these situations that the physician bears the greatest responsibility in clearly spelling out the various options for care and the potential or likely consequences of each of these; it is also at these times that physicians must bear in mind that they share the privilege of caring for the patient for what amounts to a relatively brief period of time, and it is the parents who bear the long-term responsibility of caring for their child. It is not the physician but the parents who are the appropriate surrogates for the child, provided that they are educated as to what is possible or not possible and what is likely or not likely and are informed of the societal perspective represented by court precedents as pertinent to their situation. Thus the moral imperative would be to defer to the parents when the outcome is in question and the medical choices are unclear.

Summary

Management of difficult deliveries and the subsequent resuscitation of the newborn are among the most intensely scrutinized and frequently criticized medical activities in medicolegal litigation (Table 38.4). HCPs charged with caring for newborns immediately after birth are both obligated and well advised to ensure that resuscitation of the neonate is consistently performed skillfully and expeditiously according to the most recent guidelines. Optimal resuscitation requires anticipation, preparation, intense collaboration, and effective communication between and among the obstetric and neonatal team members. Resuscitation should begin in a timely fashion and follow the evidence-based algorithm for assessment and intervention. Conducting an effective resuscitation requires cognitive (knowledge), technical (hands-on), and behavioral (working effectively as a team under pressure) skills. These skills must also be regularly practiced in order to maintain a high level of team performance. Skillful resuscitation may decrease the severity of any prenatal injury. This will continue to be an area of active research for the foreseeable future.

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Table 38.4 Partial Listing of Aspects of Neonatal Resuscitation Creating Medicolegal Risk

Failure to recognize a newborn in need of resuscitation
Failure to anticipate the need for extended resuscitation
Failure to assemble appropriately trained personnel in a timely fashion
Failure to follow hospital policies regarding treatment of the newborn
Ineffective communication between the obstetric team and the neonatal team
Ineffective communication among neonatal team members
Poorly performed cardiopulmonary resuscitation
Failure to recognize and treat an incorrectly placed endotracheal tube
Failure to achieve timely umbilical venous access for medication or volume delivery
Incorrectly placed umbilical venous catheter
Over- or underdosage of medication
Failure to recognize a pneumothorax, pneumomediastinum, or pneumopericardium in a patient receiving positive-pressure ventilation
Failure to recognize the hypovolemic/anemic newborn
Delivery of peak inspiratory pressures that are too low or too high
Delivery of positive-pressure ventilations at too slow or too fast a rate
Delivery of medications through the endotracheal tube that should be administered only via the intravascular route
Failure to effectively communicate with parents
Initiating/continuing/discontinuing resuscitation against parental wishes
Lack of accurate and comprehensive documentation
Conflicting or incorrect documentation

References

1. Joint Commission. Sentinel Event Alert 30, July 21, 2004. Available at www.jointcommission.org/sentinelevents/sentineleventalert/sea_30.htm (accessed February 2008).
2. Perlman JM, Wyllie J, Kattwinkel J, et al. Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations, part 7. *Circulation* 2015; **132**(16 Suppl 1): S204–41.
3. Wyllie J, Perlman JM, Kattwinkel J, et al. Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations, part 7. *Resuscitation* 2015; **95**: e169–201.
4. Perlman JM, Wyllie J, Kattwinkel J, et al. Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations, part 7. *Pediatrics* 2015; **136**(Suppl 2): S120–66.
5. Weiner GM. *Neonatal Resuscitation Textbook*, 7th edn. Elk Grove Village, IL: American Academy of Pediatrics, American Heart Association, 2016.
6. Lockwood CJ, Lemons JA, eds. *Guidelines for Perinatal Care*, 6th edn. Elk Grove Village, IL: American Academy of Pediatrics, American College of Obstetricians and Gynecologists, 2007.
7. Oh W, Fanaroff AA, Carlo WA, et al. Effects of delayed cord clamping in very-low-birth-weight infants. *J Perinatol* 2011; **31**(Suppl 1): S68–71.
8. Strauss RG, Mock DM, Johnson KJ, et al. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. *Transfusion* 2008; **48**(4): 658–65.
9. March MI, Hacker MR, Parson AW, et al. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. *J Perinatol* 2013; **33**(10): 763–7.
10. Katheria AC, Leone TA, Woelkers D, et al. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. *J Pediatr* 2014; **164**(5): 1045–50.
11. Mullany LC, Katz J, Khatry SK, et al. Risk of mortality associated with neonatal hypothermia in southern Nepal. *Arch Pediatr & Adolesc Med* 2010; **164**(7): 650–6.
12. Laptook AR, Salhab W, Bhaskar B. Admission temperature of low birth weight infants: predictors and associated morbidities. *Pediatrics* 2007; **119**(3): e643–9.
13. Halbower AC, Jones MD. Physiologic reflexes and their impact on resuscitation of the newborn. *Clin Perinatol* 1999; **26**: 621–7.
14. Vain NE, Szyld EG, Prudent LM, et al. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicentre, randomized controlled trial. *Lancet* 2004; **364**: 597–602.
15. Wiswell TE, Gannon CM, Jacob J, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter,

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international collaborative trial. *Pediatrics* 2000; **106**: 1–7.

16. Halliday HL. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database Syst Rev* 2001; **1**: CD000500.
17. Manganaro R, Mami C, Palmara A, et al. Incidence of meconium aspiration syndrome in term meconium-stained babies managed at birth with selective tracheal intubation. *J Perinat Med* 2001; **29**(6): 465–8.
18. Summary AAP/AHA 2015 guidelines for cardiopulmonary resuscitation and emergency cardiovascular care of the neonate, 2015. Available at www2.aap.org/nrp/docs/15535_NRP%20Guidelines%20Flyer_English_FINAL.pdf (accessed January 2016).
19. Bennett S, Finer NN, Rich W, et al. A comparison of three neonatal resuscitation devices. *Resuscitation* 2005; **67**: 113–18.
20. Aziz HF, Martin JB, Moore JJ. The pediatric disposable end-tidal carbon dioxide detector role in endotracheal intubation in newborns. *J Perinatol* 1999; **19**: 110–13.
21. Repetto JE, Donohue PCP, Baker SF, et al. Use of capnography in the delivery room for assessment of endotracheal tube placement. *J Perinatol* 2001; **21**: 284–7.
22. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *JAMA* 2014; **312**(24): 2629–39.
23. Esmail N, Saleh M, Ali A. Laryngeal mask airway versus endotracheal intubation for Apgar score improvement in neonatal resuscitation. *Eg J Anesth* 2002; **18**: 115–21.
24. Milner AD, Saunders RA. Pressure and volume changes during the first breath of human neonates. *Arch Dis Child* 1977; **52**: 918–24.
25. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959; **97**: 517–23.
26. Gerhardt T, Bancalari E. Chest wall compliance in full term and preterm infants. *Acta Paediatr Scand* 1980; **69**: 359–64.
27. Heldt G, McIlroy MB. Dynamics of chest wall in preterm infants. *J Appl Physiol* 1987; **62**: 170–4.
28. Morley CJ. Continuous distending pressure. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F152–6.
29. Saunders RA, Milner AD, Hopkin IE. The effects of continuous positive airway pressure on lung mechanics and lung volumes in the neonate. *Biol Neonate* 1976; **29**: 178–86.
30. Richardson CP, Jung AL. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. *Pediatr Res* 1978; **12**: 771–4.
31. Cotton RB, Lindstom DP, Kanarek KS, et al. Effect of positive-end-expiratory-pressure on right ventricular output in lambs with hyaline membrane disease. *Acta Paediatr Scand* 1980; **69**: 603–6.
32. Ramji S, Ahuja S, Thirupuram S, et al. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. *Pediatr Res* 1993; **34**: 809–12.
33. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial. The Resair 2 Study. *Pediatrics* 1998; **102**: e1.
34. Ramji S, Rasaily R, Mishra PK, et al. Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: a multicentric trial. *Indian Pediatr* 2003; **40**: 510–17.
35. Saugstad OD, Ramji S, Irani SF, et al. Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months. *Pediatrics* 2003; **112**: 296–300.
36. Vento M, Asensi M, Sastre J, et al. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. *Pediatrics* 2001; **107**: 642–7.
37. Vento M, Asensi M, Sastre J, et al. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr* 2003; **142**: 240–6.
38. Kapadia VS, Chalak LF, Sparks JE, et al. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics*. 2013; **132**(6): e1488–96.
39. Rabi Y, Singhal N, Nettel-Aguirre A. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. *Pediatrics*. 2011; **128**(2): e374–81.
40. Rook D, Schierbeek H, Vento M, et al. Resuscitation of preterm infants with different inspired oxygen fractions. *J Pediatr* 2014; **164**(6): 1322–6.
41. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics* 2009; **124**(3): e439–49.
42. Wang CL, Anderson C, Leone TA, et al. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008; **121**(6): 1083–9.
43. Rajani AK, Chitkara R, Oehlert J, Halamek LP. Comparison of umbilical venous and intraosseous access during simulated neonatal resuscitation. *Pediatrics*. 2011; **128**(4): e954–8.

44. Kitterman JA, Phibbs RH, Tooley WH. Catheterization of umbilical vessels in newborn infants. *Pediatr Clin North Am*. 1970; **17**: 895–912.
45. Heinild S, Søndergaard T, Tudvad F. Bone marrow infusion in childhood: experiences from a thousand infusions. *J Pediatr* 1947; **30**: 400–12.
46. Glaeser PW, Losek JD, Nelson DB, et al. Pediatric intraosseous infusions: impact on vascular access time. *Am J Emerg Med* 1988; **6**: 330–2.
47. Ellemunter H, Burkhart S, Trawoger R, et al. Intraosseous lines in preterm and full term neonates. *Arch Dis Child Fetal Neonatal Ed* 1999; **80**: F74–5.
48. International Liaison Committee on Resuscitation. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: neonatal resuscitation. *Pediatrics* 2006; **117**: e978–88.
49. Romero T, Friedman WF. Limited left ventricular response to volume overload in the neonatal period: a comparative study with the adult animal. *Pediatr Res* 1979; **13**: 910–15.
50. So KW, Fok TF, Ng PC, et al. Randomized, controlled trial of colloid or crystalloid in hypotensive preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**: F43–6.
51. Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. *J Perinatol* 2003; **23**: 473–6.
52. Emery EF, Greenough A, Gamsu HR. Randomised, controlled trial of colloid infusions in hypotensive preterm infants. *Arch Dis Child* 1992; **67**: 1185–8.
53. Srinivasan G, Pildes RS, Caughey M, et al. Plasma glucose values in normal neonates: a new look. *J Pediatr* 1986; **109**: 114–17.
54. Bishop RL, Weisfeldt ML. Sodium bicarbonate administration during cardiac arrest: effect on arterial pH, PCO_2 and osmolality. *JAMA* 1976; **235**: 506–9.
55. Berenyi KJ, Wolk M, Killip T. Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest. *Circulation* 1975; **52**: 319–24.
56. Simmons MA, Adcock EW, Bard H, et al. Hypernatremia and intracranial hemorrhages in neonates. *N Engl J Med* 1974; **291**: 6–10.
57. Papile L, Burnstein J, Burnstein R, et al. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. *J Pediatr* 1978; **93**: 834–6.
58. Johnson PJ. Sodium bicarbonate use in the treatment of acute neonatal lactic acidosis:benefit or harm? *Neonatal Network* 2011; **30**(3): 199–205.
59. Chernick V, Manfreda J, De Booy V, et al. Clinical trial of naloxone in birth asphyxia. *J Pediatr* 1988; **113**: 519–25.
60. Halamek, LP. The advantages of prenatal consultation by a neonatologist. *J Perinatol* 2001; **21**: 116–20.
61. Halamek LP. Prenatal consultation at the limits of viability. *NeoReviews* 2003; **4**: e153–6.
62. Saigal S. The limits of viability. *Pediatr Res* 2001; **49**: 451.
63. Wood NS, Marlow N, Costeloe K, et al. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000; **343**: 378–84.
64. Costeloe K, Hennessy E, Gibson AT, et al. The EPICure Study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 2000; **106**: 659–71.
65. deLeeuw R, Cuttini M, Nadai M, et al. Treatment choices for extremely preterm infants: an international perspective. *J Pediatr* 2000; **137**: 608–15.
66. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopment and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics* 2000; **105**: 1216–26.
67. El-Metwally D, Vohr B, Tucker R. Survival and neonatal morbidity at the limits of viability in the mid 1900s: 22 to 25 weeks. *J Pediatr* 2000; **137**: 616–22.
68. Watts J, Saigal S. Replies to malcontent: fumes from the spleen. *Pediatr Perinat Epidemiol* 1995; **9**: 375–9.
69. Saigal S, Stoskopf BL, Feeny D, et al. Differences in preferences for neonatal outcomes among health care professionals, parents and adolescents. *JAMA* 1999; **281**: 1991–7.
70. Lorenz JM, Paneth N. Treatment decisions for the extremely premature infant. *J Pediatr* 2000; **137**: 593–5.
71. Stevenson DK, Goldworth A. Ethical dilemmas in the delivery room. *Semin Perinatol* 1998; **22**: 198–206.

Chapter

39

Improving Performance, Reducing Error, and Minimizing Risk in the Delivery Room

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Introduction

In 1999, the Institute of Medicine (IOM) published *To Err Is Human: Building a Safer Health System*, a report on human error and patient safety in the United States [1]. In this report, the authors estimate that between 44,000 and 98,000 Americans die each year as a result of medical errors. Although this figure has been highly debated, it is based on extrapolation of the data contained in published studies out of Colorado, Utah, and New York [2–4]. The 1999 report was followed in 2001 and 2004 by additional reports from the IOM, *Crossing the Quality Chasm: A New Health System for the 21st Century* and *Patient Safety: Achieving a New Standard of Care*, respectively, in which the types of interventions, including training methodologies, necessary to improve patient safety were discussed [5–7]. In 2004, the Joint Commission (JC) published a *Sentinel Event Alert* describing ineffective communication as a major cause in almost three-quarters of the cases of neonatal mortality or severe neonatal morbidity (lifelong serious neurologic compromise) reported to that agency [6]. The JC recommended that hospitals that deliver newborns establish a system of training that incorporates behavioral skills such as teamwork and effective communication and that they conduct regular clinical drills in delivery room emergencies followed by constructive debriefings. Despite the recommendations by the IOM and the JC, healthcare has yet to fully examine the complex relationship among training, human performance, and medical error, and the development and implementation of such training programs remain challenging.

While many factors influence the incidence of medical error in the United States today, this chapter focuses on human performance and its impact on patient safety. Similarly, while medical errors occur across every medical specialty and affect all patients, this chapter centers on the factors that affect patient safety in the delivery room. First, the approach taken by the aviation industry to improve human performance and its effect on flight safety will be reviewed. Next, the use of simulation to examine the performance of healthcare professionals working in dynamic environments will be highlighted. Finally, we will underscore how human factors research in healthcare can be used to improve patient safety.

Lessons Learned from Other High-Risk Industries

Dynamic medical domains such as the delivery room are similar to other domains such as commercial aviation in that they are all characterized by an inherent risk to human life and intense time pressure. There is a direct relationship between actions and outcomes. Communication in these domains is primarily verbal and immediate, involves multiple personnel, and is characterized by changes in pitch, intensity, and word compression as well as nonverbal cues including eye movement and body language. Effective human interface with technology is critical to both flying aircraft and resuscitating neonates in the delivery room. The tradition of the pilot as commander-in-chief is similar to that of the physician bearing ultimate responsibility for the care of a newborn. Thus healthcare shares many characteristics with aviation and stands to benefit from adopting similar training methodologies.

Commercial aircraft accidents are devastating in terms of both loss of human life and destruction of expensive technology. Because of this, the commercial aviation industry long ago recognized the need to develop a better understanding of why planes crash in an effort to reduce the incidence of such events. One of the first steps in this effort was to equip the cockpits of commercial aircraft with devices that record the communications of the crew and the readings of the plane's instruments. These devices provide an objective, time-coded record of the events as they occur during flight. Analysis of the data from these "black boxes" indicated

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that approximately two-thirds of airline accidents occurred not because of major mechanical failures or lack of technical knowledge on the part of the crew but rather because of suboptimal communication and teamwork by those responsible for flying the plane [8]. This information was surprising in that the pilots, copilots, and flight engineers flying these large commercial aircraft were some of the most experienced in the industry, having logged thousands of hours of flight time in a variety of aircraft under a wide array of conditions and yet were unable to use and integrate their collective skills during in-flight crises.

In response to these findings, the aviation industry developed a training program known as *Crew* (or *Cockpit*) *Resource Management* (CRM) [9]. In CRM, crews are taught the appropriate technical responses to in-flight crises. In addition, heavy emphasis is placed on the necessary behavioral responses (effective teamwork and communication) vital to optimal crew performance. The key to effective CRM training is creating a "suspension of disbelief" in those participating in the exercise; this is greatly enhanced by creating a training environment that simulates a cockpit with high fidelity. Flight simulators are designed to be identical to the physical layout of a real cockpit and provide realistic visual, auditory, tactile, and kinesthetic cues to those training within the simulator. The simulator contains working controls, alarms, and other devices; these must be operated as in real life, or the desired responses by the simulated aircraft will not occur. It is not possible simply to talk one's way out of a problem, nor pick the correct solution from a list of multiple-choice options, in a flight simulator. If the crew does not exhibit the correct technical and behavioral responses to the events in the simulator exactly as would be necessary in the real cockpit during actual flight, the scenario cannot be completed successfully and the simulator "crashes." Ultimately, the goal of these efforts is to prevent errors and improve the safety of passengers and crew. Evaluation of the effects of simulation-based flight training indicates that the experience gained in realistic simulators improves crew performance. Although confounded by concomitant advances in technology, passenger safety has improved since the initiation of mandatory annual CRM training by all flight crews of major commercial airlines.

Given the similarities between these high-risk domains, what can be done in healthcare to mimic the successes in safety and human performance experienced by commercial aviation?

Using Simulation to Examine Patient Safety Issues in the Delivery Room

The delivery room possesses many similarities to the cockpit. Both are characterized by high risk, intense time pressure, and reliance on technical skills and verbal communication. As in the cockpit, high-quality human performance is a critical component of the team's ability to execute its tasks. Human performance refers to the process of carrying out a physical or mental task, action, or function. It is influenced by elements that are both intrinsic and extrinsic to the human being. Intrinsic components consist of (1) cognitive abilities, including but not limited to knowledge, decision making, and critical thinking; (2) physical capabilities such as vision, hearing, strength, coordination, and dexterity; and (3) behavioral capacities that allow an individual to manage stressors and function as part of a team. Limitations in any of these intrinsic attributes will obviously affect a human's ability to perform.

Simulation is a tremendously powerful tool for both training and evaluating human performance, be it of the individual or of the team. In a properly designed simulation-based study of human performance, all aspects of a clinical scenario can be standardized so that a high degree of uniformity exists in the nonhuman facets, and the only variable in play is the performance of the human subject(s) involved in the scenario. Researchers at the Center for Advanced Pediatric and Perinatal Education at Packard Children's Hospital at Stanford (CAPE) have conducted several such studies in which all aspects of the simulated clinical environment were highly standardized to examine human performance. In the work by Chitkara et al., heart rate assessment was examined under realistic delivery room conditions [10]. In this simulation-based study of the ability of human healthcare professionals to accurately detect heart rate via auscultation and palpation, the following elements were standardized across all scenarios and all subjects:

- Heartbeat: rate, volume, tone, location
- Umbilical cord pulsations: frequency, amplitude, location
- Stethoscope: type and quality
- Reaction of the simulated neonate to interventions (scripted)
- Responses of the bedside nurse (scripted)

- Responses of the bedside respiratory therapist (scripted)
- Structure of the physical space
- Availability, location, and function of equipment
- Availability and location of supplies
- Ambient (environmental) noise.

This study demonstrated that experienced healthcare professionals trained in neonatal resuscitation were unable to accurately determine heart rate on a consistent basis during simulated neonatal resuscitation whether using auscultation or palpation. This inability was associated with numerous errors of omission and commission that would produce patient harm if replicated in the real clinical environment.

Similarly, Rajani et al. showed that in a simulated delivery room setting, intraosseous (IO) needle placement can be performed more quickly than umbilical venous catheter (UVC) insertion without any difference in technical error rate or perceived ease of use [11]. In this study, the subjects participated in simulated neonatal resuscitation scenarios that required the placement of either an IO needle or UVC. The clinical scenario, neonatal patient simulator, IO needle, and UVC catheter were standardized for all study subjects. Based on this study, the authors determined that IO needle placement is a viable alternative to UVC insertion in term neonates. While this is a distinct variation from the current recommendations of the Neonatal Resuscitation Program (NRP) algorithm, these rigorous human performance data suggest a change in practice that would improve the safety of neonates born in hospitals where healthcare professionals do not routinely place UVCs but have experience with IO needle placement techniques.

In addition to the study of technical skills, these types of standardized clinical scenarios can also be used to examine behavioral skills and their effect on human performance by allowing investigators to control clinical factors such as the severity of clinical presentation, neonatal patient manikin, patient vital signs, communication by confederate clinicians, and medical supplies for all subjects. For example, Yamada et al. explored the utility of standardized communication techniques to reduce human error and improve adherence to the NRP algorithm during simulated neonatal resuscitation [12]. This study found that healthcare professionals can consistently implement the use of standardized communication techniques, and this led to a trend of improved adherence to the NRP algorithm. In another example, Thomas et al. published several studies that demonstrate that healthcare professionals can be trained to demonstrate increased teamwork behaviors such as communication, vigilance, workload management, and leadership skills [13–15].

Applying Human Factors Science to Delivery Room Medicine

Human factors is the scientific discipline seeking to understand interactions between humans and other elements of complex systems. Professionals in human factors study human-environmental interactions and apply the information learned to maximize human strengths and minimize weaknesses [16]. Human factors fundamentals have long been applied to aviation, aerospace, industrial engineering, workplace design, and product development. In contrast, there has been minimal integration of human factors principles and theory into patient care.

An area requiring intense investigation is the application of human factors engineering to patient monitoring [17–19]. Patient data must be presented in a manner in which it can be easily detected, assimilated, interpreted, and acted on. Therefore, one cannot simply study just the patient or just the technology but also must critically examine how the human beings responsible for delivering care to the patients interface with that technology [20]. The design of patient monitors, specifically the display parameters and alarms, is a critical element in enabling HCPs to recognize and respond to abnormalities and changes in patient physiology. Simply providing more data in the delivery room will not necessarily translate into more useful information.

Not only does human factors engineering influence how technology is used to present data, it can also be used to improve how healthcare professionals act on those data. Fuerch et al. examined the effect of a decision-support tool on human performance during simulated neonatal resuscitation [21]. This device continuously displayed the patient data required to implement the NRP algorithm and provided a combination of auditory and visual prompts. Healthcare professionals using a decision-support tool exhibited significantly fewer deviations from the NRP algorithm than those working from memory alone, suggesting that the use of a decision-support tool during neonatal resuscitation in the real clinical environment can improve human performance by reducing errors.

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Decision-support tools such as these function to improve human performance by reducing cognitive workload and improving the situational awareness of healthcare professionals involved in neonatal resuscitation.

What is a safe delivery room from the perspective of human factors? A safe delivery room is one that is staffed by professionals who not only have mastered the appropriate body of content knowledge specific to their domain and are highly trained in the necessary technical skills but also have practiced and demonstrated behavioral skills such as teamwork and effective communication. These professionals are supported by clinical information systems that use human factors engineering to assimilate, analyze, and display patient data in a format that can be easily visualized and interpreted, in real time, in the real environment.

Conclusion

Improvement in the safety of newborns and their mothers will require a new focus on the role of human factors in the delivery room. Rather than asking, "Can we afford to do this?," the proper question to be asked is, "Can we afford not to do this?" The IOM, in its 1999 report, states: "The status quo is not acceptable and cannot be tolerated any longer. Despite the cost pressures, liability constraints, resistance to change and other seemingly insurmountable barriers, it is simply not acceptable for patients to be harmed by the same health care system that is supposed to offer healing and comfort . . . A comprehensive approach to improving patient safety is needed" [1].

Just as other high-risk industries such as commercial aviation have applied simulation-based training and research strategies as well as human factors science to the challenges inherent in complex tasks, the healthcare industry must aggressively use these same tools to identify and remediate human and system weaknesses inherent in patient care. Only then will we be able to improve performance, reduce error, and minimize risk.

References

1. Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy of Sciences, 2000.
2. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. *Quality & Safety in Health Care* 2004; **13**: 145–51; discussion 151–2.
3. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; **324**: 377–84.
4. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care* 2000; **38**: 261–71.
5. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy of Sciences, 2001.
6. Preventing infant death and injury during delivery. *Sentinel Event Alert* 2004: 1–3.
7. Aspden P, Corrigan JM, Wolcott J, Erickson SM, eds. *Patient Safety: Achieving a New Standard for Care*. Washington, DC: National Academy of Sciences, 2004.
8. Billings CE, Reynard WD. Human factors in aircraft incidents: results of a 7-year study. *Aviat Space Environ Med* 1984; **55**: 960–5.
9. *Cockpit Resource Management*. San Diego: Academic Press, 1993.
10. Chitkara R, Rajani AK, Oehlert JW, et al. The accuracy of human senses in the detection of neonatal heart rate during standardized simulated resuscitation: implications for delivery of care, training and technology design. *Resuscitation* 2013; **84**: 369–72.
11. Rajani AK, Chitkara R, Oehlert J, Halamek LP. Comparison of umbilical venous and intraosseous access during simulated neonatal resuscitation. *Pediatrics* 2011; **128**: e954–8.
12. Yamada NK, Yaeger KA, Halamek LP. Analysis and classification of errors made by teams during neonatal resuscitation. *Resuscitation* 2015; **96**: 109–13.
13. Thomas EJ, Sexton JB, Lasky RE, et al. Teamwork and quality during neonatal care in the delivery room. *J Perinatol* 2006; **26**: 163–9.
14. Thomas EJ, Taggart B, Crandell S, et al. Teaching teamwork during the Neonatal Resuscitation Program: a randomized trial. *J Perinatol* 2007; **27**: 409–14.
15. Thomas EJ, Williams AL, Reichman EF, et al. Team training in the neonatal resuscitation program for interns: teamwork and quality of resuscitations. *Pediatrics* 2010; **125**: 539–46.
16. International Ergonomics Association. Available at www.iea.cc/whats/index.html (accessed July 14, 2015).
17. Gawron VJ, Drury CG, Fairbanks RJ, Berger RC. Medical error and human factors engineering: where are we now? *Am J Med Qual* 2006; **21**: 57–67.

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18. Gosbee J. Human factors engineering and patient safety. *Quality & Safety in Health Care* 2002; **11**: 352–4.

19. Walsh T, Beatty PC. Human factors error and patient monitoring. *Physiol Meas* 2002; **23**: R111–32.

20. Hunt EA, Nelson KL, Shilkofski NA. Simulation in medicine: addressing patient safety and improving the interface between healthcare providers and medical technology. *Biomed Instrum Technol* 2006; **40**: 399–404.

21. Fuerch JH, Yamada NK, Coelho PR, et al. Impact of a novel decision support tool on adherence to Neonatal Resuscitation Program algorithm. *Resuscitation* 2015; **88**: 52–6.

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Chapter

40 Extended Management Following Resuscitation

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Introduction

After the initial resuscitation of an encephalopathic infant, the extended management of the patient becomes critical in order to prevent or ameliorate secondary injury. There are many different management protocols that are acceptable, and it is not the intent of this chapter to review all used for the various conditions encountered in neonatal intensive care. Rather, we focus on the early transitional period following birth and resuscitation, during which the condition of the depressed infant can be substantially improved by expert care.

As noted in Chapters 2 and 41, the encephalopathic period involves a continuum of biologic events associated with secondary energy failure lasting up to 48–72 hours after the initial insult. These events include the reperfusion period with the elaboration of oxygen free radicals and various cytokines as well as the necrosis and apoptosis that ensue. It is imperative that the extended management of these infants be implemented in an optimal and timely fashion at a facility that can provide hypothermia and/or other novel neuroprotective interventions.

Unfortunately, the windows of opportunity may be short and variable depending on the nature of the intervention and injury and could change as further research informs practice. Thus, there is an obligation for practitioners to be well informed about progress in the standard of care and knowledgeable with respect to current neuroprotective strategies. Various neuroprotective mechanisms after hypoxic-ischemic injury are discussed in detail in Chapter 41.

The condition of the infant during this period may have been determined by circumstances that occurred prior to or during delivery and/or initial resuscitation, many of which are beyond the control of the obstetrician and neonatologist. It is also important to recognize that significant neurologic or physiologic compromise is not always evident during an early evaluation; and an infant with good initial Apgar scores may present with significant problems later, even after an apparently successful resuscitation. Nonetheless, it is possible to identify many infants who require continued intensive care, including all those who require vigorous resuscitation and those who remain depressed or are dependent on cardiopulmonary support. The roles of pharmacologic therapy in extended intensive care and in the management of refractory neonatal hypoxemia have been reviewed in detail [1], although altered pharmacokinetics in the context of therapeutic hypothermia is also an important consideration [2,3]. This chapter provides an overview of the aspects of extended intensive care that address the maintenance of cerebral integrity in appropriate facilities that can provide specialized therapy and provides recommendations for the implementation of these interventions by the primary care practitioner [4]. These interventions consist of sustaining ventilation, supporting cardiac output, correcting anemia, and evaluating and initiating therapy for hypoxemia.

Fluid Management

Although there is little evidence to guide fluid administration in infants with hypoxic-ischemic injury and encephalopathy, the risk for exacerbating cerebral edema is real. Hyponatremia may exist if excessive free water is administered or in the context of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In addition, capillary leak syndrome associated with asphyxia may lead to intravascular volume depletion with appropriate secretion of ADH, and any relative water load can set the stage for the development of hyponatremia. Thus intravascular volume depletion should be treated with crystalloids or colloids; whereas, continuous intravenous (IV) fluid administration should be restricted, limiting free water in the context of a low glomerular filtration

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rate (GFR) or oliguric renal failure. However, it is paramount to avoid dehydration and possible hypotension and to maintain good cardiac output and perfusion. Enteral feeding is usually eschewed in the first several days of life in order to avoid damage to or impair perfusion of the gastrointestinal tract, particularly in the setting of continued need for inotropic support. This is discussed in Chapter 43.

Supporting Ventilation

Assisted ventilation should be provided for any infant who is not able to maintain acceptable arterial blood gas levels or who does so only with extreme effort. The range of desired arterial oxygen tensions depends on the clinical circumstances, as indicated in Chapter 38. In premature infants, an arterial oxygen tension (PaO_2) of 50–60 mmHg (6.7–8.0 kPa) is usually adequate, but a PaO_2 slightly higher than 100 mmHg (13.3 kPa) may be more desirable in infants with persistent pulmonary hypertension of the newborn (PPHN). In some situations, extreme vigorous support (with a concomitant risk of adverse effects, such as pneumothorax, adult respiratory distress syndrome [ARDS], or bronchopulmonary dysplasia [BPD]) may be required to achieve optimal blood gas parameters. In such high-risk clinical scenarios, one may decide to accept lower oxygen tensions (35–50 mmHg [4.7–6.7 kPa]) if this allows less vigorous use of positive-pressure ventilation (PPV) or greatly reduced inspired oxygen concentrations as long as both the oxygen-carrying capacity of the blood and cardiac output are maintained.

Similarly, higher than normal arterial carbon dioxide ($PaCO_2$) target ranges are often accepted as long as arterial pH levels are not excessively depressed because these values may be achieved with less aggressive mandatory ventilation. Hyperventilation to achieve elevated pH values has been used in the treatment of PPHN [5,6]. However, extreme hyperventilation results in hypocapnia and alkalosis and shifts the hemoglobin-oxygen dissociation curve to the left, which may adversely affect tissue oxygenation. The effects of hyperventilation on cerebral metabolism are not fully understood but may lead to compromised blood flow to the brain [7]. Cerebral vascular autoregulation may also be impaired in critically ill neonates, and blood flow patterns may change due to hypocapnia [8–11]. Retrospective clinical studies have also suggested an association of hyperventilation, as part of a therapeutic approach to PPHN, with later sensorineural hearing loss and poorer neurodevelopmental outcomes [12–14]. Moreover, significant risks of pulmonary injury, including pneumothorax and pulmonary interstitial emphysema (PIE), may occur with excessively vigorous mechanical ventilation. Recognition of the potential short- and long-term complications associated with hyperventilation, along with the availability of improved adjuvant therapies (see below), allows tertiary care centers to now employ more conservative ventilation strategies in the management of PPHN [15,16]. However, support for any specific ventilatory regimen is still limited by the paucity of randomized controlled trials.

Recent evidence has suggested that changes in lung volumes rather than changes in applied proximal airway pressures may be most important in the development of chronic lung disease (CLD) in ventilated infants. This has led to the adoption of high-frequency ventilation (HFV), including high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), high-frequency flow interruption (HFFI), and high-frequency positive-pressure ventilation (HFPPV), as strategies for supporting gas exchange while minimizing pulmonary injury [17]. In general, the strategy for use of these devices is to maintain lung volumes above their functional residual capacity using constant distending pressures and delivering small tidal volumes at 2–20 Hz. HFV appears to be at least as effective as conventional PPV for managing premature infants with respiratory distress syndrome (RDS) and may be the preferred mode of ventilation in infants with PIE or other air-leak syndromes. Both HFOV and HFJV have been studied as methods to rescue infants with severe respiratory failure who qualify for extracorporeal membrane oxygenation (ECMO) while on conventional ventilation [17–19]. Such HFV rescue has been shown to most likely succeed in infants with severe RDS and less so for those with meconium aspiration or congenital diaphragmatic hernia (CDH). However, there are very few randomized controlled trials in this area [20], making establishment of clear recommendations difficult. Plans for further trials of ventilatory strategies alone are complicated by use of other adjuvant interventions, as well as by dissimilar diagnoses and responses among infants with pulmonary failure. Increasing use of HFV in combination with other therapies is likely responsible for the dramatic decrease in the need for ECMO in neonates with

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PPHN [21]. Numerous studies of differing designs evaluating the potential benefit of elective or rescue HFV in the management of RDS have also arrived at different conclusions. Reviews and meta-analyses of available studies were unable to recommend any particular ventilatory strategy conclusively [22,23].

To facilitate safe and effective ventilatory management, it is occasionally necessary to provide pharmacologic neuromuscular blockade. The administration of pancuronium bromide or vecuronium iodide allows for neuromuscular relaxation, produces significant improvement in gas exchange, and reduces the risk of barotrauma [24,25]. Vecuronium has weak atropine-like and histamine-releasing effects, which may cause hypotension, tachycardia, and an apparent increase in skin perfusion. In contrast, pancuronium has been shown to decrease blood histamine levels and is less likely to cause hypotension because of direct effects on heart function. It is also possible that these drugs may increase the risk of intracranial hemorrhage. Provision of analgesia with morphine sulfate or fentanyl and sedation with midazolam is recommended during neuromuscular blockade. However, prolonged use of neuromuscular blockade with sedative and analgesic exposures must be balanced against the potential negative impact of these agents on the developing brain [26,27].

A major advancement in the management of respiratory insufficiency in preterm infants occurred with the introduction of surfactant replacement therapy. Investigational use of surfactants became widespread by 1989, and commercial products were introduced in 1990 (Exosurf, an entirely synthetic surfactant) and 1991 (Survanta, a bovine surfactant-based product). Other exogenous surfactant preparations such as Infasurf and Curosurf have since been marketed in the United States and Europe. Use of exogenous surfactant in preterm infants with RDS has been associated with reduced mortality, fewer pneumothoraces, and lower oxygen requirements and ventilatory settings in these patients [28–30]. Weight-specific mortality has been substantially reduced, especially in infants of less than 28 weeks' gestation. This single therapeutic innovation reduced the total neonatal mortality rate in the United States by 10% in the year it was introduced. Unfortunately, the prevalence of BPD appears not to have changed significantly. This is most likely explained by improved survival among the sickest premature infants since the implementation of surfactant therapy and a concomitant change in the pathophysiology of BPD [31]. However, a recent meta-analysis of randomized controlled trials of synthetic surfactant treatment in preterm infants does suggest a decrease in the risk of BPD as well as neonatal mortality [30].

Term infants with severe respiratory failure have also been shown to benefit from surfactant therapy. Meconium, blood, and infection may inactivate or wash out endogenously produced surfactant; thus, replacement with exogenous surfactant has been added to the armamentarium of treatments for severe respiratory failure in newborns [32]. A multicenter randomized, double-blind, placebo-controlled trial demonstrated that a four-dose regimen of beractant (Survanta) decreases the need for ECMO without increasing complications in critically ill term and near-term infants with meconium aspiration, sepsis, or PPHN, especially if the treatment is administered early in the course [33]. In term infants, surfactant treatment is most often used in combination with other advanced ventilatory and therapeutic modalities. Administration of surfactant occasionally results in desaturation episodes, which could prove life threatening for patients with severe pulmonary hypertension. Therefore, prudence and safety dictate that surfactant treatment of critically ill and unstable neonates be initiated in a facility where other therapies such as inhaled nitric oxide (iNO) and ECMO may be offered.

Surfactant use has not been associated with significant adverse effects. Neither the incidence of intraventricular hemorrhage (IVH) nor that of patent ductus arteriosus (PDA) has been consistently increased in clinical trials. Some trials have suggested an increased frequency of pulmonary hemorrhage, but this appears to result from increased recognition rather than a true increase in the incidence of this complication. The major hazards of surfactant use relate to hypoxic episodes if the agent is given too rapidly and to air-leak complications if ventilatory support is not reduced appropriately as lung mechanics improve after surfactant administration. Newer surfactant delivery mechanisms, such as aerosolized administration, are under development and may be of benefit in reducing the occurrence of hypoxia. Finally, although the course of illness is much less severe in treated infants, the time to recovery is not greatly reduced, and infants with significant RDS can still be expected to require assisted ventilation and careful monitoring. For these reasons, it is

important that all infants who are treated with exogenous surfactant receive their care in nurseries that are appropriately equipped and staffed to provide this ongoing care.

iNO has dramatically affected the way in which term and near-term infants with respiratory failure are managed. The Neonatal Inhaled Nitric Oxide Study (NINOS) Group demonstrated that iNO significantly reduced the need for ECMO in term infants with hypoxic respiratory failure other than CDH but did not reduce mortality [34,35]. The US Food and Drug Administration (FDA) approval of iNO for specific use in term and near-term newborns with hypoxic respiratory failure was obtained in 1999. Application of iNO therapy for severe respiratory failure in premature infants has also been investigated. A recent multicenter randomized, double-blinded, controlled clinical trial of iNO for preterm infants with severe respiratory failure sponsored by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network suggested in a post hoc analysis that the rates of death and BPD are reduced for infants with birth weights over 1,000 g and up to 1,500 g, in contrast to those weighing 1,000 g or less, who had more severe IVH and death [36]. These data suggest the need for further study. A multicenter randomized controlled trial of early administration of iNO in term and near-term infants with respiratory failure demonstrated that iNO can decrease the need for ECMO but had no apparent effect on mortality [34]. Nonetheless, neurodevelopmental impairment or hearing loss was not increased at follow-up. Many centers have also now made iNO available for transport, allowing stabilization of extremely critical neonates who may otherwise not survive transfer to a higher level of care. Complacency as to the reliable effectiveness of iNO therapy in avoiding ECMO may be developing, however, and a temptation to use iNO routinely at non-ECMO centers has followed. The potential danger in this scenario should not be underestimated. The appropriate and safe use of iNO requires an integrated team comprised of respiratory therapists, nurses, and physicians and is best carried out at a center where ECMO is readily available.

Sustaining Cardiac Output

If the cardiac output remains impaired after correction of bradycardia (by assisted ventilation or the administration of epinephrine, isoproterenol, or atropine), hypovolemia, and metabolic disorders (acidemia, hypoglycemia, and hypocalcemia), as described in Chapter 38, inotropic or vasodilator drug therapy may be required.

Inotropic Drugs

Infants may be at risk for myocardial injury and dysfunction because of sepsis or severe asphyxia. Less commonly, myocardial edema, as with hydrops, may compromise myocardial contractility. Administration of β-mimetic catecholamines may increase the stroke volume and cardiac output under such conditions with a structurally normal heart. Infants of poorly controlled diabetic mothers may have a temporary congenital defect characterized by hypertrophic cardiomyopathy. These infants respond with a reduced cardiac output when treated with such drugs because of narrowing of the right ventricular infundibulum [37]; the use of such drugs would be relatively contraindicated in such a scenario. Finally, benefit with inotropes is unlikely if the heart rate or diastolic ventricular volume is inadequate, the pH is below 7.1, or the drug is inactivated by admixture with alkaline solutions for infusion. In general, peripheral IV administration of the drug should be avoided due to the potential for severe local ischemia following extravasation, but it can be tolerated for short periods in larger term or near-term infants. Intraarterial infusions of catecholamines are contraindicated.

Dopamine

Dopamine is the cardiotonic drug most frequently used in the level III nursery. Its effects are dose dependent and similar to those seen in adult patients. Measurable beneficial effects may occur at doses as low as 0.8 μg/kg per minute. Typically, however, the initial dose is 2 μg/kg per minute. At this rate of administration, the effect is predominantly dopaminergic receptor–mediated dilation of renal and splanchnic vessels causing an increase in GFR, urine output, and urinary sodium excretion. β-adrenergic effects result in improved cardiac contractility, a moderate increase in the heart rate, and mild peripheral vasodilation, all contributing to an increased cardiac output [38,39]. Such effects can be observed with doses over 5 μg/kg per minute, but α-adrenergic effects dominate at doses over 15 μg/kg per minute. These effects may result in increased systemic vascular resistance and arterial blood pressures, with a reduction in cardiac output and renal perfusion. The effects

on the pulmonary vascular resistance and pulmonary artery pressure may be less pronounced under some conditions, and the α-adrenergic effects of dopamine may be useful in establishing a favorable ratio of systemic to pulmonary vascular resistance leading to decreased right-to-left shunting in infants with hypoxemia refractory to mechanical ventilation. This differential systemic vasoconstriction may be observed at doses between 10 and 25 μg/kg per minute, particularly when combined with vasodilator infusion.

Despite its frequent use in newborn intensive care, dopamine is not a harmless medicine. It should only be used for appropriate indications, and its use requires continued monitoring. Even when used properly, it can increase myocardial oxygen demands and sometimes causes tachyarrhythmias. In unusual infants, it can also cause intensive vasoconstriction and hypertension at doses that would be considered dopaminergic. This phenomenon is most common with excessive doses.

Dobutamine

This selective β-adrenergic drug can increase cardiac contractility and cardiac output, but has minimal effects on heart rate and vascular tone [38]. It has been used primarily for cardiac shock refractory to dopamine infusion and is often used in conjunction with dopamine. It is administered at a dose between 2.5 and 15 μg/kg per minute, titrated to achieve the desired improvement in cardiac performance. It may be the drug of choice in the initial management of the hypotensive neonate with myocardial dysfunction who does not have evidence of significant peripheral vasodilation [38].

Epinephrine (Adrenaline)

For cardiogenic shock unresponsive to other catecholamines, epinephrine infusion (50–250 ng/kg per minute) may have to be used [38]. However, the benefits of increased contractility are often balanced against the adverse effects of increased vascular resistance.

Afterload Reduction

Another strategy for the management of severely compromised myocardial function is to decrease the systemic vascular resistance (afterload). This should be attempted only after aggressive management of the heart rate, preload, and inotropic therapy has been optimized to improve the cardiac output. Administration of a vasodilator may improve the Frank-Starling relationship between cardiac output and end-diastolic ventricular volumes, moving the curve upward and to the left [40], without affecting myocardial function itself. Dilation of arterioles and precapillary sphincters may reduce the systemic vascular resistance, resulting in increased cardiac output. However, cardiac output may decrease because of reduced preload, which is due to increased venous capacitance, or it may be unchanged if these effects are balanced. Therefore, use of these drugs requires meticulous monitoring and management. This treatment is seldom used in neonatal intensive care, and agents that have been used include nitroprusside and milrinone. The use of bipyridine phosphodiesterase inhibitors (such as milrinone) may provide an alternative to nitroprusside for treating low cardiac output in neonates without adversely affecting endogenous catecholamine levels.

Management of Anemia

The oxygen-carrying capacity of the blood is especially important for newborn infants. Hemoglobin F interacts less well with 2,3-diphosphoglycerate, thus limiting any compensatory response to hypoxia by a shift in the hemoglobin-oxygen dissociation curve [41]. Practically, an oxygen-carrying capacity of at least 16 mL of oxygen/dL may provide a margin of safety for oxygenation in the asphyxiated infant with a normal cardiac output. This translates to a hemoglobin concentration of 12 mg/dL because 1 g of hemoglobin can bind 1.34 mL of oxygen. The minimal desirable hematocrit level of approximately 40% for a distressed neonate is thus derived. In infants for whom optimal oxygen tensions cannot be achieved, the increased oxygen-carrying capacity imparted by an elevation of the hematocrit level to 50% may ensure adequate tissue oxygen delivery, allowing marginal oxygen tensions to be better tolerated.

Evaluation and Management of Refractory Hypoxemia

The infant who remains hypoxemic despite ventilation with 100% oxygen is at risk for cerebral injury depending on the severity and duration of the hypoxemic episode. Although the metabolic hallmark of severe hypoxemia is metabolic acidosis, it is better to suspect hypoxemia and initiate a thorough evaluation

and appropriate therapy than to identify its late consequences. The practitioner should recognize that hypoxemia might be present despite a normal arterial oxygen tension (PaO_2 level > 50 mmHg [6.7 kPa]) or hemoglobin saturation (>90%). In particular, severe anemia (or normotonic hypoxemia) is a common and easily correctable problem, which may have consequences as serious as those created by a low oxygen tension. In fact, infants with severe anemia may present with respiratory distress despite having normal arterial oxygen tensions and oxygen saturations. A normal PaO_2 value may be falsely reassuring in the presence of pallor caused by anemia or acidosis. Thus one should remember that cyanosis might not always be observed with clinically significant hypoxemia. Conversely, a PaO_2 level as low as 40 mmHg (5.3 kPa) may be associated with an oxygen saturation exceeding 90% and adequate oxygen delivery to tissues, especially if hemoglobin F is the predominant hemoglobin and the oxygen-carrying capacity (red cell mass) is normal. Conditions in normotonic hypoxemic infants (methemoglobinemia, hemoglobinopathies) are uncommon causes of hypoxemia in the newborn. From a practical perspective, most infants with reduced arterial oxygen contents have PaO_2 levels below 50 mmHg (6.7 kPa) and present with respiratory difficulty. The physiologic processes contributing to this syndrome include alveolar hypoventilation, impaired diffusion of oxygen from alveoli into blood, ventilation-perfusion mismatching, and right-to-left shunting. Studies useful in evaluation of the neonate with hypotonic hypoxemia (PaO_2 < 50 mmHg [6.7 kPa]) are listed in Table 40.1 and discussed below. In addition, the medical record should include a careful history and physical examination, which may contribute to the diagnosis suggested by those studies. Metabolic disorders (e.g., acidosis, hypoglycemia, and hypocalcemia) and rheologic abnormalities (e.g., hyperviscosity) should always be ruled out before this evaluation is initiated. It should be noted that many of the procedures that have been used in the past to differentiate primary pulmonary disease from cardiac abnormalities have been replaced by the use of echocardiography. We continue to prescribe these evaluations in case an echocardiogram is not available.

Hyperoxia Test

By definition, infants with refractory hypoxemia have already been subjected to the hyperoxia test, which consists simply of determining the PaO_2 level during the administration of 100% oxygen. Most infants who have low arterial oxygen tensions under these conditions have right-to-left shunting as a result of congenital heart disease or pulmonary vascular disease. However, some infants with severe pulmonary parenchymal disease may have persistently low PaO_2 levels owing to diffusion block or ventilation-perfusion mismatching. Those with the latter conditions often respond well to administration of continuous positive airway pressure at 5–6 cmH_2O (0.5–0.6 kPa), with a significant increment in the PaO_2 value. Contrarily, infants with pulmonary hypertension or congenital heart disease usually do less well during such administration and require additional evaluation.

Detection of Ductal Shunting

Simultaneous measurements of pre-ductal (temporal or right radial artery) and post-ductal (umbilical, dorsalis pedis, or posterior tibial artery) oxygen tensions can be performed at the bedside while the infant is breathing 100% oxygen. If the post-ductal PaO_2 level exceeds the pre-ductal value, transposition of the great arteries can be suspected clinically. Right-to-left ductal shunting is present if the pre-ductal PaO_2 level exceeds the post-ductal value by more than 15–20 mmHg (2.0–2.7 kPa). If both the pre- and post-ductal PaO_2 values are low, the absence of such a difference does not exclude ductal shunting. Shunting at other levels (foramen ovale, intrapulmonary) cannot be either excluded or detected by this test. Measurements of systemic blood pressures and assessments of systemic cardiac outputs are essential in interpreting this observation because right-to-left shunting may result from decreases in the systemic arterial pressures or cardiac outputs, as well as increased pulmonary arterial pressures. These hemodynamic abnormalities must be corrected before evaluation of the cause of refractory hypoxemia can be completed using the studies described below.

In current practice, measurement of pre- and post-ductal arterial oxygen tensions to detect right-to-left ductal shunting is complemented by color Doppler echocardiography. This technology permits detection of cardiac structural abnormalities as well as shunt flows at the foramen ovale or ductus arteriosus and should be readily available in all high-level or regional intensive care nurseries.

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Table 40.1 Evaluation of the Neonate with Hypotonic Hypoxemia

Test	Result	Probable diagnosis	Potential causes of error	Additional studies
Hyperoxia	PaO_2 > 150 mmHg (20 kPa)	Pulmonary parenchymal disease	Reactive pulmonary hypertension	Consider pre- and post-ductal PaO_2 or echocardiography
	PaO_2 100–150 mmHg (13–20 kPa)		All diagnoses possible	
	PaO_2 < 100 mmHg (13 kPa)	Right-to-left shunting	Severe pulmonary parenchymal disease	Compare pre- and post-ductal PaO_2; consider trial of continuous positive airway pressure
Pre- and post-ductal PaO_2	Pre-ductal < post-ductal	Transposition of great arteries	Venous pre-ductal sample	Echocardiogram
	Pre-ductal = post-ductal	Intracardiac or intrapulmonary right-to-left shunting	May result from cardiac disease, severe parenchymal disease, or severe pulmonary hypertension	Echocardiogram, electrocardiogram
	Pre-ductal > post-ductal	Ductal right-to-left shunting	Must distinguish pulmonary hypertension from reduced left ventricular output	Assess systemic blood pressure and cardiac output

Source: From Stevenson and Benitz [4].

Information obtained from these diagnostic maneuvers must be combined with that obtained from other studies including chest radiography and echocardiography. These data often do not correspond precisely to a description of a typical infant with any of the conditions listed in Table 40.2 and may appear to be contradictory or confusing. Thoughtful synthesis of all available information, including that from the history, physical examination, and laboratory studies, is required. All diagnostic information must be reevaluated frequently if it becomes apparent that the infant's condition has changed or that the initial diagnostic impression was incorrect or incomplete.

The physician should have a clear understanding of the priorities in the management of neonatal hypoxemia. These priorities are summarized in Table 40.3. The management of any infant with the syndrome of refractory hypoxemia should be discussed with the neonatologist at the regional high-level intensive care nursery while transport is being arranged. The details of this management depend on the diagnosis, the facilities available, and the input of the consulting neonatologist. A comprehensive discussion of the management of conditions that cause refractory hypoxemia is beyond the scope of this chapter; a brief review of three common categories of disease is given in the following sections.

Severe Pulmonary Parenchymal Disease

Diuretic therapy may help to improve pulmonary gas exchange if there is significant pulmonary edema.

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Table 40.2 Pathophysiologic Categories of Refractory Hypoxemia

Category	Characteristics
Reduced systemic pressure	Ductal or intracardiac right-to-left shunting
	Usually no improvement in PaO_2 during hyperventilation
	Reduced systemic blood pressure or cardiac output
Pulmonary hypertension	Ductal or intracardiac right-to-left shunting
	Hyperventilation produces PaO_2 > 100 mmHg (13 kPa) in conditions associated with partially reversible pulmonary arterial constriction
	If the cause of pulmonary hypertension is not associated with reversible arterial constriction of the pulmonary vasculature, the diagnosis depends on recognition of prolonged right ventricular systolic time intervals and exclusion of intrapulmonary right-to-left shunting, cardiac malformations, and systemic hypotension
Congenital heart disease	Ductal or intracardiac right-to-left shunting
	No improvement in PaO_2 during hyperventilation
	Echocardiogram usually diagnostic
Intrapulmonary shunting	No demonstrable ductal shunt
	Modest or no improvement in PaO_2 during hyperventilation
	Usually no evidence for pulmonary hypertension

Source: From Stevenson and Benitz [4].

Table 40.3 Priorities in the Management of Neonatal Hypoxemia

Promote oxygenation by administering appropriate oxygen and assisted ventilation
Correct hypotension and/or anemia by correcting bradycardia and administering plasma and/or blood
Correct metabolic acidosis
Correct hypoglycemia
Correct hypocalcemia
Maintain acid-base homeostasis
Avoid hyperthermia, hypoxia, hyperoxia, severe hypocarbia, and severe hypercarbia
Correct polycythemia, if present
Obtain cultures and treat potential infection with antibiotics

Note: Although these interventions are listed sequentially, it is imperative that they are carried out as expeditiously as possible; it is not appropriate to delay subsequent items while observing the response to initial measures.
Source: Adapted from Stevenson and Benitz [4].

Diuretics are most effective in patients with hypervolemia or pulmonary overperfusion but should be used with great caution in infants with pulmonary edema due to increased capillary permeability (e.g., in postasphyxial or septic infants), in whom intravascular volumes may already be diminished. The effects of diuretics result primarily from the decrease in vascular volume achieved by diuresis, but furosemide also increases venous capacitance, allowing translocation of pulmonary interstitial fluid into the venous system. Prolonged use of furosemide may lead to hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. Moreover, long-term furosemide use may be associated with renal calculi, related to hypercalciuria [42]. Thus the use of other diuretics such as chlorothiazide may be considered.

Persistent patency of the ductus arteriosus beyond the first 48 hours of life may be associated with the shunting of blood from the aorta into the pulmonary artery, causing pulmonary congestion, increased

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interstitial lung fluid, and congestive heart failure. This can exacerbate pulmonary disease in premature infants, leading to a requirement for increased mechanical ventilatory support and consequent complications. There is no uniform agreement regarding the optimal overall approach to ductal closure (medical versus surgical) or the protocol for medical management. In fact, individual trials and meta-analyses have not been able to demonstrate any long-term benefit of medical or surgical intervention to achieve ductal closure [43]. In most centers, active intervention is reserved for selected infants with demonstrable cardiovascular effects and respiratory compromise due to left-to-right shunting. Initial management often consists of fluid restriction and diuretic therapy and may be successful.

If symptomatic ductal patency persists, attempted closure of the ductus with indomethacin is appropriate if there are no contraindications to administration of the drug. Indomethacin is most effective if given in the first few days of life. Closure is achieved most consistently in premature infants with birth weights greater than 1,000 g. A multicenter randomized trial demonstrated that ibuprofen may be as effective as indomethacin in the pharmacologic treatment of PDA in preterm infants [44]. Surgical ligation may be required for infants who do not improve after treatment with indomethacin. The effect of prophylactic treatment with indomethacin on short-term outcome in preterm infants has also been studied by a number of groups, and the drug is routinely used in some institutions. Dosage regimens have varied enormously. A meta-analysis of randomized, controlled trials concluded that prophylactic treatment with IV indomethacin results in significant reductions in symptomatic PDA and severe IVH [45]. Available long-term follow-up studies suggest that such therapy did not improve rates of survival without neurosensory impairment at 18 months [46], but is not associated with adverse neurodevelopmental outcomes at 36 or 54 months' corrected age [47]. In a follow-up evaluation by Ment et al., it was found that males who received prophylactic indomethacin had significantly less IVH and parenchymal hemorrhage and improved verbal scores at 3 and 8 years of age [48]. This improvement was not noted in the girls who were given prophylactic indomethacin. The incidence of a clinically significant ductus arteriosus, in fact, varies greatly among institutions, also reflecting differences in fluid management and ventilator management.

Glomerular filtration, urinary sodium excretion, and urine output can be affected adversely after treatment with indomethacin, especially in infants who already have compromised renal function because of a large PDA [49]. Indomethacin should not be given to an infant with impaired renal function, as evidenced by a creatinine level greater than 1.8 mg/dL or oliguria (urine output < 0.5 mL/kg per hour in the preceding 8 hours). Because platelet function may also be compromised, indomethacin should not be used in infants with a bleeding diathesis or a platelet count of less than 60,000/μL. Spontaneous gastrointestinal perforation has been found to be increased in preterm infants receiving concomitant hydrocortisone and indomethacin [50]. Because necrotizing enterocolitis and focal gastrointestinal perforation have also been associated with oral indomethacin use, the drug should not be used in infants with clinical or radiographic evidence of gastrointestinal dysfunction. Intracranial hemorrhage may also be a relative contraindication to treatment with indomethacin.

Additional discussion of surfactant replacement therapy, use of HFV, and iNO treatment for refractory hypoxemia can be found in the section "Supporting Ventilation" above.

Pulmonary Arterial Disease

Intrinsic disease of the pulmonary arteries is encountered most frequently in cases of PPHN. Pulmonary vascular disease is also a common correlate of disorders that produce an imbalance between pulmonary blood flow and the ability of the pulmonary vascular bed to accommodate flow in utero, such as may occur with pulmonary hypoplasia (e.g., with CDH), premature (intrauterine) closure of the ductus arteriosus, and cardiac malformations associated with increased pulmonary blood flow or pulmonary venous obstruction. Infants with these disorders have both structural and functional abnormalities of the pulmonary arteries, typified by excessive muscularity and hyperreactivity to a variety of stimuli, including hypoxia

and acidemia. These conditions are characterized by increased pulmonary arterial and right heart pressures and right-to-left shunting via the ductus arteriosus and foramen ovale. The diagnosis and management of these disorders are addressed in greater detail in Chapter 36.

Cyanotic Congenital Heart Disease

Maintaining patency of the ductus arteriosus may be lifesaving in a variety of congenital cardiac malformations, including those in which pulmonary blood flow must be derived from the aorta via the ductus arteriosus (because of obstruction of the right heart), those in which systemic perfusion depends on blood flow from the pulmonary artery to the aorta via the ductus arteriosus (due to left-sided heart obstruction), and those in which admixture of blood from the systemic and pulmonary circulations is essential for maintaining a reasonable systemic arterial oxygen content (Table 40.4). This can be accomplished with the infusion of 50–100 ng/kg per minute of prostaglandin E (PGE), gradually decreasing to 10–30 ng/kg per minute in many cases once patency is established [51]. Higher doses of PGE can be associated with diarrhea, fever, tachyarrhythmias, and systemic hypertension. Apnea can also be associated with use of PGE.

Table 40.4 PDA-Dependent Cardiac Malformations

Right-sided heart obstruction
Tricuspid atresia
Pulmonary atresia or severe stenosis
Truncus arteriosus with ductus-dependent pulmonary arteries
Tetralogy of Fallot with obstruction of pulmonary blood flow
Left-sided heart obstruction
Coarctation of the aorta (pre-ductal or juxta-ductal)
Interruption of the aortic arch
Severe aortic stenosis
Mitral atresia/aortic atresia (HLHS spectrum)
Mixing-dependent lesions
Transposition of the great arteries

Source: Modified from Benitz et al. [1].

Management of Cerebral Edema

The management of cerebral edema in infants with hypoxic-ischemic encephalopathy (HIE) remains a controversial issue. Although data in human adults and in intrauterinely asphyxiated fetal monkeys demonstrated that cerebral edema is a major complication of HIE and begins soon after the asphyxial episode, extrapolation of these observations to the human infant is speculative at best [52–54]. Studies in neonatal rats and dogs suggest that the immature brain is relatively resistant to the development and severity of the edema that is seen in the mature animal [55,56]. Based on studies by Brann and Meyers and by Myers in fetal monkeys [52–54], it has been postulated that intrauterine asphyxia leads to intracellular edema, followed by generalized cerebral edema and increased intracranial pressure (ICP). This, in turn, leads to decreased cerebral blood flow and necrosis of brain tissue. Excellent reviews by Volpe, Lupton et al., and Hill suggest an alternative theory [57-59] that following an asphyxial episode, there is loss of vascular autoregulation of cerebral blood flow. Coupled with systemic hypotension, this leads to brain injury and necrosis, which are then followed by the development of cerebral edema.

Not only is there controversy regarding the mechanisms by which cerebral edema occurs, but the incidence and severity of the brain swelling following HIE have not been clearly elucidated. Lupton et al. evaluated 32 asphyxiated term infants during their first week of life with serial ICP measurements using the Ladd ICP monitor, and 26 of the 32 infants had correlative CT scans performed as well [58]. They found that 22% of the infants had increased ICP and that the pressure reached maximum levels between 36 and 72 hours rather than within the first few hours of life. Levene and Evans, using catheters placed in the subarachnoid space to measure ICP, found that 70% of severely asphyxiated newborns had a sustained increase in ICP of greater than 10 mmHg for at least 60 minutes [60]. Of 23 severely asphyxiated infants, 9 did not have increased ICP at any time, 9 had marked and sustained ICPs that were resistant to medical therapy consisting of hyperventilation and infusions of mannitol, and 5 had sustained but mild elevations of ICP that did not respond to infusions of mannitol. Of these five infants, three died, but two infants survived and were subsequently found to be normal. In this series, intracranial monitoring of the 23 infants was of benefit to two infants who responded to

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mannitol and survived. In later reviews, Levene noted that "there is no evidence that routine monitoring of ICP and appropriate management of the elevation of ICP make any improvement in outcome" in the severely asphyxiated newborn [61,62].

Methods of Decreasing Cerebral Edema

Since many infants with HIE have SIADH, fluid restriction and the avoidance of fluid overload are of primary concern. Careful monitoring of fluid intake and output as well as serum electrolytes is indicated in the asphyxiated infant. Other methods of decreasing cerebral edema, such as hyperventilation or the use of steroids and mannitol, are not routinely recommended, although briefly discussed here.

Hyperventilation

Infants have variable respiratory responses to HIE. Some will hyperventilate, some will have normal respiratory rates, and some will hypoventilate and be unresponsive to hypercarbia. By hyperventilating to hypocarbic ranges, cerebral blood flow can be reduced significantly. By decreasing the $PaCO_2$ by 1 mmHg, the cerebral blood flow will be decreased by 3% over the physiological $PaCO_2$ range [8,63]. The response is lessened when the $PaCO_2$ is decreased to 20 mmHg or less [8]. Follow-up of infants with PPHN demonstrated that infants with abnormal neurologic findings in early childhood had longer periods of both hypotension and hypocarbia ($PaCO_2$ < 25 mmHg) than did infants without neurologic sequelae [64].

Bifano and Pfannenstiel also demonstrated that the surviving infants with PPHN who had adverse neurologic sequelae had longer periods of hypocarbia than did survivors without neurologic impairment [12]. Similar to the data of Bernbaum et al. [64], the infants who were treated with prolonged hyperventilation were most likely those infants who were most severely affected with PPHN.

Gleason et al., studying paralyzed and sedated newborn lambs, evaluated the effects of 6 hours of hypocarbia with $PaCO_2$ levels down to 15±2 mmHg on cerebral blood flow. Although the cerebral blood flow was decreased by 35% initially, it returned to baseline levels by 6 hours. Abrupt termination of the hyperventilation resulted in a marked increase in cerebral blood flow within 30 minutes [8]. These authors cautioned that if hypocarbia occurs after hyperventilation is stopped, it could possibly increase the incidence of intracranial hemorrhage. Such situations occur clinically in neonates who fail to respond to hyperventilation and then require treatment with iNO or ECMO.

Wiswell et al. studied a group of prematurely born infants of 33 weeks' gestation or less who were treated with HFJV during the first 72 hours of life [65]. They found that the incidence of cystic periventricular leukomalacia (cPVL) was much greater in infants with greater cumulative periods of hypocarbia during the first 24 hours of life. Other factors, such as degree of hypertension, acidosis, or hypoxemia, did not increase the incidence of cPVL.

A study of 790 infants of 28 weeks' gestation or less who had hypocarbia during their first day of life also reported an increased risk for echolucency on univariate analysis, although the association was diminished in a multivariate analysis [66]. Nevertheless, it is apparent that hypocarbia should be avoided in the infant if at all possible.

Studies by Vannucci et al. using an asphyxiated neonatal rat model demonstrated a protective effect of mild to moderate hypercarbia in animals with asphyxia [67]. Severe hypocarbia did not offer this protective effect [68].

To date, there have been no reported clinical studies evaluating hyperventilation and subsequent hypocarbia as an adjunct in the therapy of infants with HIE. Recommendations that hyperventilation be used to prevent or treat cerebral edema must be viewed with caution. It is currently recommended that normocarbic levels be maintained in these infants and that hyper- or hypocarbia be avoided.

Corticosteroids or Mannitol

Corticosteroids have been used effectively in reducing vasogenic cerebral edema, but they have had little, if any, effect on edema secondary to HIE, meningitis, or edema following trauma to the cranium [69,70]. Levene and Evans found no improvement of cerebral perfusion pressure when using dexamethasone in the treatment of infants with HIE [71]. Barks et al. and Tuor et al. have shown that when neonatal rats were pretreated 24 hours or more with dexamethasone, even at low doses, they were protected from subsequent episodes of cerebral damage due to asphyxia [72,73]. Treatment with

dexamethasone, even in large amounts, had no protective effect if given less than 24 hours prior to or within 24 hours of the asphyxial event. These data are interesting in light of the fact that preterm infants of mothers who had been pretreated with betamethasone and dexamethasone had a decreased incidence and severity of IVH in the neonatal period [74]. Hydrocortisone has been administered for hypotension and presumed adrenal insufficiency in preterm and critically ill term neonates, but its specific effect on cerebral edema has not been investigated. Severe HIE is also a stimulus to the hypothalamic-pituitary-adrenal axis, resulting in elevated endogenous cortisol levels with unclear effects in the context of therapeutic hypothermia. Because there are numerous side effects of steroids, including hypertension, hyperglycemia, and electrolyte aberrations, in addition to potential long-term neurodevelopmental sequelae, the use of these agents in an already fragile patient is not recommended.

Mannitol and other hyperosmolar agents have been used to reduce the amount of cerebral edema following brain injury [75]. Adhikari et al. treated 12 severely asphyxiated infants with a single infusion of 1 g/kg of mannitol and compared them with 13 similarly affected infants who were not given mannitol [75]. No differences were found in the mortality rate, the severity of cerebral edema as measured ultrasonographically, or short-term outcome. In an uncontrolled study, Marchal et al. treated over 200 asphyxiated infants with IV mannitol either before or after 2 hours of age [76]. There were fewer deaths and better neurologic outcomes in infants who were treated early than in those treated after 2 hours. Unfortunately, the types of infants treated and the variability in the severity of disease processes make the interpretation of these data difficult. Although some investigators report that IV mannitol reduces ICP in asphyxiated newborns with cerebral edema, brain injury may not be altered, and most authorities currently do not recommend its use as an adjunct in the treatment of infants with HIE [59,68]. Other potential strategies as adjuncts in the management of infants with hypoxic-ischemic encephalopathy are listed in Table 40.5.

Neuroprotective strategies including hypothermia for infants with HIE are discussed in detail in Chapter 41. A brief overview of some of these potential strategies is included here.

Table 40.5 Potential Strategies Used as Adjuncts in the Management of Infants with HIE

Hypothermia
Barbiturates
Excitatory amino acid (EAA) receptor inhibitors
Oxygen free-radical inhibitors
Monosialgangliosides (GM1)
Lazaroids
Growth factors, including erythropoietin
Xenon
Neuromonitoring

Hypothermia

The use of hypothermia has been evaluated intensively over the past 10 years and is described at length in Chapter 41. Because an encephalopathic infant has a decreased ability to regulate his or her temperature, he or she is at the mercy of the environment. Perinatal hyperthermia, due to maternal fever and/or increased temperature levels in the delivery room, has been shown to be associated with increased risks for developing neonatal encephalopathy and cerebral palsy [77–79]. Shankaran et al., in a multicenter study conducted through the NICHD Neonatal Research Network, found that longer durations of cooling (up to 120 hours) or greater depth of cooling (down to 32° C) did not reduce rates of death [80]. Ongoing research focuses on the effectiveness of therapeutic hypothermia for preterm infants after birth asphyxia and on the use of combination therapies with hypothermia to treat HIE.

Barbiturates

While barbiturates are readily used to control seizures that often accompany severe HIE (see Chapter 42), their use to prevent further brain damage after an asphyxial episode has also been recommended. Since the early 1970s, investigators have demonstrated that barbiturates decrease the rates of cerebral metabolism, decrease ICP, and reduce cellular injury due to the elaboration of oxygen free radicals.

Prior to the advent of therapeutic hypothermia, Svenningsen et al. demonstrated a reduction in mortality and the incidence of neurodevelopmental handicaps when prophylactic phenobarbital at 10 mg/kg was given to term infants with neonatal asphyxia in

two separate time periods [81]. Hall et al. studied the effects of phenobarbital given to term infants with severe asphyxia in a randomized controlled prospective trial [82]. After the infant's blood pressure, ventilation, and acid-base status were stabilized, the infants were given 40 mg/kg of phenobarbital. Seizures occurred in 9 of 15 study infants and 14 of 16 control infants. A follow-up evaluation 3 years later revealed that 11 of 15 infants in the treatment group had normal outcomes, but only 3 of 16 in the control group were normal [82]. There were a number of limitations to the study: no placebo was used; after infant randomization, caretakers were not blinded to the type of treatment; and infants were lost to follow-up (two in the treatment group and three in the control group). Nevertheless, most important, this study showed that no adverse effects were observed with a drug that is often used in an intensive care nursery and that its use appeared to result in a significant decrease in neurologic damage. In the era of therapeutic hypothermia for HIE, phenobarbital as an adjunct treatment has also been investigated. A retrospective study of 68 asphyxiated infants of 36 or more weeks' gestation who received hypothermia for moderate or severe HIE found that infants receiving phenobarbital before hypothermia had increased rates of death or abnormal brain MRI findings [83]. However, some of these infants may have been administered phenobarbital for clinical seizures, which could indicate a more severe initial brain injury. In another retrospective study of 42 infants undergoing whole-body cooling for HIE, prophylactic phenobarbital administration was found to reduce the rate of clinical seizures but not neurodevelopmental impairment [84]. While animal studies suggest that exposure to phenobarbital may lead to apoptotic neurodegeneration in the developing brain [85,86], neonatal seizures may also be associated with worsened neurodevelopmental impairment [87]. Use of other prophylactic anticonvulsant agents (e.g., topiramate or levetiracetam) may warrant further investigation in combination with hypothermia treatment.

A systematic review of anticonvulsant treatment of infants with perinatal asphyxia has concluded that such therapy should be reserved for treatment of clinical seizures. Prophylactic therapy with barbiturates has not been shown to be effective, but aggressive treatment of seizures should be initiated [88]. Until further trials are conducted with long-term neurodevelopmental follow-up, the use of phenobarbital for neuroprotection in the context of hypothermia remains controversial.

Excitatory Amino Acid (EAA) Receptor Inhibitors

EAAs, especially glutamate and aspartate, are the major neurotransmitters found in mammalian brain. The EAAs also have a trophic effect on differentiating neurons and are involved in the regulation of neuroendocrine function as well [89]. When hypoxic-ischemic insults occur, there is increased release of these EAAs up to 100-fold in the brains of adult animals and to a much lesser extent in fetal and neonatal brain tissues [89]. EAAs activate postsynaptic receptors, which, in turn, are coupled to channels that regulate the flow of sodium and calcium ions into the cell. There are two major types of receptors, metabotropic and ionotropic, the latter of which has been studied extensively. The major subtypes of the ionotropic receptors are *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). This latter receptor also mediates the effects of kainic acid and is referred to as the *AMPA/kainic acid (KA) receptor* [90].

Antagonists to these receptors have been studied and used and have also been divided into competitive and noncompetitive antagonists. The competitive antagonists block the glutamate site directly, but because they are polar substances, they do not cross the blood-brain barrier readily. The noncompetitive antagonists to NMDA are used more frequently because they do cross the blood-brain barrier readily. These compounds include ketamine, phencyclidine (PCP or "angel dust"), dizocilpine (MK-801), aptiganel hydrochloride (CNS 112, Cerestat), and dextrorotary opioid derivatives such as dextrorphan and dextromethorphan [90,91].

MK-801, which has the highest affinity for the ion-channel site, has been shown to possess significant neuroprotective properties in both adult and newborn animals. This agent is effective when given prior to or following the asphyxial event in decreasing, but not abolishing, the neuronal damage. However, the toxicity of the agent is profound, even when used in low dosage, and neurobehavioral changes in the surviving animals have been noted as well [91].

Dextromethorphan is another noncompetitive NMDA antagonist and has demonstrated neuroprotective effects in a rabbit model of transient ischemia [92]. The use of this agent as an adjunct to prophylactic therapy in patients undergoing neurosurgical procedures has also demonstrated beneficial effects with modest and reversible side effects [90]. Whether this agent will prove to have neuroprotective effects remains to be seen.

A competitive NMDA receptor antagonist, selfotel, which binds directly to the NMDA site of the glutamate receptor, had been shown to limit neuronal damage in several animal stroke studies. Unfortunately, in humans it was shown to be ineffective after acute ischemic stroke and even exhibited neurotoxic effects in patients with brain ischemia [93].

The magnesium ion also acts as a noncompetitive NMDA antagonist [94], has improved survival following myocardial infarctions, and has been associated with decreased neurologic damage following traumatic brain injury and strokes in adults [95]. Magnesium sulfate ($MgSO_4$) has been used as a tocolytic agent, as an antihypertensive agent, and as protection against the development of seizures in women with preeclampsia [96].

$MgSO_4$ has reduced the severity of asphyxial brain damage in immature rats and mice, but when studied in near-term fetal lambs and piglets, it did not reduce injury to the cerebral cortex [97–100]. Several studies have evaluated the postnatal administration of $MgSO_4$ for the purposes of neuroprotection. Levene et al. evaluated two different doses of $MgSO_4$ in a group of infants when 10-minute Apgar scores were less than 6 or when 5-minute Apgar scores were less than 6 with other clinical and laboratory evidence of fetal distress [101]. The infants received either 250 or 400 mg/kg IV. All the infants receiving 400 mg/kg had cessation of respiratory function for 3–6 hours, but since the infants had already been intubated and ventilated, no harm was encountered. The electroencephalogram (EEG) did not change, but muscle tone and activity were diminished. The infants also had significant lowering of blood pressure. The lower dose did not cause hypotension but did cause some respiratory depression. These authors have advised against using the higher dose of $MgSO_4$ and also have cautioned that respiratory failure can occur even with the lower dose. A multicenter randomized, controlled trial designed to evaluate whether $MgSO_4$ is neuroprotective after birth asphyxia has been suspended [102].

Antenatal $MgSO_4$ administration has also been evaluated extensively. In a review by Marret et al., the results of four major randomized, controlled trials of antenatal $MgSO_4$ therapy in fetuses of less than 34 weeks' gestation were collated and analyzed [103]. Overall, there were no significant differences in mortality or the development of cerebral palsy at follow-up. One of the studies did demonstrate that significant motor dysfunction was found in fewer of the $MgSO_4$-treated infants when they were studied at 2 years of age [104]. Rouse et al. and the Maternal-Fetal Medicine Unit Network of the NICHD investigated the use of $MgSO_4$ in preventing cerebral palsy for women between 24 and 31 weeks' gestation in a large multicenter trial. Fetal exposure to $MgSO_4$ reduced the rate of moderate or severe cerebral palsy (relative risk [RR] 0.55, 95% confidence interval [CI] 0.32–0.95) but did not alter the risk of death [105]. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine released a joint clinical opinion in 2010 stating that available evidence suggests that $MgSO_4$ is a fetal neuroprotectant [106]. Many obstetricians are now routinely administering $MgSO_4$ for fetal neuroprotection to women in preterm labor, and its use may be soon adopted as standard clinical practice.

Calcium-Channel Blockers

Because of the toxicity of increased intracellular calcium accumulation that occurs when a cell is damaged, various drugs have been developed to prevent the influx of the ion into neurons. Investigators from New Zealand demonstrated a neuroprotective effect of one of these blockers, flunarizine, in immature rats [107], as well as in fetal sheep [108]. However, when Levene et al. used nicardipine, another calcium-channel blocker, on four severely asphyxiated neonates, they had severe complications [109]. The mean arterial blood pressure decreased in three infants, and two developed sudden and dramatic hypotension. The authors strongly cautioned against the use of this drug in infants with HIE.

Oxygen Free-Radical Inhibitors

The mechanisms by which oxygen free radicals initiate and perpetuate cellular damage are clearly elucidated in Chapter 3. Although the body produces

naturally occurring antioxidants such as catalase, superoxide dismutase, endoperoxidases, glutathione, and cholesterol, as well as using vitamins C and E in such situations, the elaboration of the oxygen free radicals following an asphyxial event may exceed the infant's ability to generate adequate protection [110]. Drugs such as superoxide dismutase, glutathione peroxidase, and catalase have been used primarily in laboratory animals, but they have limitations, such as a prolonged period to traverse the blood-brain barrier and a narrow therapeutic dosage range. They also have to be given hours before the insult.

Vitamins C and E have also been proven ineffective in these infants. Allopurinol, a xanthine oxidase inhibitor that is converted to oxypurinol, has been shown by Palmer et al. to be of benefit in rats during the reperfusion period [111]. Several investigators have evaluated allopurinol in postasphyxial infants. Van Bel et al. studied 22 infants of 35 weeks' or more gestation who had severe HIE [112], 11 of whom were given 40 mg/kg IV allopurinol and 11 who served as controls. In their report, as well as in a follow-up abstract, a beneficial neurologic outcome was observed. However, in a more recent study from the same center, infants with severe encephalopathy treated with allopurinol showed no differences in mortality or short-term morbidity compared with control infants [113].

Lastly, Gunes et al. evaluated 60 infants with mild, moderate, and severe encephalopathy. Half were treated with 40 mg/kg IV allopurinol daily for 3 days, whereas the other half were given saline [114]. Those with mild encephalopathy did well in both groups, but those with moderate or severe encephalopathy who were treated with allopurinol had decreased NO concentrations in their sera and CSF compared with controls and also had better neurologic and neurodevelopmental outcome at 12 months of age. Obviously, there is still much to be learned regarding the use of allopurinol, especially in the timing of the initiation of therapy, the dosage, and the length of treatment required.

Another antioxidant with considerable promise is melatonin. It also has anti-inflammatory effects and reduces apoptosis in the brain. Melatonin has been shown to be neuroprotective in animal models, both with and without associated hypothermia treatment [115,116]. In a small randomized, controlled trial, Aly et al. studied 15 control infants, 15 infants with HIE treated with hypothermia alone, and 15 infants with HIE receiving both hypothermia and five daily enteral doses (10 mg/kg) of melatonin. The melatonin/hypothermia group had fewer seizures on EEG, fewer white matter abnormalities on MRI, and improved survival without neurologic abnormalities at 6 months of age [117]. Larger studies with long-term follow-up are necessary to evaluate the utility of melatonin as an adjunctive strategy for neonates with HIE.

Monosialogangliosides

These glycosphingolipids, found throughout the body, are found in high concentrations in the nervous system and are important components of cell membranes. Monosialoganglioside (GM1) crosses the placenta and blood-brain barrier and can be incorporated into neural cell membranes. Tan et al., in elegant studies using a fetal sheep model, showed that GM1 given prior to and following repeated episodes of asphyxial damage protected the animals from neurologic sequelae that would ordinarily have occurred [118]. These authors demonstrated that "systemic treatment with GM1 reduced morphologic, biochemical, neurophysiological and behavioral manifestation of hypoxic-ischemic brain damage" [118]. The agent did not cause hypotension or metabolic disturbances in the animals. To date, this form of therapy has not been reported in human neonates.

Lazaroids (21-Aminosteroids)

Methylprednisone has been used for many years to diminish the severity of sequelae following brain and spinal cord injuries [119]. When given in high doses, some beneficial effect was noted in a few patients. Subsequent studies demonstrated that the therapeutic effect was not related to the glucocorticoid or mineralocorticoid actions of the drug but to its effect of limiting lipid peroxidation [120]. Thus 21-aminosteroids were developed as inhibitors of lipid peroxidation. These agents have neither glucocorticoid nor mineralocorticoid activities and are essentially nontoxic. The 21-aminosteroid that has been selected for the acute treatment of brain and spinal injury, ischemic stroke, and subarachnoid hemorrhage is tirilazad mesylate, which is a potent inhibitor of oxygen-radical-induced, ion-catalyzed lipid peroxidation. It appears to exert its effect by a radical scavenging activity and by stabilization of the cellular membrane. This agent also prevents the posttraumatic

permeability of the blood-brain barrier, reduces the extent of cerebral edema, and maintains and preserves endogenous vitamin E levels in tissue [121].

The vast majority of studies with the lazaroids have been accomplished in laboratory animals, including subhuman primates, and phase I trials in humans showed that tirilazad mesylate did not affect cardiovascular parameters, nor did it have any adverse interaction with the calcium-channel blocker nimodipine. In phase II studies of 245 patients with aneurysmal subarachnoid hemorrhage, symptomatic vasospasm was reduced and the Glasgow outcome score was improved in the lazaroid-treated patients compared with controls [121]. Kavanagh and Kam have reviewed studies evaluating the efficacy of lazaroids in the treatment of trauma to the brain and ischemic and subarachnoid hemorrhage and noted that the routine clinical use of these agents was not warranted [122]. Further studies using this agent in acute head and spinal injury, aneurysmal subarachnoid hemorrhage, and ischemic stroke should be forthcoming, and if the drugs have beneficial effects in these patients, use in neonates with HIE may prove beneficial as well. To date, no reports of the use of lazaroids in human neonates have been published.

Growth Factors

The use of various growth factors in the treatment of neonatal encephalopathy is described in Chapter 41. One of the additional neuroprotective agents is erythropoietin. This endogenously produced cytokine promotes red blood cell maturation. McPherson and Juul have reviewed the neuroprotective effects of the agent in the treatment of extremely premature infants and those with neonatal encephalopathy [123]. Most of the studies have been performed in laboratory animals, and they have demonstrated a remarkable potential of erythropoietin as a neuroprotective agent. However, higher doses of the agent were required because only a small fraction, less than 2%, crossed the blood-brain barrier. Thus even 10 times the dose used to treat anemias has been required if neuroprotection is to be achieved. In newborn rat studies, erythropoietin has been shown to significantly protect brain tissues and improve functional recovery 2 weeks following stroke [124]. Wu et al. performed a safety and pharmacokinetics study of 1,000 units/kg IV erythropoietin in 24 neonates undergoing hypothermia for HIE. This dose was well tolerated and produced plasma concentrations previously found to be neuroprotective in animals [125]. Several ongoing trials will help to determine whether this agent can be used in neonatal encephalopathy.

Xenon

Xenon gas is another promising agent that is undergoing extensive evaluation as an adjunctive therapy to hypothermia for HIE. Xenon is a noble gas used as an anesthetic agent that also blocks the NMDA receptor as an EAA receptor inhibitor. Xenon does not cause any increase in apoptotic cell death but does upregulate cytoprotective proteins, including erythropoietin [126]. Several functional and histopathologic animal studies have demonstrated the enhancement of hypothermic neuroprotection after xenon administration [127–129]. Thoresen et al. have also completed a xenon feasibility study in 14 neonates undergoing hypothermia. They found no acute cardiovascular or respiratory complications and no adverse neurodevelopmental effects at the 18-month follow-up [130]. Further neonatal trials with xenon and hypothermia are forthcoming.

Neuromonitoring

Continuous EEG monitoring, magnetic resonance spectroscopy (MRS), near-infrared spectroscopy (NIRS), and monitoring of cerebral blood flow could potentially enhance management of infants with HIE. Some of these technologies are discussed in more detail in Chapters 19. Bedside monitoring with amplitude-integrated EEG (aEEG) or continuous video-EEG during hypothermia can provide important information regarding the occurrence of electrographic seizures requiring anticonvulsant therapy in addition to patterns predictive of outcome. Multiple studies have demonstrated that severely abnormal background activity on aEEG and absent or abnormal sleep-wake cycling patterns are predictive of outcome [131–133]. Hypothermia treatment appears to delay the time at which the aEEG pattern is prognostic, and neonates who recovered aEEG background activity up to 48 hours after birth could still have normal outcomes [134]. Limited studies using bedside NIRS have found that increased cerebral oxygenation levels at 24 hours are associated with death or adverse neurodevelopment outcomes [135,136], likely reflecting diminished oxygen utilization by a severely injured brain. Cerebral blood flow and oxygenation levels may also be beneficial to guide treatment decisions

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when the clinician is faced with fluctuating $PaCO_2$ levels, systemic hypotension, and refractory hypoxemia in an asphyxiated infant. Ongoing neuromonitoring and brain imaging may further assist with decisions regarding redirection of care for neonates with HIE.

Conclusions

Following the resuscitation and stabilization of the encephalopathic infant, it is imperative that the newborn continues to receive intensive observation and care in order to obtain optimal outcome. Knowledge of the factors involved in the encephalopathic process and the provision of meticulous and intensive therapy are paramount if the infant is to survive with as few handicaps as possible. The avoidance of over- and underventilation and hypo- and hyperoxia, appropriate correction of chemical and metabolic abnormalities, judicious monitoring of blood pressure and adequacy of the circulation, and avoidance of hyperthermia are key in enhancing improved outcome. In addition, treatment of definite and suspected bacterial, viral, and fungal infections, after appropriate cultures have been obtained, is also extremely important in the management of the obtunded child. Immediate referrals to centers that can provide specialized therapy such as hypothermia within a small window of opportunity are critical as well. As newer therapies are developed for these infants, it is hoped that we can limit the severity of brain injury and thereby improve neurodevelopmental outcomes. This is an exciting time for our ability to provide these innovative therapies for affected infants, and newer techniques including the use of stem cell therapy are on the horizon. However, it is also important to recognize that many of the encephalopathic infants may have sustained injury days to weeks prior to delivery; in such unfortunate situations, all the technology and therapeutic advantages that we currently have at our disposal will be ineffective in altering the ultimate outcome.

References

1. Benitz WE, Frankel LR, Stevenson DK. The pharmacology of neonatal resuscitation and cardiopulmonary intensive care. II. Extended intensive care. *West J Med* 1986; **145**: 47–51.
2. van den Broek MP, Groenendaal F, Egberts AC, Rademaker CM. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin Pharmacokinet* 2010; **49**: 277–94.
3. Zanelli S, Buck M, Fairchild K. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. *J Perinatol* 2011; **31**: 377–86.
4. Stevenson DK, Benitz WE. A practical approach to diagnosis and immediate care of the cyanotic neonate: stabilization and preparation for transfer to level III nursery. *Clin Pediatr (Phila)* 1987; **26**: 325–31.
5. Bruce DA. Effects of hyperventilation on cerebral blood flow and metabolism. *Clin Perinatol* 1984; **11**: 673–80.
6. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000; **105**: 14–20.
7. Kusuda S, Shishida N, Miyagi N, et al. Cerebral blood flow during treatment for pulmonary hypertension. *Arch Dis Child Fetal Neonatal Ed* 1999; **80**: F30–3.
8. Gleason CA, Short BL, Jones MD Jr. Cerebral blood flow and metabolism during and after prolonged hypocapnia in newborn lambs. *J Pediatr* 1989; **115**: 309–14.
9. Liem KD, Hopman JC, Oeseburg B, et al. Cerebral oxygenation and hemodynamics during induction of extracorporeal membrane oxygenation as investigated by near infrared spectrophotometry. *Pediatrics* 1995; **95**: 555–61.
10. Toft PB, Leth H, Lou HC, et al. Local vascular CO_2 reactivity in the infant brain assessed by functional MRI. *Pediatr Radiol* 1995; **25**: 420–4.
11. Chalak LF, Tarumi T, Zhang R. The "neurovascular unit approach" to evaluate mechanisms of dysfunctional autoregulation in asphyxiated newborns in the era of hypothermia therapy. *Early Hum Dev* 2014; **90**: 687–94.
12. Bifano EM, Pfannenstiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. *Pediatrics* 1988; **81**: 657–61.
13. Hendricks-Munoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 1988; **81**: 650–6.
14. Leavitt AM, Watchko JF, Bennett FC, Folsom RC. Neurodevelopmental outcome following persistent pulmonary hypertension of the neonate. *J Perinatol* 1987; **7**: 288–91.
15. Walsh-Sukys MC, Cornell DJ, Houston LN, et al. Treatment of persistent pulmonary hypertension of

the newborn without hyperventilation: an assessment of diffusion of innovation. *Pediatrics* 1994; **94**: 303–6.

16. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985; **76**: 488–94.
17. Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. *J Pediatr* 1994; **124**: 447–54.
18. Baumgart S, Hirschl RB, Butler SZ, et al. Diagnosis-related criteria in the consideration of extracorporeal membrane oxygenation in neonates previously treated with high-frequency jet ventilation. *Pediatrics* 1992; **89**: 491–4.
19. deLemos R, Yoder B, McCurnin D, et al. The use of high-frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) in the management of the term/near term infant with respiratory failure. *Early Hum Dev* 1992; **29**: 299–303.
20. Bhuta T, Henderson-Smart DJ. Rescue high frequency oscillatory ventilation versus conventional ventilation for pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 1998; **2**: CD000438.
21. Hintz SR, Suttner DM, Sheehan AM, et al. Decreased use of neonatal extracorporeal membrane oxygenation (ECMO): how new treatment modalities have affected ECMO utilization. *Pediatrics* 2000; **106**: 1339–43.
22. Cools F, Offringa M. Meta-analysis of elective high frequency ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 1999; **80**: F15–20.
23. Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2003; **4**: CD000104.
24. Crone RK, Favorito J. The effects of pancuronium bromide on infants with hyaline membrane disease. *J Pediatr* 1980; **97**: 991–3.
25. Goudsouzian NG, Liu LM, Savarese JJ. Metocurine in infants and children: neuromuscular and clinical effects. *Anesthesiology* 1978; **49**: 266–9.
26. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial: neonatal outcome and prolonged analgesia in neonates. *Arch Pediatr Adolesc Med* 1999; **153**: 331–8.
27. Grunau RE, Whitfield MF, Petrie-Thomas J, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain* 2009; **143**: 138–46.
28. Jobe AH. Pulmonary surfactant therapy. *N Engl J Med* 1993; **328**: 861–8.
29. Kendig JW, Ryan RM, Sinkin RA, et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. *Pediatrics* 1998; **101**: 1006–12.
30. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 1998; **3**: CD001149.
31. Bancalari E, del Moral T. Bronchopulmonary dysplasia and surfactant. *Biol Neonate* 2001; **80**(Suppl 1): 7–13.
32. Greenough A. Expanded use of surfactant replacement therapy. *Eur J Pediatr* 2000; **159**: 635–40.
33. Lotze A, Mitchell BR, Bulas DI, et al. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. *J Pediatr* 1998; **132**: 40–7.
34. Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med* 1997; **336**: 597–604.
35. Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics* 1997; **99**: 838–45.
36. Van Meurs KP, Wright LL, Ehrenkranz RA, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med* 2005; **353**: 13–22.
37. Breitweser JA, Meyer RA, Sperling MA, et al. Cardiac septal hypertrophy in hyperinsulinemic infants. *J Pediatr* 1980; **96**: 535–9.
38. Seri I. Systemic and pulmonary effects of vasopressors and inotropes in the neonate. *Biol Neonate* 2006; **89**: 340–2.
39. Zaritsky A, Chernow B. Use of catecholamines in pediatrics. *J Pediatr* 1984; **105**: 341–50.
40. Friedman WF, George BL. Treatment of congestive heart failure by altering loading conditions of the heart. *J Pediatr* 1985; **106**: 697–706.
41. Bard H. Hemoglobin synthesis and metabolism during the neonatal period. In Christensen RD, ed., *Hematologic Problems of the Neonate*. Philadelphia: Saunders, 2000: 374–7.
42. Yeh TF, Shibli A, Leu ST, et al. Early furosemide therapy in premature infants (less than or equal to 2000 g) with respiratory distress syndrome: a randomized, controlled trial. *J Pediatr* 1984; **105**: 603–9.

43. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol* 2010; **30**: 241–52.
44. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000; **343**: 674–81.
45. Fowlie PW. Intravenous indomethacin for preventing mortality and morbidity in very low birth weight infants. *Cochrane Database Syst Rev* 2000; **2**: CD000174.
46. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344**: 1966–72.
47. Ment LR, Vohr B, Allan W, et al. Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000; **105**: 485–91.
48. Ment LR, Vohr BR, Makuch RW, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004; **145**: 832–4.
49. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate strategies. *J Pediatr* 1996; **128**: 601–7.
50. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics* 2004; **114**: 1649–57.
51. Heymann MA. Pharmacologic use of prostaglandin E1 in infant with congenital heart disease. *Am Heart J* 1981; **101**: 837–43.
52. Brann AW, Jr., Myers RE. Central nervous system findings in the newborn monkey following severe in utero partial asphyxia. *Neurology* 1975; **25**: 327–38.
53. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol* 1972; **112**: 246–76.
54. Myers RE. Experimental models of perinatal brain damage: relevance to human pathology. In Gluck L, ed., *Intrauterine Asphyxia and the Developing Fetal Brain*. Chicago: Year Book, 1977: 37–97.
55. Mujsce DJ, Christensen MA, Vannucci RC. Cerebral blood flow and edema in perinatal hypoxic-ischemic brain damage. *Pediatr Res* 1990; **27**: 450–3.
56. Young RS, Yagel SK. Cerebral physiological and metabolic effects of hyperventilation in the neonatal dog. *Ann Neurol* 1984; **16**: 337–42.
57. Hill A. Current concepts of hypoxic-ischemic cerebral injury in the term newborn. *Pediatr Neurol* 1991; **7**: 317–25.
58. Lupton BA, Hill A, Roland EH, et al. Brain swelling in the asphyxiated term newborn: pathogenesis and outcome. *Pediatrics* 1988; **82**: 139–46.
59. Volpe JJ. Hypoxic-ischemic encephalopathy. In Volpe JJ, ed., *Neurology of the Newborn*. Philadelphia: Saunders, 2001: 217–394.
60. Levene MI, Evans DH. Continuous measurement of subarachnoid pressure in the severely asphyxiated newborn. *Arch Dis Child* 1983; **58**: 1013–5.
61. Levene MI. Management and outcome of birth asphyxia. In Levene MI, Lilforde RJ, eds., *Fetal and Neonatal Neurology and Neurosurgery*. Edinburgh: Churchill Livingston, 1995: 427–42.
62. Levene MI, Evans DH, Forde A, Archer LN. Value of intracranial pressure monitoring of asphyxiated newborn infants. *Dev Med Child Neurol* 1987; **29**: 311–9.
63. Rosenberg AA, Jones MD Jr, Traystman RJ, et al. Response of cerebral blood flow to changes in PCO_2 in fetal, newborn, and adult sheep. *Am J Physiol* 1982; **242**: H862–6.
64. Bernbaum JC, Russell P, Sheridan PH, et al. Long-term follow-up of newborns with persistent pulmonary hypertension. *Crit Care Med* 1984; **12**: 579–83.
65. Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics* 1996; **98**: 918–24.
66. Dammann O, Allred EN, Kuban KC, et al. Hypocarbia during the first 24 postnatal hours and white matter echolucencies in newborns ≤28 weeks gestation. *Pediatr Res* 2001; **49**: 388–93.
67. Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM. Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. *Pediatrics* 1995; **95**: 868–74.
68. Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ. Effect of extreme hypercapnia on hypoxic-ischemic brain damage in the immature rat. *Pediatr Res* 2001; **49**: 799–803.
69. Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury: a prospective double-blind study. *J Neurosurg* 1979; **51**: 307–16.
70. Dearden NM, Gibson JS, McDowall DG, et al. Effect of high-dose dexamethasone on outcome from severe head injury. *J Neurosurg* 1986; **64**: 81–8.
71. Levene MI, Evans DH. Medical management of raised intracranial pressure after severe birth asphyxia. *Arch Dis Child* 1985; **60**: 12–6.

72. Barks JD, Post M, Tuor UI. Dexamethasone prevents hypoxic-ischemic brain damage in the neonatal rat. *Pediatr Res* 1991; **29**: 558–63.

73. Tuor UI, Simone CS, Barks JD, Post M. Dexamethasone prevents cerebral infarction without affecting cerebral blood flow in neonatal rats. *Stroke* 1993; **24**: 452–7.

74. National Institutes of Health Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation of Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1994; **273**: 413–8.

75. Adhikari M, Moodley M, Desai PK. Mannitol in neonatal cerebral oedema. *Brain Dev* 1990; **12**: 349–51.

76. Marchal C, Costagliolu P, Leaveau P, Wong RJ. Treatment de la souffrance cerebrale neonatale d'orisivie anoxique par le mannitol. *Rev Pediatr* 1974; **9**: 581–9.

77. Adamson SJ, Alessandri LM, Badawi N, et al. Predictors of neonatal encephalopathy in full-term infants. *BMJ* 1995; **311**: 598–602.

78. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998; **317**: 1554–8.

79. Shankaran S. The postnatal management of the asphyxiated term infant. *Clin Perinatol* 2002; **29**: 675–92.

80. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *JAMA* 2014; **312**: 2629–39.

81. Svenningsen NW, Blennow G, Lindroth M, et al. Brain-orientated intensive care treatment in severe neonatal asphyxia: effects of phenobarbitone protection. *Arch Dis Child* 1982; **57**: 176–83.

82. Hall RT, Hall FK, Daily DK. High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 1998; **132**: 345–8.

83. Sarkar S, Barks JD, Bapuraj JR, et al. Does phenobarbital improve the effectiveness of therapeutic hypothermia in infants with hypoxic-ischemic encephalopathy? *J Perinatol* 2012; **32**: 15–20.

84. Meyn DF Jr, Ness J, Ambalavanan N, Carlo WA. Prophylactic phenobarbital and whole-body cooling for neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 2010; **157**: 334–6.

85. Diaz J, Schain RJ. Phenobarbital: effects of long-term administration on behavior and brain of artificially reared rats. *Science* 1978; **199**: 90–1.

86. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci USA* 2002; **99**: 15089–94.

87. Miller SP, Weiss J, Barnwell A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology* 2002; **58**: 542–8.

88. Evans DJ, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. *Cochrane Database Syst Rev* 2007; **3**: D001240.

89. Giacoia GP. Asphyxial brain damage in the newborn: new insights into pathophysiology and possible pharmacologic interventions. *South Med J* 1993; **86**: 676–82.

90. Muir KW, Lees KR. Clinical experience with excitatory amino acid antagonist drugs. *Stroke* 1995; **26**: 503–13.

91. Levene M. Role of excitatory amino acid antagonists in the management of birth asphyxia. *Biol Neonate* 1992; **62**: 248–51.

92. Steinberg GK, Bell TE, Yenari MA. Dose escalation safety and tolerance study of the N-methyl-D-aspartate antagonist dextromethorphan in neurosurgery patients. *J Neurosurg* 1996; **84**: 860–6.

93. Davis SM, Lees KR, Albers GW, et al. Selfotel in acute ischemic stroke: possible neurotoxic effects of an NMDA antagonist. *Stroke* 2000; **31**: 347–54.

94. Parikka H, Toivonen L, Naukkarinen V, et al. Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infarction. *Eur Heart J* 1999; **20**: 111–20.

95. Lampl Y, Gilad R, Geva D, et al. Intravenous administration of magnesium sulfate in acute stroke: a randomized double-blind study. *Clin Neuropharmacol* 2001; **24**: 11–5.

96. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; **333**: 201–5.

97. de Haan HH, Gunn AJ, Williams CE, et al. Magnesium sulfate therapy during asphyxia in near-term fetal lambs does not compromise the fetus but does not reduce cerebral injury. *Am J Obstet Gynecol* 1997; **176**: 18–27.

98. Marret S, Gressens P, Gadisseux JF, Evrard P. Prevention by magnesium of excitotoxic neuronal death in the developing brain: an animal model for clinical intervention studies. *Dev Med Child Neurol* 1995; **37**: 473–84.

99. McDonald JW, Silverstein FS, Johnston MV. Magnesium reduces N-methyl-D-aspartate (NMDA)–mediated brain injury in perinatal rats. *Neurosci Lett* 1990; **109**: 234–8.

100. Penrice J, Amess PN, Punwani S, et al. Magnesium sulfate after transient hypoxia-ischemia fails to prevent delayed cerebral energy failure in the newborn piglet. *Pediatr Res* 1997; **41**: 443–7.

101. Levene M, Blennow M, Whitelaw A, et al. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. *Arch Dis Child Fetal Neonatal Ed* 1995; **73**: F174–7.

102. Robertson NJ, Edwards AD. Recent advances in developing neuroprotective strategies for perinatal asphyxia. *Curr Opin Pediatr* 1998; **10**: 575–80.

103. Marret S, Doyle LW, Crowther CA, Middleton P. Antenatal magnesium sulphate neuroprotection in the preterm infant. *Semin Fetal Neonatal Med* 2007; **12**: 311–7.

104. Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized, controlled trial. *JAMA* 2003; **290**: 2669–76.

105. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.

106. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Magnesium sulfate before anticipated preterm birth for neuroprotection (Committee Opinion No. 455). *Obstet Gynecol* 2010; **115**: 669–71.

107. Gunn AJ, Mydlar T, Bennet L, et al. The neuroprotective actions of a calcium channel antagonist, flunarizine, in the infant rat. *Pediatr Res* 1989; **25**: 573–6.

108. Gunn AJ, Williams CE, Mallard EC, et al. Flunarizine, a calcium channel antagonist, is partially prophylactically neuroprotective in hypoxic-ischemic encephalopathy in the fetal sheep. *Pediatr Res* 1994; **35**: 657–63.

109. Levene MI, Gibson NA, Fenton AC, et al. The use of a calcium-channel blocker, nicardipine, for severely asphyxiated newborn infants. *Dev Med Child Neurol* 1990; **32**: 567–74.

110. Buonocore G, Groenendaal F. Anti-oxidant strategies. *Semin Fetal Neonatal Med* 2007; **12**: 287–95.

111. Palmer C, Towfighi J, Roberts RL, Heitjan DF. Allopurinol administered after inducing hypoxia-ischemia reduces brain injury in 7-day-old rats. *Pediatr Res* 1993; **33**: 405–11.

112. Van Bel F, Shadid M, Moison RM, et al. Effect of allopurinol on postasphyxial free radical formation, cerebral hemodynamics, and electrical brain activity. *Pediatrics* 1998; **101**: 185–93.

113. Benders MJ, Bos AF, Rademaker CM, et al. Early postnatal allopurinol does not improve short term outcome after severe birth asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2006; **91**: F163–5.

114. Gunes T, Ozturk MA, Koklu E, et al. Effect of allopurinol supplementation on nitric oxide levels in asphyxiated newborns. *Pediatr Neurol* 2007; **36**: 17–24.

115. Welin AK, Svedin P, Lapatto R, et al. Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. *Pediatr Res* 2007; **61**: 153–8.

116. Robertson NJ, Faulkner S, Fleiss B, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. *Brain* 2013; **136**: 90–105.

117. Aly H, Elmahdy H, El-Dib M, et al. Melatonin use for neuroprotection in perinatal asphyxia: a randomized controlled pilot study. *J Perinatol* 2015; **35**: 186–91.

118. Tan WK, Williams CE, Mallard CE, Gluckman PD. Monosialoganglioside GM1 treatment after a hypoxic-ischemic episode reduces the vulnerability of the fetal sheep brain to subsequent injuries. *Am J Obstet Gynecol* 1994; **170**: 663–9.

119. Hall ED. The neuroprotective pharmacology of methylprednisolone. *J Neurosurg* 1992; **76**: 13–22.

120. Amar AP, Levy ML. Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. *Neurosurgery* 1999; **44**: 1027–39; discussion 39–40.

121. Hall ED, McCall JM, Means ED. Therapeutic potential of the lazaroids (21-aminosteroids) in acute central nervous system trauma, ischemia and subarachnoid hemorrhage. *Adv Pharmacol* 1994; **28**: 221–68.

122. Kavanagh RJ, Kam PC. Lazaroids: efficacy and mechanism of action of the 21-aminosteroids in neuroprotection. *Br J Anaesth* 2001; **86**: 110–9.

123. McPherson RJ, Juul SE. Recent trends in erythropoietin-mediated neuroprotection. *Int J Dev Neurosci* 2008; **26**: 103–11.

124. Gonzalez FF, McQuillen P, Mu D, et al. Erythropoietin enhances long-term neuroprotection and neurogenesis in neonatal stroke. *Dev Neurosci* 2007; **29**: 321–30.

125. Wu YW, Bauer LA, Ballard RA, et al. Erythropoietin for neuroprotection in neonatal encephalopathy: safety and pharmacokinetics. *Pediatrics* 2012; **130**: 683–91.

126. Sabir H, Bishop S, Cohen N, et al. Neither xenon nor fentanyl induces neuroapoptosis in the newborn pig brain. *Anesthesiology* 2013; **119**: 345–57.

127. Ma D, Hossain M, Chow A, et al. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Ann Neurol* 2005; **58**: 182–93.

128. Hobbs C, Thoresen M, Tucker A, et al. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. *Stroke* 2008; **39**: 1307–13.

129. Chakkarapani E, Dingley J, Aquilina K, et al. Effects of xenon and hypothermia on cerebrovascular pressure reactivity in newborn global hypoxic-ischemic pig model. *J Cereb Blood Flow Metab* 2013; **33**: 1752–60.

130. Dingley J, Tooley J, Liu X, et al. Xenon ventilation during therapeutic hypothermia in neonatal encephalopathy: a feasibility study. *Pediatrics* 2014; **133**: 809–18.

131. Osredkar D, Toet MC, van Rooij LG, et al. Sleep-wake cycling on amplitude-integrated electroencephalography in term newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 2005; **115**: 327–32.

132. Hellstrom-Westas L, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **72**: F34–8.

133. Toet MC, Hellstrom-Westas L, Groenendaal F, et al. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F19–23.

134. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* 2010; **126**: e131–9.

135. Ancora G, Maranella E, Grandi S, et al. Early predictors of short term neurodevelopmental outcome in asphyxiated cooled infants: a combined brain amplitude integrated electroencephalography and near infrared spectroscopy study. *Brain Dev* 2013; **35**: 26–31.

136. Toet MC, Lemmers PM, van Schelven LJ, van Bel F. Cerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. *Pediatrics* 2006; **117**: 333–9.

Chapter

41 Endogenous and Exogenous Neuroprotective Mechanisms after Hypoxic-Ischemic Injury

Joanne O. Davidson, Laura Bennet, and Alistair J. Gunn*

Introduction

Nearly all infants are exposed to periods of compromised gas exchange before and during labor (see Chapter 14), and yet only a remarkably small proportion of newborns develop hypoxic-ischemic encephalopathy (HIE). Indeed, even severe metabolic acidosis at birth is associated with HIE in less than half of cases [1]. Similarly, experimental studies typically report that cerebral injury occurs only in a very narrow temporal window between survival with complete recovery and death [2,3]. Partly this is a reflection of the efficiency of the fetal adaptations that maintain perfusion to the essential organs. However, it also reflects a fine balance between injurious events triggered by hypoxia-ischemia and countervailing endogenous protective processes that help limit neural injury. These processes may be modified, raising the possibility of treating acute encephalopathy.

Biphasic Cell Death after Hypoxic-Ischemic Injury

The critical observation from experimental studies in vivo and in vitro and clinical observations is that HIE is not a single "event" but rather is an evolving process (Figure 41.1). During the immediate period of hypoxia-ischemia (which may be termed the *primary phase* of the insult), high-energy metabolites are depleted, with progressive depolarization of cells, severe cytotoxic edema (cell swelling) [4], and extracellular accumulation of excitatory amino acids due to failure of reuptake by astroglia and excessive depolarization-mediated release [5]. Although neurons may die during a sufficiently prolonged period of ischemia or asphyxia, many neurons initially recover, at least partially, from the insult in a so-called latent phase, only to die many hours or even days later (secondary or delayed cell death). Using magnetic resonance spectroscopy (MRS), Wyatt et al. showed that many infants with evidence of moderate to severe asphyxia show initial, transient recovery of cerebral oxidative metabolism after birth, followed by secondary deterioration with cerebral energy failure from 6 to 15 hours after birth [6]. The severity of the secondary deterioration is closely correlated with neurodevelopmental outcome at 1 and 4 years of age [7], and infants with encephalopathy who do not show initial recovery of cerebral oxidative metabolism have extremely poor outcomes [6]. An identical pattern of initial recovery of cerebral oxidative metabolism followed by delayed (secondary) energy failure is also seen after hypoxia-ischemia in the piglet, rat, and fetal sheep and is closely correlated with the severity of neuronal injury [8–10]. The timing of energy failure after hypoxia-ischemia is tightly coupled with the appearance of histologic brain damage [11], implying that it is primarily a function of evolving cell death (Figure 41.1).

It is this delay before secondary deterioration in a latent phase that offers the tantalizing possibility for therapeutic intervention. More recent studies have provided a detailed time course of the evolution of injury. Because oxidative synthesis of ATP is mediated through the mitochondrial electron transport chain, loss of the terminal electron acceptor, cytochrome oxidase (CytOx), is a close surrogate for mitochondrial failure and loss of the ability to produce high-energy phosphates [12]. Continuous, non-invasive measurements with near-infrared spectroscopy (NIRS) demonstrate that after severe asphyxia in fetal sheep there is initial recovery of CytOx values, followed by a progressive fall, starting from approximately 3–4 hours and continuing until approximately 48 hours after asphyxia [10]. Delayed

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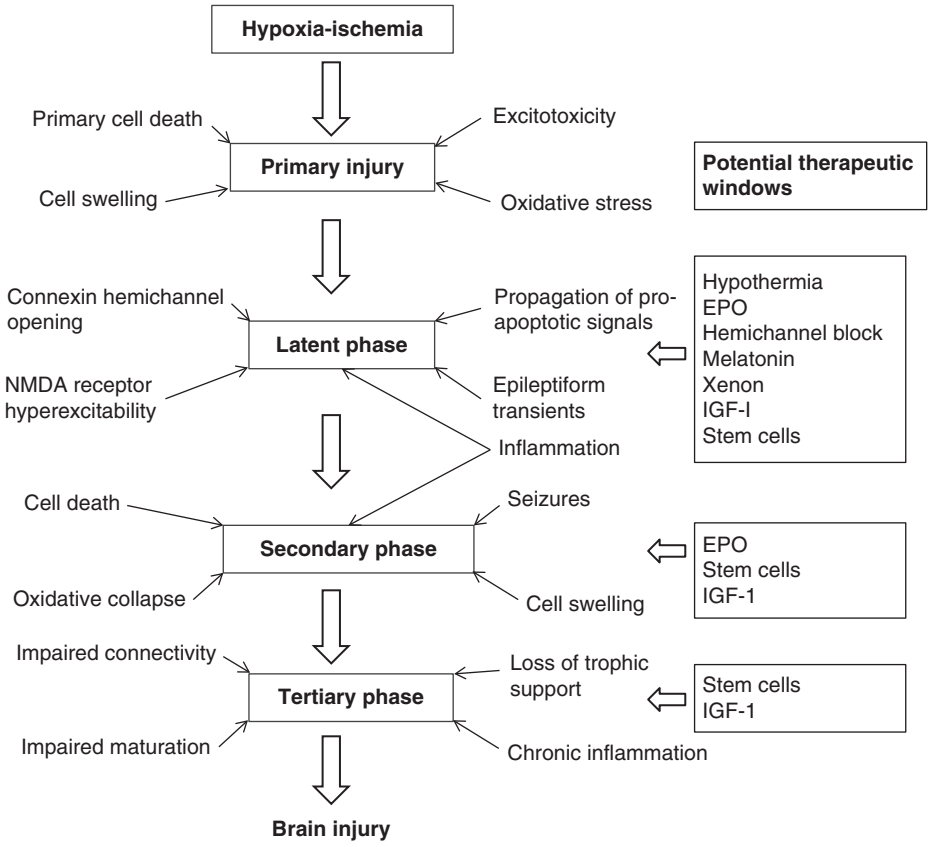


Figure 41.1 Mechanisms of injury contributing to the primary phase, latent phase, and secondary and tertiary phases leading to the evolution of brain damage and disability. Potential therapeutic windows of opportunity for intervention in the evolution of injury are shown for each phase.

loss of mitochondrial activity was associated with a marked *increase* in relative intracerebral oxygenation consistent with impaired ability to use oxygen [10].

Characteristic pathophysiologic events may be distinguished during this critical latent phase compared with the secondary phase (Figure 41.2). After restoration of circulation and oxygenation, the initial hypoxia-induced impairments of cerebral oxidative metabolism, cytotoxic edema, and accumulation of excitatory amino acids resolve over approximately 30–60 minutes [4,5]. Despite normalization of oxidative cerebral energy metabolism and mitochondrial activity [10], mean electroencephalogram (EEG) activity remains depressed [13], while cerebral blood flow (CBF) initially recovers, followed by a transient secondary fall [4,10]. During the subsequent secondary deterioration starting many hours later (approximately 6–15 hours after the insult) and continuing over many days, delayed seizures develop [4,10], accompanied by secondary cytotoxic edema (cell swelling) [4], accumulation of excitotoxins [5] and failure of cerebral mitochondrial activity [8,10] and, ultimately, cell death [4]. In contrast, secondary energy failure is not seen after lesser insults that do not produce brain dysfunction [14].

These concepts – that an acute, global insult can trigger evolving injury and that characteristic events are seen at different times after the insult – are central to understanding the causes and treatment of neonatal encephalopathy.

Therapeutic Hypothermia

Compelling experimental evidence from multiple preclinical paradigms [15] led to multiple randomized, controlled trials (RCTs) of mild induced hypothermia for neonatal HIE. A systematic meta-analysis of 11

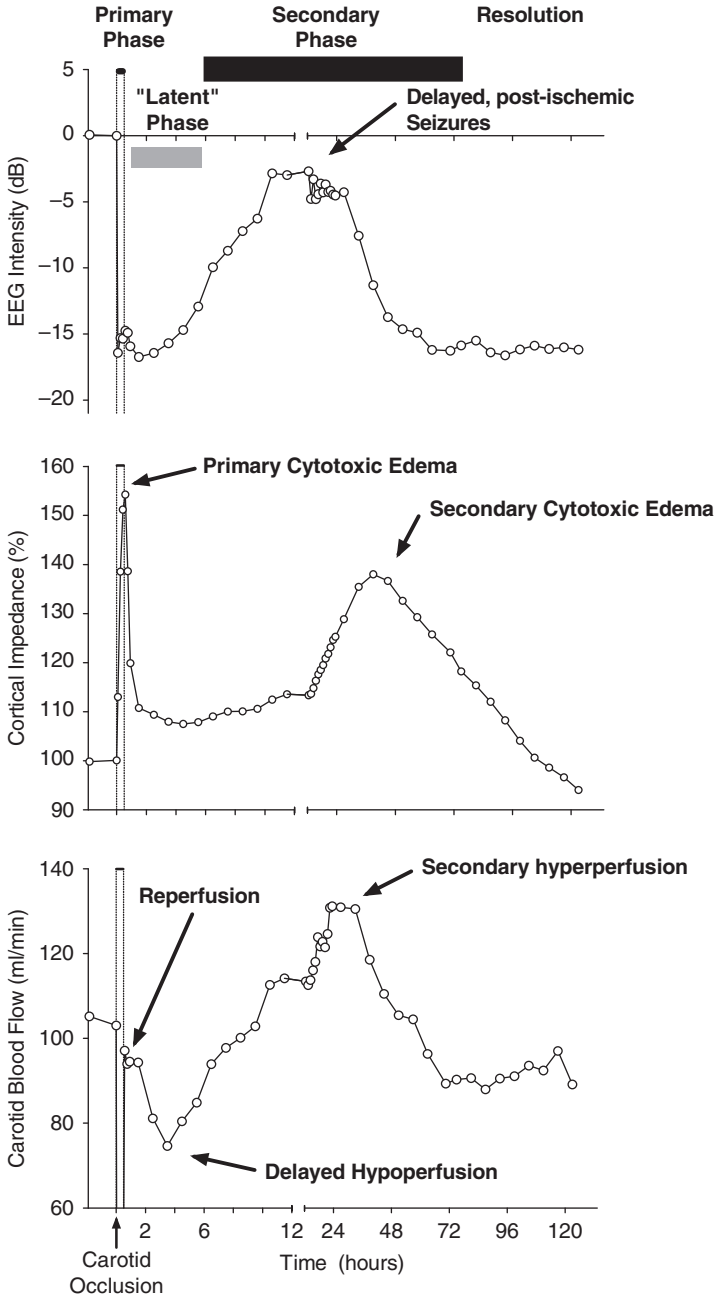


Figure 41.2 An illustration of the pathophysiologic phases of injury after 30 minutes of global cerebral ischemia in fetal sheep ($n = 7$). See the text for details. (Data derived from Gunn et al. [4].)

RCTs of either selective head cooling or whole-body cooling initiated within 6 hours of birth involving 1,505 term and late-preterm infants with moderate/severe HIE found highly consistent beneficial effects after hypothermia [16]. Mild hypothermia was associated with reduced mortality or major neurodevelopmental disability by 18 months of age (relative risk [RR] 0.75, 95% confidence interval [CI] 0.68–0.83). Cooling reduced mortality (RR 0.75, 95% CI 0.64–0.88, 11 studies, 1,468 infants), with reduced neurodevelopmental disability in survivors (typical RR 0.77, 95% CI 0.63–0.94, 8 studies, 917 infants).

Long-term follow-up of these studies is ongoing; the available evidence suggests a similar improvement in outcomes in middle childhood after mild induced hypothermia for HIE [17–19]. For example, the Total

Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) has shown that significantly more children in the mild hypothermia group survived with an IQ score of 85 or more compared with the control group (52% versus 39%; RR 1.31, $p = 0.04$) and that more children in the hypothermia group survived without neurologic abnormalities than in the control group (45% versus 28%; RR 1.60, 95% CI 1.15–2.22) [18]. Further, there was a significant reduction in the risk of cerebral palsy (21% versus 36%; $p = 0.03$) and of moderate or severe disability (22% versus 37%; $p = 0.03$).

It Is Possible to Further Optimize Therapeutic Hypothermia?

Despite significantly reducing death and disability, current protocols for therapeutic hypothermia are only partially neuroprotective, with a number needed to treat of 7 (95% CI 5–10, 8 studies, 1,344 infants) [16]. As reviewed, the experimental efficacy of hypothermia is highly dependent on *the timing of initiation* and *depth and duration* of cooling [15]. Thus, potentially, it may be possible to further optimize regimens for therapeutic hypothermia.

The Timing of Initiation of Hypothermia

There is highly consistent evidence that hypothermia must be started as early as possible within the latent phase for optimal benefit. In near-term fetal sheep, moderate hypothermia induced 90 minutes after reperfusion from a severe episode of cerebral ischemia, in the early latent phase, and continued until 72 hours after ischemia prevented secondary cytotoxic edema and improved EEG recovery [4]. There was a concomitant substantial reduction in cortical infarction and improvement in neuronal loss scores in all regions (Figure 41.3). Similar neuroprotective effects were seen when treatment was delayed until 3 hours after the end of ischemia, but when the start of hypothermia was delayed until just before the onset of secondary seizures (5.5 hours after reperfusion), only partial neuroprotection was seen [20]. With further delay until after seizures were established (8.5 hours after reperfusion), there was no electrophysiologic or overall histologic protection with cooling [21].

Similar results have been reported in a wide range of species and paradigms. For example, in anaesthetized neonatal rats subjected to moderate hypoxia-ischemia, mild hypothermia (2–3°C decrease in brain temperature) for 72 hours from the end of hypoxia prevented cortical infarction, whereas cooling delayed until 6 hours after the insult had an intermediate, nonsignificant effect [22]. In anesthetized piglets exposed to either hypoxia with bilateral carotid ligation or hypoxia with hypotension, either 12 hours of mild whole-body hypothermia (35°C) or 24 hours of head cooling with mild systemic hypothermia started immediately after hypoxia prevented delayed energy failure, reduced neuronal loss, and suppressed posthypoxic seizures [23,24].

Clinical evidence supports the importance of the delay in initiation of hypothermia, with infants treated within 3 hours of birth having significantly better motor outcomes than those treated after 3 hours [25]. However, in a controlled trial, hypothermia was only started in 12% of infants within 4 hours of birth; at that time, many infants were already showing electrographic seizures [26]. This is earlier than typically reported in preclinical studies and is consistent with clinical evidence that many hypoxic-ischemic insults evolve over time before birth. Thus the timing of the insult is often not clearly known [27]. Moreover, accurate staging of encephalopathy can be

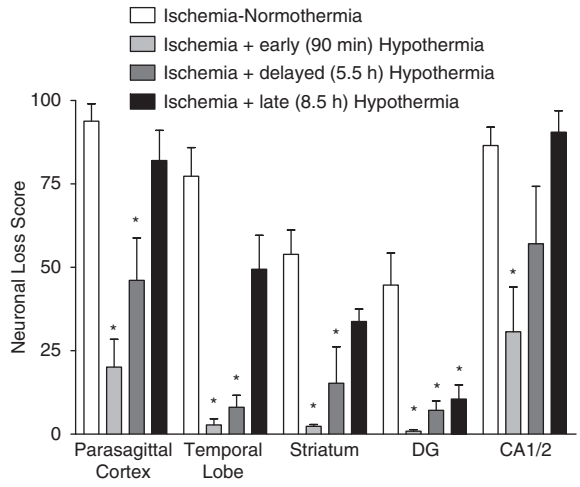


Figure 41.3 The effect of cerebral cooling in fetal sheep started at different times after reperfusion and continued until 72 hours on neuronal loss after 5 days of recovery from 30 minutes of cerebral ischemia [4,20,21]. Compared with sham cooling ($n = 13$), cooling started 90 minutes after reperfusion ($n = 7$) was highly protective. In contrast, cooling started just before the end of the latent phase (5.5 hours after reperfusion, $n = 11$) was partially protective, and cooling started shortly after the start of the secondary phase (8.5 hours after reperfusion, $n = 5$) was not. DG, dentate gyrus of the hippocampus; CA1/2, cornu ammonis fields 1 and 2 of the hippocampus. *$p < 0.005$ compared with sham-cooled (control) fetuses; data are mean ± SEM.

difficult in the critical latent phase of injury, so diagnosis may be delayed until after the onset of seizure activity, by which time the efficacy of hypothermia is greatly reduced.

How Deep Is Too Deep?

The critical depth of hypothermia required for protection seems to vary depending on the delay before initiation and the severity and nature of the insult. For example, in the infant rat, mild cooling of just 1–2°C was highly protective, provided that it was started immediately after hypoxia [22]. In contrast, when cooling was delayed until 6 hours, in both adult rodents and fetal sheep, greater functional and histologic neuroprotection was seen with a 5°C reduction than with 3°C [28]. A recent study in neonatal piglets showed that whole-body hypothermia, with a reduction in body temperature of between 3.5 and 5°C was associated with significant neuroprotection, whereas a reduction of 8°C was detrimental after global cerebral ischemia [29]. These findings suggest that there is a relatively broad range in which cooling is beneficial for the brain, and thus, reassuringly, it should not be generally necessary to reduce core temperatures by more than approximately 3.5°C.

If Some Is Good, Is More Better?

Relatively extended periods of cooling, of between 12 and 72 hours, have been associated with the most consistent evidence of neuroprotection [15]. Critically for clinical practice, the greater the delay before starting cooling or the more severe the insult, the greater is the duration of cooling required for protection. For example, in the adult gerbil, when the delay before initiating a 24-hour period of cooling was increased from 1 to 4 hours, neuroprotection in the CA1 region of the hippocampus after 6 months of recovery fell from 70% to 12% [30]. Subsequent studies demonstrated that protection could be restored by extending the duration of moderate (32–34°C) hypothermia to 48 hours or more, even when the start of cooling was delayed until 6 hours after reperfusion [31]. Similarly, in near-term fetal sheep, cooling started after 5.5 hours and continued until 72 hours was still partially protective [20] (Figure 41.3).

Given this compelling evidence that hypothermia must be continued for at least 48–72 hours, there is now increasing interest in whether further prolonging the duration of hypothermia may be associated with greater benefit. However, in term-equivalent fetal sheep, when delayed hypothermia starting 3 hours after ischemia was prolonged from 3 to 5 days, there was no further improvement in electrophysiologic recovery or neuronal survival or reduction in cortical microglial induction, and indeed, there was a small reduction in neuronal survival in the parasagittal cortex and the dentate gyrus [32]. Consistent with these experimental data, a recent clinical trial of prolonged duration and increased depth of therapeutic hypothermia was abandoned due to a likely lack of effect and safety concerns [33]. The adjusted risk ratio for death in the neonatal intensive care unit after cooling for 120 hours compared with 72 hours was 1.37 (95% CI 0.92–2.04) and for the 32°C compared with 33.5°C was 1.24 (95% CI 0.69–2.25).

These studies suggest that current protocols are reasonably close to optimal. The best established way to further improve outcomes from therapeutic hypothermia in infants with HIE is to start cooling earlier, as soon as possible after birth. Alternatively, cooling plus other pharmacologic neuroprotective agents may enable further improvements in outcome. There is currently considerable interest in such options based on potentially neuroprotective endogenous compounds found in the body as well as exogenous agents.

Therapeutic Targets for Neuroprotection

The clinical and experimental data just reviewed suggest that the latent phase between the initial insult and secondary energy failure corresponds with the activation of cell death processes. Major initial triggers of the delayed death cascade during exposure to hypoxia-ischemia include exposure to oxygen free-radical toxicity, excessive levels of excitatory amino acids, and intracellular calcium accumulation down the concentration gradient due to failure of energy-dependent pumps during hypoxia and opening of channels linked to the excitatory neurotransmitters [34]. However, these events rapidly resolve during reperfusion from the insult and thus cannot readily be related to the effects of postinsult interventions such as cooling. It is striking that even in vitro neuronal degeneration can be prevented by cooling initiated well after exposure to an insult [35]. Thus the critical effects of hypothermia must be on secondary consequences of hypoxia-ischemia, such as the intracellular progression of programmed cell death

(apoptosis), the inflammatory reaction, and abnormal receptor activity [36].

Programmed Cell Death

There is good histologic evidence that activation of preexisting programmed cell death pathways is a significant contributor to posthypoxic cell death in the developing human brain. In reality, post-hypoxic-ischemic cell death is not purely apoptotic but rather includes elements of both apoptotic and necrotic processes, with one or the other being most prominent depending on factors such as maturity and the severity of insult [37]. Consistent with the hypothesis that apoptotic processes are a key therapeutic target, post-insult hypothermia started after severe hypoxia-ischemia was reported to reduce apoptotic cell death but not necrotic cell death in the piglet [38]. Similarly, protection with post-hypoxic-ischemic hypothermia in fetal sheep has been closely linked with suppression of activated caspase-3 [39].

Inflammatory Second Messengers

Brain injury leads to induction of the inflammatory cascade with increased release of cytokines [40]. These compounds are believed to exacerbate delayed injury, whether by direct neurotoxicity and induction of apoptosis or by promoting stimulation of leukocyte adhesion and infiltration into the ischemic brain. Experimentally, cooling can potently suppress this inflammatory reaction [15]. For example, in vitro, hypothermia inhibits proliferation and superoxide and nitric oxide production by cultured microglia, and in adult rats, hypothermia suppresses the post-traumatic release of interleukin-1β and accumulation of polymorphonuclear leukocytes. Similarly, neuroprotection with postinsult hypothermia was associated with suppression of microglial activation in fetal sheep [32,39,41].

Other receptor and non-receptor-mediated toxic factors are likely to contribute to neural injury in the latent phase. For example, there is some evidence from preterm fetal sheep for delayed production of oxygen free radicals after hypoxia-ischemia [42], which may be particularly associated with death of oligodendroglia.

Excitotoxity after Hypoxia-Ischemia

Pathologically elevated levels of extracellular excitatory amino acids such as glutamate are seen in a biphasic pattern. The initial increase occurs *during* hypoxia-ischemia, which resolves rapidly after reperfusion to control values [5]. Levels remain low throughout the latent phase and then secondarily rise many hours later in association with delayed seizures and cytotoxic edema [5,43]. In term-equivalent fetal sheep, for example, intense seizures are seen from approximately 9 ± 2 to 30 ± 3 hours after cerebral ischemia; completely suppressing these large-amplitude seizures with a selective glutamate antagonist was associated with very limited reduction in neuronal damage in more mildly affected regions but no effect on infarction of the parasagittal cortex and no improvement in recovery of EEG activity [44]. Moreover, combined antiglutamate treatment and mild whole-body hypothermia after severe asphyxia showed nonadditive neuroprotection in fetal sheep [45].

Interestingly, there is now evidence that in preterm fetal sheep, low-amplitude epileptiform EEGs occur in the latent phase of recovery from severe asphyxia (Figure 41.4) and that numbers of transients were strongly associated with greater subcortical brain injury [3,46]. This is consistent with clinical evidence that such transients are common in preterm infants and that their frequency is strongly associated overall with poor outcome [47]. These events are mediated by activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor [48]. Interestingly, in preterm fetal sheep, neuroprotection with delayed, prolonged head cooling after severe asphyxia was associated with potent, specific suppression of epileptiform transients in the early recovery phase, whereas hypothermia did not affect numbers of subsequent classic seizures [46]. Thus increased epileptiform transients in the latent phase may be a useful biomarker of evolving neuronal injury in the immature brain [49].

Metabolism and Prolonged Hypoperfusion

Ischemia is well known to be associated with delayed onset of transient hypoperfusion, as illustrated in Figure 41.2 [4]. Although the significance of this hypoperfusion has been controversial, overall, evidence suggests that it is an actively mediated suppression of cerebral metabolism that leads to increased tissue oxygen levels [50]. Hypothermia has been shown to be associated with marked exaggeration of this transient period of hypoperfusion during the latent phase and with suppression of subsequent hyperperfusion, both clinically and experimentally [4,51]. This effect of hypothermia is likely mediated by hypothermic

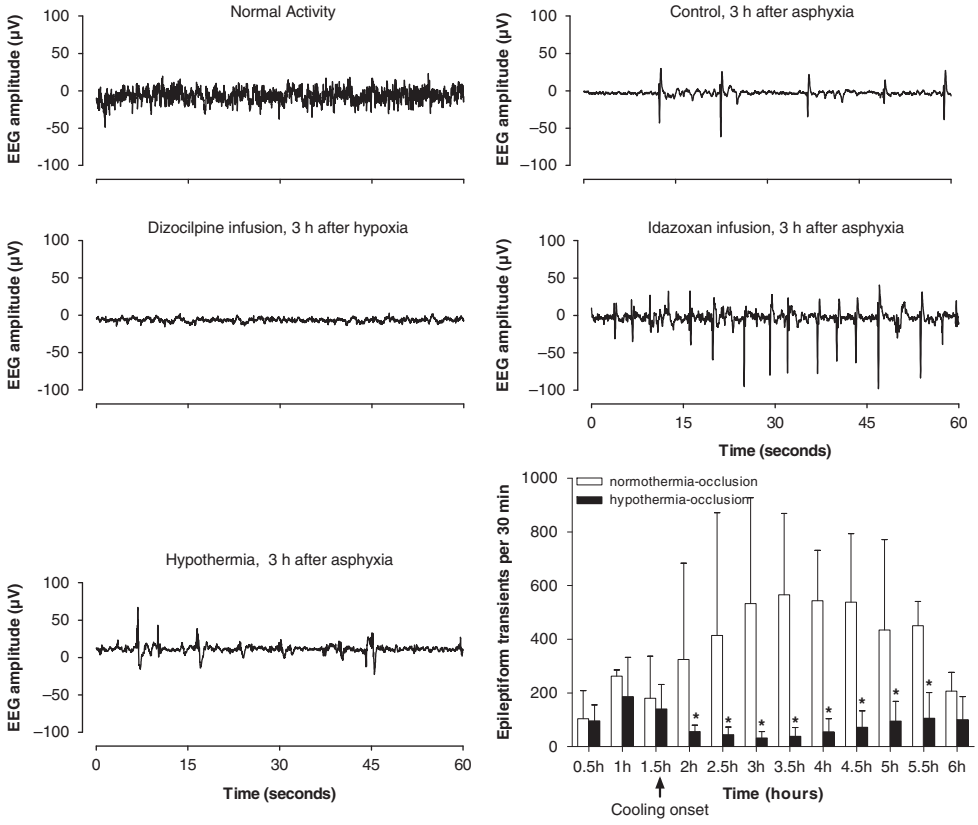


Figure 41.4 Examples of raw EEG data from preterm fetal sheep showing normal discontinuous mixed-frequency EEG activity, epileptiform transients superimposed on a suppressed EEG background, 3 hours after an episode of reversible severe asphyxia. Postasphyxial infusion of an inhibitory α2-adrenergic receptor antagonist, idazoxan, was associated with a marked increase in numbers of transients [100]. Conversely, these EEG transients were almost completely suppressed by *N*-methyl-D-aspartate blockade with dizocilpine [48] and were partially suppressed by cerebral hypothermia [46]. The time course of epileptiform transients during the latent phase and the effect of cerebral hypothermia are shown in the bottom right panel [46]. *$p < 0.05$ hypothermia occlusion versus normothermia occlusion.

suppression of brain metabolism of approximately 5% per 1°C [52].

Exploiting Endogenous Neuroprotection Pathways

While hypoxia can trigger many cytotoxic pathways within the brain, an important observation from experimental studies is that these damaging events are often associated with endogenous inhibitory neuroprotective responses that help to limit the degree of injury. For example, the dramatic rise in extracellular glutamate during hypoxia-ischemia in gray matter is closely accompanied by accumulation of endogenous inhibitory neuromodulators such as γ-aminobutyric acid (GABA) and adenosine in term-equivalent (0.8–0.9 of gestation) fetal sheep [5,53,54]. Indeed, the relative rise in GABA is reported to be greater than that of glutamate in the near-term fetus [5], and there is compelling evidence that intrahypoxic accumulation of adenosine mediates the initial rapid depression of EEG activity and that this reduces hippocampal, striatal, and parasagittal neuronal loss after 72 hours of recovery [54]. These inhibitory neuromodulators mediate the actively regulated suppression of metabolic rate during hypoxia or ischemia before energy stores are depleted that is termed *adaptive hypometabolism* [55].

Treatment with Insulin-Like Growth Factors (IGFs)

A large array of growth factors contributes to regulating brain growth. IGF-I is particularly important, as shown by the association of overexpression of the IGF-I gene with brain overgrowth and of IGF-I knockouts or excess expression of IGF binding

proteins with reduced growth [56]. IGF-I is potently antiapoptotic, as well as promoting neural stem cell proliferation, differentiation, maturation, myelination, neurite outgrowth, and synaptogenesis. There is marked upregulation of endogenous IGF-I in injured areas of the brain after injury, which is suggested to contribute to cerebral repair and functional recovery [56]. However, preceding this phase, in the neonatal rat there is a global *reduction* in all components of the IGF system during the latent phase after hypoxia-ischemia, suggesting the hypothesis that relative lack of neurotrophic support after injury may contribute to delayed cell death [57].

There is consistent evidence that postischemic administration of exogenous IGF-I can attenuate the severe delayed postischemic neuronal and oligodendrocyte cell loss and associated demyelination after cerebral ischemia or hypoxia-ischemia in the rat and in near-term fetal sheep (Figure 41.4) [56]. For example, in term-equivalent fetal sheep, IGF-I given as a 1-hour infusion intracerebroventricularly (i.c.v) was associated with reduced loss of oligodendrocytes after severe ischemia in the intragyral white matter, reduced demyelination, reduced tissue swelling, but upregulation of astrocytes and microglia [58]. Delayed cotreatment with IGF-I plus hypothermia after cerebral ischemia did not improve white matter damage compared with hypothermia alone, suggesting that their mechanisms of neuroprotection are overlapping [59].

IGF-I treatment was associated with reduced caspase-3 activation and increased glial proliferation in a similar dose-dependent manner [60]. Caspase-3 was only expressed in oligodendrocytes that showed apoptotic morphology. Proliferating cell nuclear antigen colocalized with oligodendrocytes, astrocytes, and microglia. Thus increased oligodendrocyte numbers after IGF-I treatment is partly due to suppression of apoptosis and partly to increased proliferation. In contrast, the increase in reactive glia was related only to proliferation. These intriguing data raise the possibility that protective effects by reactive glia may partly mediate white matter protection by IGF-I [61] and thus, speculatively, that chronic treatment with this or other growth factors could help to restore production of oligodendrocytes in premature infants.

Erythropoietin

Erythropoietin (EPO) has a central role in erythropoiesis and is now used routinely as a treatment for anemia in premature infants [62]. In addition, there is increasing clinical and experimental evidence suggesting that EPO may be neuroprotective after HIE, acting via the EPO receptor (EPOR) on neurons and glia as well as erythroid precursors. Endogenous EPO production is upregulated after hypoxia via increased expression of hypoxia inducible factor 1 (HIF-1) [63].

Although EPO has a high molecular weight, the increased permeability of the blood-brain barrier after hypoxia-ischemia allows exogenous EPO to enter the brain in a dose-dependent manner [64]. In both the adult and neonatal brain, EPO can promote expression of antiapoptotic over proapoptotic genes, inhibit caspase activation, attenuate the inflammatory response to hypoxia-ischemia, and increase neurogenesis [65]. EPO treatment after hypoxic-ischemic injury and stroke in neonatal rodents improved recovery of sensorimotor function and behavioral and cognitive performance and histologic integrity [65]. Of interest, exogenous human EPO improved neuronal survival in the hippocampus after pilocarpine-induced status epilepticus in adult rats [66]. This is potentially important given that drug-resistant status epilepticus is highly associated with adverse outcomes after asphyxia [67].

There is limited evidence for the effect of combined treatment with hypothermia and EPO. After HI in P7 neonatal rats, investigators have variably reported both no significant neuroprotection with combined EPO with hypothermia [68] and a borderline additive effect of EPO plus hypothermia on sensorimotor function but not on brain histology [69]. More encouragingly, in nonhuman primates after umbilical cord occlusion at term, treatment with hypothermia and EPO improved motor and cognitive responses and cerebellar growth and reduced death or disability [70].

There is reasonable clinical evidence of safety. A recent meta-analysis of five studies involving 233 patients including very low-birth-weight infants and premature infants showed that recombinant EPO administration was not associated with adverse effects and was associated with improved neurodevelopmental outcome [71]. In full-term neonates with HIE, two studies have also shown that EPO treatment was safe. Low-dose EPO (300 or 500 units/kg) was associated with a reduced risk of death or disability in term infants with moderate, but not severe, HIE [72]. Further, high-dose recombinant EPO (2,500 units/kg) started within the first 48 hours of life was shown to improve neurodevelopmental outcome in

term neonates with mild/moderate HIE and was also associated with a significant reduction in seizure activity, improved abnormal EEG background at 2 weeks, and decreased neurologic abnormalities at 6 months [73].

Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is a naturally occurring indolamine secreted by the pineal gland to regulate circadian rhythm that also has antioxidant properties [65]. It has clinical potential as a prophylactic treatment for fetuses at high risk of perinatal hypoxia because it readily crosses the placenta [65]. When given before and immediately after hypoxia-ischemia, melatonin is neuroprotective in postnatal rodents, as reviewed previously [65]. In term-equivalent fetal sheep, maternal prophylactic melatonin (1 mg total) given before 10-minute umbilical cord occlusion was associated with reduced brain lipid peroxidation, neuronal death, microglial activation, and astrogliosis [74]. In preterm fetal sheep at 0.7 gestation, maternal low-dose melatonin infusion was associated with faster fetal EEG recovery, delayed onset of seizures, improved survival of mature oligodendrocytes, and reduced microglial activation in the periventricular white matter [75].

There is emerging evidence for neuroprotection with postinsult treatment with melatonin. In preterm fetal sheep at 0.6 gestation, infusion of high-dose (20 mg/kg) melatonin for 6 hours from shortly after umbilical cord occlusion was associated with reduced apoptosis and microglia in the white matter, although cell survival was not quantified [76]. High-dose melatonin (5 mg/kg per hour over 6 hours) given immediately after hypoxia-ischemia in postnatal term piglets strikingly augmented protection from therapeutic hypothermia on both MRS markers of anaerobic stress and histopathology [77].

An important potential limitation of these studies is that melatonin is a hydrophobic molecule, and therefore, ethanol is frequently used as a diluent, which may adversely affect the developing brain. Postnatally, very high-dose melatonin (10 mg/kg) dissolved in ethanol was associated with hypotension and increased inotrope requirements after hypoxia-ischemia in term piglets; it is unknown whether the melatonin or ethanol or the combination mediated this adverse effect [77]. Further, in a recent study of prophylactic maternal melatonin before severe asphyxia in preterm fetal sheep, there was evidence that although melatonin was associated with faster recovery of the fetal EEG and improved white matter recovery compared with the 2% ethanol vehicle, melatonin and ethanol vehicle were associated with similar improvement in neuronal survival in the striatum and reduced postasphyxial seizures [75]. Moreover, ethanol was also associated with greater neuronal loss in the CA3 and CA4 regions of the hippocampus and reduced white matter proliferation, with greater induction of amoeboid microglia. These findings strongly suggest that even small amounts of ethanol may confound any neuroprotective effects of melatonin and thus that it is essential to test alternate diluents.

Clinically, small studies suggest that melatonin has not been associated with adverse outcomes and may improve survival of neonates with septic shock and reduce ventilator-associated lung injury in preterm infants [78].

Stem Cell Therapies

Over the past decade, there has been increasing interest in the use of stem cells as a treatment for infants suffering HIE and even for children with cerebral palsy. The media have reported a handful of cases showing apparent recovery, leading to inflated expectations and pressure from parents of children with cerebral palsy to use stem cells as a routine treatment strategy despite a lack of rigorous evidence [79]. In preclinical studies in rat and mouse models, the effects of neonatal hypoxia-ischemia have been highly variable [79], likely reflecting considerable differences in type, dose, and timing of infusion of the stem cells after injury.

There is increasing evidence that significant functional improvements can occur without significant functional engraftment [79], suggesting that the effects of stem cells are likely mediated by neurotrophic and immunomodulatory/immune-suppressive factors. Consistent with this, in rabbits exposed to intrauterine hypoxia-ischemia at 70% gestation, subsequent infusion of human umbilical cord blood cells at birth was associated with a dose-dependent improvement in the motor problems despite little penetration of the cells into the brain [80]. Promisingly, combined treatment with mesenchymal stem cell therapy and 24 hours of hypothermia, started 6 hours after the end of hypoxia ischemia in the P7 rat, showed greater improvement with combined treatment than either treatment alone

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[81], as measured at P42 by MRI and functional behavioral tests.

There are currently 12 clinical trials of stem cell therapy for neonatal hypoxia-ischemia or cerebral palsy listed on Clinicaltrials.gov as recruiting, underway, or completed. One small double-blind, randomized, placebo-controlled trial in 96 children with cerebral palsy receiving rehabilitation therapy found that treatment with a combination of umbilical cord blood and recombinant erythropoietin ameliorated motor and cognitive dysfunction after 6 months of treatment more than rehabilitation therapy with or without erythropoietin [82]. Interestingly, a pilot study suggested that treatment with allogenic umbilical cord blood from healthy infants ($n = 3$) may reduce proinflammatory plasma cytokines compared with autologous umbilical cord blood ($n = 4$) [83]. Thus potentially the origin of cord blood cells may be important.

Nevertheless, stem cell therapy shows promise as a treatment for HIE, whether given alone or in combination with therapeutic hypothermia [80]. In order to optimize the potential of this treatment, further systematic studies of the mechanisms of action, optimal dosing and timing, and type of stem cells are needed.

Exogenous Neuroprotective Strategies

Xenon

Xenon is an inert noble gas used for its anesthetic properties, mediated via competitive binding at the glycine binding site of the NMDA subtype of glutamate receptor [84]. In addition to potentially attenuating excitotoxicity, xenon may also activate pro-survival kinases such as p-Akt and the antiapoptotic factor Bcl-2 and potentially inhibit opening of the mitochondrial permeability pore [85].

There is evidence of additive protection from combined xenon and hypothermia treatment. Xenon and hypothermia administered together either immediately or as late as 4 hours after hypoxia-ischemia in neonatal rats significantly reduced apoptotic cell death and loss of brain matter while improving long-term neurologic motor function and coordination [65]. In the newborn piglet, the combination of xenon with whole-body cooling was associated with a 75% reduction in global neuropathology after perinatal asphyxia [86]. In a similar paradigm, others found that xenon-augmented hypothermia reduced cerebral MRS abnormalities and cell death markers in some brain regions compared with no treatment, although the effect was not significant compared with hypothermia alone [87].

The limited natural availability of xenon and thus high price mean that it needs to be used with a recirculating ventilator [88], and thus it is unlikely to ever be available outside tertiary units. The feasibility of combined treatment with xenon and hypothermia is being evaluated in phase 2 trials (TOBYXeNCT00934700 and CoolXenon2-NCT01545271) [85].

Magnesium Sulfate ($MgSO_4$)

Magnesium has natural excitotoxic effects by binding to the magnesium site on the NMDA receptor, raising the possibility that it may be neuroprotective [89]. Meta-analysis of RCTs of maternal $MgSO_4$ treatment for preterm birth suggests that it may be associated with a small but significant reduction in the risk of cerebral palsy and gross motor dysfunction in early childhood [90]. However, there was no significant effect on the combined outcome of death or disability, and it is unclear whether there is long-term benefit [91].

However, its effects on hypoxic-ischemic injury at term are unclear. A recent systematic analysis of preclinical studies of $MgSO_4$ for neuroprotection at term equivalent found that while 7 of 15 studies reported improved neuronal outcomes with $MgSO_4$ treatment, these studies did not adequately control environmental or body temperature [89]. In contrast, studies that controlled environmental or body temperature did not find significant neuroprotective effects of $MgSO_4$. This analysis strongly suggests that the apparent protective effects of magnesium may be confounded by iatrogenic hypothermia and thus that further investigation is essential before considering large clinical trials of $MgSO_4$ for HIE at term.

Blockade of Connexin Hemichannels

One of the most striking features of hypoxic-ischemic brain injury is that injury consistently spreads overtime from severely affected regions to areas that were originally intact [92]. This pattern is consistent with the long-standing hypothesis that cell-to-cell communication might contribute to spreading injury. The gap junctions that link adjacent cells to allow transport of small molecules, ions, and second messengers [93] are formed by docking of hexamer hemichannels (connexons) from the adjacent cells. There is increasing evidence that these connexin hemichannels are not just passively waiting to dock but are themselves

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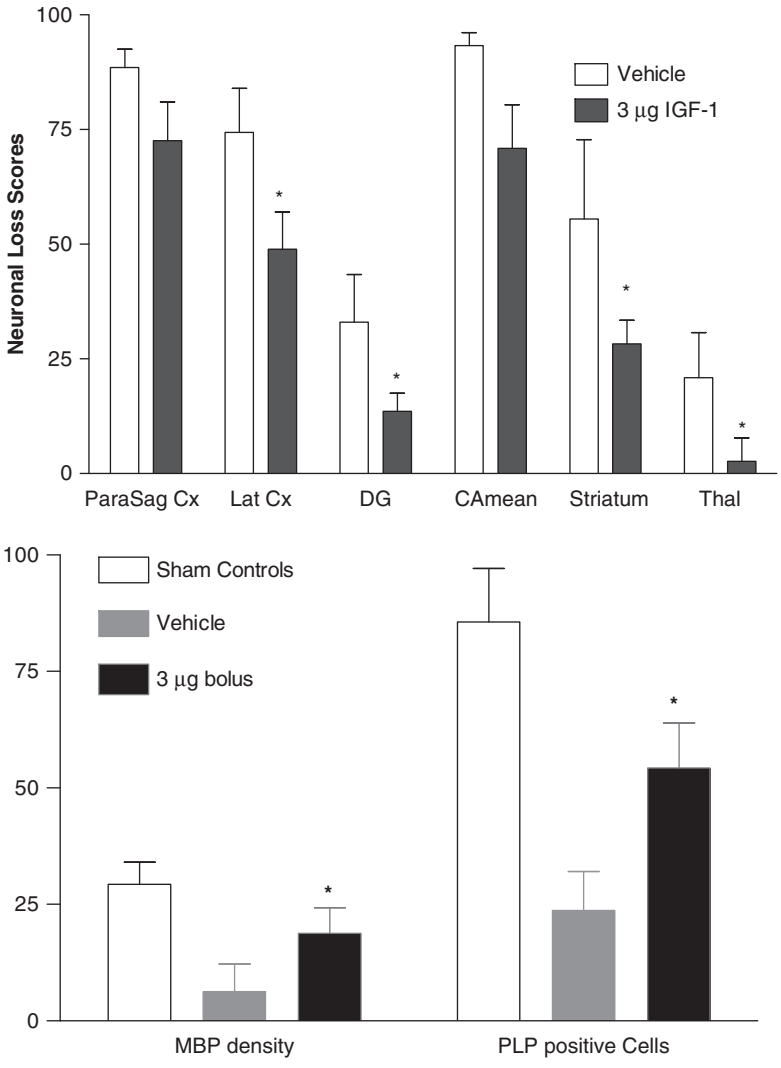


Figure 41.5 Improvement in histologic injury with IGF-I therapy given intracerebroventricularly 2 hours after 30 minutes of cerebral ischemia in the fetal sheep, assessed after 96 hours of recovery. This insult leads to a watershed pattern of neuronal loss, greatest in the parasagittal cortex (ParaSag Cx). Note the significant improvement in the lateral (Lat Cx, i.e., temporal cortex) and subcortical structures, including the dentate gyrus of the dorsal hippocampus (DG), striatum and thalamus (Thal, top panel), and in myelin basic protein (MBP) and numbers of proteolipid protein (PLP) expressing mature oligodendrocytes (bottom panel). There was no significant improvement in the mean of the cornu ammonis regions of the hippocampus (CAmean). *$p < 0.05$ versus vehicle control. (Data derived in part from Guan et al. [101].)

active under normal physiologic conditions, for example, via purinergic signaling by regulated release of ATP [93]. Critically, pathologic conditions such as ischemia may cause unregulated opening, compromising the resting membrane potential and allowing transmitters such ATP or glutamate into the extracellular space [93].

An elegant study by Orellana et al. showed that connexin 43 hemichannels can open *after* hypoxia in cultured astrocytes [94], as shown by increased dye uptake in connexin 43–containing astrocytes but not connexin 43–deficient astrocytes, and that blockers of connexin 43 hemichannels prevented dye uptake and death of astrocytes. In fetal sheep, intracerebroventricular infusion of a mimetic peptide at a dose concentration that blocks connexin 43 hemichannels (95), started 90 minutes after either cerebral ischemia or profound asphyxia and continued for 25 hours, improved EEG recovery and reduced white and gray matter damage [96,97]. In term-equivalent fetal sheep, this mimetic peptide infusion was associated with a striking reduction in status epilepticus after ischemia, consistent with the hypothesis that connexin hemichannels play a key role in propagating these intense seizures [96]. Conversely, blockade of connexin 43 hemichannels during ischemia in term-equivalent fetal sheep had no effect on subsequent EEG recovery or cell death (Figure 41.6) [98]. These data show that connexin hemichannels play a key role in the downstream propagation of injury

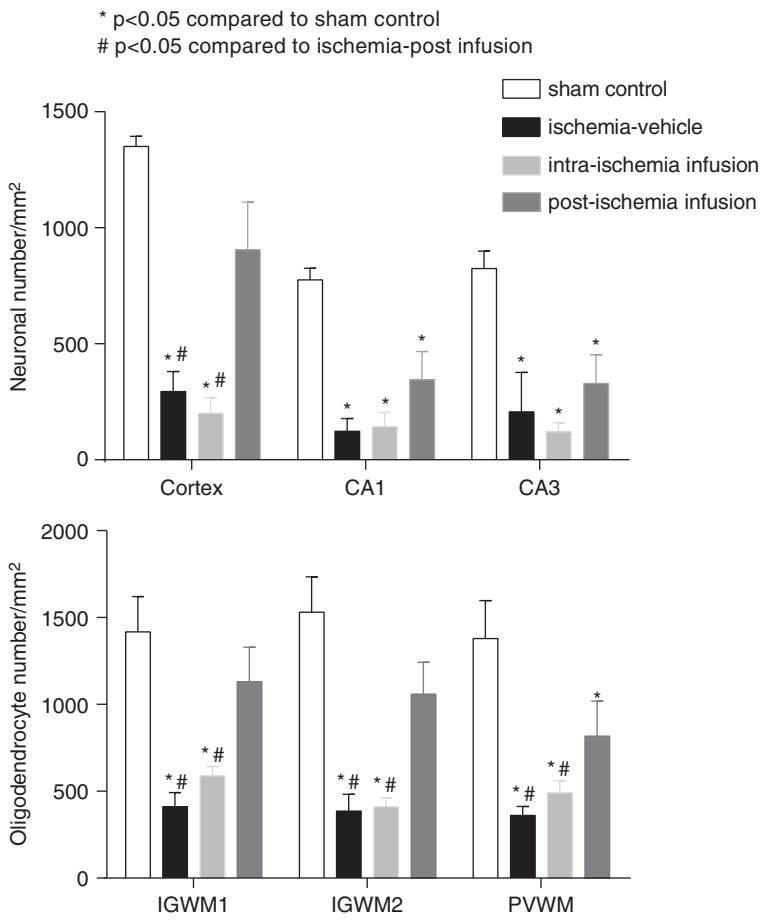


Figure 41.6 Neuronal and oligodendrocyte cell survival with connexin hemichannel blockade using peptide 5 given intracerebroventricularly from either 1 hour before and continued throughout 30 minutes of global cerebral ischemia (intrainfusion) or from 90 minutes after the end and continued for 25 hours (postinfusion). Ischemia was associated with a significant reduction in neuronal survival in the cortex and CA1 and CA3 of the hippocampus. Postinfusion, but not intrainfusion, blockade of connexin hemichannels was associated with a significant improvement in neuronal survival in all areas ($p < 0.05$). Ischemia was associated with a significant reduction in oligodendrocyte survival in both areas of the intragyral white matter and the periventricular white matter. Postinfusion, but not intrainfusion, blockade of connexin hemichannels was associated with a significant improvement in oligodendrocyte survival in the intragyral ($p < 0.05$) but not periventricular white matter. Data are mean ± SEM. (Data derived in part from Davidson et al. [98].)

after ischemia. Further studies are needed to address the therapeutic window of opportunity for treatment with hemichannel blockade and determine whether hemichannel blockade is additive with mild hypothermia.

Conclusion

Therapeutic hypothermia is now established as standard care that improves neurologic recovery in infants with moderate to severe HIE, but current protocols are only partially effective [16]. It is clear that the most effective way to optimize treatment with hypothermia is to start treatment as soon as possible after resuscitation [99]. The key practical challenge is to identify patients who would benefit from treatment in such a limited time frame [49]. As reviewed in this chapter, the combination of posthypoxic EEG transients with overall EEG suppression may be an effective biomarker of evolving damage in the latent phase, supporting universal real-time EEG monitoring of high-risk infants.

In addition to earlier treatment, further improvements in neurodevelopmental outcomes are most likely to come from combining hypothermia with endogenous or exogenous neuroprotective agents. Endogenous neuroprotective compounds such as EPO and melatonin are showing particular promise, with multiple potential benefits and excellent safety records in other settings.

References

1. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol* 1997; **177**: 1391–4.
2. Gunn AJ, Parer JT, Mallard EC, et al. Cerebral histologic and electrocorticographic changes after asphyxia in fetal sheep. *Pediatr Res* 1992; **31**: 486–91.
3. George S, Gunn AJ, Westgate JA, et al. Fetal heart rate variability and brainstem injury after asphyxia in preterm fetal sheep. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R925–33.

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4. Gunn AJ, Gunn TR, de Haan HH, et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997; **99**: 248–56.
5. Tan WK, Williams CE, During MJ, et al. Accumulation of cytotoxins during the development of seizures and edema after hypoxic-ischemic injury in late gestation fetal sheep. *Pediatr Res* 1996; **39**: 791–7.
6. Azzopardi D, Wyatt JS, Cady EB, et al. Prognosis of newborn infants with hypoxic-ischemic brain injury assessed by phosphorus magnetic resonance spectroscopy. *Pediatr Res* 1989; **25**: 445–51.
7. Roth SC, Baudin J, Cady E, et al. Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. *Dev Med Child Neurol* 1997; **39**: 718–25.
8. Lorek A, Takei Y, Cady EB, et al. Delayed ("secondary") cerebral energy failure after acute hypoxia-ischemia in the newborn piglet: continuous 48-hour studies by phosphorus magnetic resonance spectroscopy. *Pediatr Res* 1994; **36**: 699–706.
9. Blumberg RM, Cady EB, Wigglesworth JS, et al. Relation between delayed impairment of cerebral energy metabolism and infarction following transient focal hypoxia-ischaemia in the developing brain. *Exp Brain Res* 1997; **113**: 130–7.
10. Bennet L, Roelfsema V, Pathipati P, et al. Relationship between evolving epileptiform activity and delayed loss of mitochondrial activity after asphyxia measured by near-infrared spectroscopy in preterm fetal sheep. *J Physiol* 2006; **572**: 141–54.
11. Vannucci RC, Towfighi J, Vannucci SJ. Secondary energy failure after cerebral hypoxia-ischemia in the immature rat. *J Cereb Blood Flow Metab* 2004; **24**: 1090–7.
12. Tsuji M, Naruse H, Volpe J, Holtzman D. Reduction of cytochrome aa3 measured by near-infrared spectroscopy predicts cerebral energy loss in hypoxic piglets. *Pediatr Res* 1995; **37**: 253–9.
13. Keogh MJ, Drury PP, Bennet L, et al. Limited predictive value of early changes in EEG spectral power for neural injury after asphyxia in preterm fetal sheep. *Pediatr Res* 2012; **71**: 345–53.
14. Williams CE, Gunn A, Gluckman PD. Time course of intracellular edema and epileptiform activity following prenatal cerebral ischemia in sheep. *Stroke* 1991; **22**: 516–21.
15. Gunn AJ, Thoresen M. Hypothermic neuroprotection. *NeuroRx* 2006; **3**: 154–69.
16. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013; **1**: CD003311.
17. Guillet R, Edwards AD, Thoresen M, et al. Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. *Pediatr Res* 2012; **71**: 205–9.
18. Azzopardi D, Strohm B, Marlow N, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *N Engl J Med* 2014; **371**: 140–9.
19. Shankaran S, Pappas A, McDonald SA, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med* 2012; **366**: 2085–92.
20. Gunn AJ, Gunn TR, Gunning MI, et al. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. *Pediatrics* 1998; **102**: 1098–106.
21. Gunn AJ, Bennet L, Gunning MI, et al. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. *Pediatr Res* 1999; **46**: 274–80.
22. Sirimanne ES, Blumberg RM, Bossano D, et al. The effect of prolonged modification of cerebral temperature on outcome after hypoxic-ischemic brain injury in the infant rat. *Pediatr Res* 1996; **39**: 591–7.
23. Thoresen M, Penrice J, Lorek A, et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr Res* 1995; **37**: 667–70.
24. Tooley JR, Satas S, Porter H, et al. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. *Ann Neurol* 2003; **53**: 65–72.
25. Thoresen M, Tooley J, Liu X, et al. Time is brain: starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. *Neonatology* 2013; **104**: 228–33.
26. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**: 663–70.
27. Westgate JA, Gunn AJ, Gunn TR. Antecedents of neonatal encephalopathy with fetal acidaemia at term. *Br J Obstet Gynaecol* 1999; **106**: 774–82.
28. Colbourne F, Auer RN, Sutherland GR. Characterization of postischemic behavioral deficits in gerbils with and without hypothermic neuroprotection. *Brain Res* 1998; **803**: 69–78.
29. Alonso-Alconada D, Broad KD, Bainbridge A, et al. Brain cell death is reduced with cooling by 3.5°C to 5°C but increased with cooling by 8.5°C in a piglet asphyxia model. *Stroke* 2015; **46**: 275–8.
30. Colbourne F, Corbett D. Delayed postischemic hypothermia: a six month survival study using behavioral and histological assessments of neuroprotection. *J Neurosci* 1995; **15**: 7250–60.

31. Colbourne F, Corbett D, Zhao Z, et al. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. *J Cereb Blood Flow Metab* 2000; **20**: 1702–8.
32. Davidson JO, Wassink G, Yuill CA, et al. How long is too long for cerebral cooling after ischemia in fetal sheep? *J Cereb Blood Flow Metab* 2015; **35**: 751–8.
33. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *JAMA* 2014; **312**: 2629–39.
34. Johnston MV. Excitotoxicity in perinatal brain injury. *Brain Pathol* 2005; **15**: 234–40.
35. Bruno VM, Goldberg MP, Dugan LL, et al. Neuroprotective effect of hypothermia in cortical cultures exposed to oxygen-glucose deprivation or excitatory amino acids. *J Neurochem* 1994; **63**: 1398–406.
36. Wassink G, Gunn ER, Drury PP, et al. The mechanisms and treatment of asphyxial encephalopathy. *Front Neurosci* 2014; **8**: 40.
37. Northington FJ, Zelaya ME, O'Riordan DP, et al. Failure to complete apoptosis following neonatal hypoxia-ischemia manifests as "continuum" phenotype of cell death and occurs with multiple manifestations of mitochondrial dysfunction in rodent forebrain. *Neuroscience* 2007; **149**: 822–33.
38. Edwards AD, Yue X, Squier MV, et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. *Biochem Biophys Res Commun* 1995; **217**: 1193–9.
39. Bennet L, Roelfsema V, George S, et al. The effect of cerebral hypothermia on white and grey matter injury induced by severe hypoxia in preterm fetal sheep. *J Physiol* 2007; **578**: 491–506.
40. Hagberg H, Mallard C, Jacobsson B. Role of cytokines in preterm labour and brain injury. *BJOG*. 2005; **112**(Suppl 1): 16–18.
41. Roelfsema V, Bennet L, George S, et al. The window of opportunity for cerebral hypothermia and white matter injury after cerebral ischemia in near-term fetal sheep. *J Cereb Blood Flow Metab* 2004; **24**: 877–86.
42. Welin AK, Sandberg M, Lindblom A, et al. White matter injury following prolonged free radical formation in the 0.65 gestation fetal sheep brain. *Pediatr Res* 2005; **58**: 100–5.
43. Fraser M, Bennet L, van Zijl PL, et al. Extracellular amino acids and peroxidation products in the periventricular white matter during and after cerebral ischemia in preterm fetal sheep. *J Neurochem* 2008; **105**: 2214–23.
44. Tan WK, Williams CE, Gunn AJ, et al. Suppression of postischemic epileptiform activity with MK-801 improves neural outcome in fetal sheep. *Ann Neurol* 1992; **32**: 677–82.
45. George SA, Barrett RD, Bennet L, et al. Nonadditive neuroprotection with early glutamate receptor blockade and delayed hypothermia after asphyxia in preterm fetal sheep. *Stroke* 2012; **43**: 3114–7.
46. Bennet L, Dean JM, Wassink G, Gunn AJ. Differential effects of hypothermia on early and late epileptiform events after severe hypoxia in preterm fetal sheep. *J Neurophysiol* 2007; **97**: 572–8.
47. Biagioni E, Bartalena L, Boldrini A, et al. Electroencephalography in infants with periventricular leukomalacia: prognostic features at preterm and term age. *J Child Neurol* 2000; **15**: 1–6.
48. Dean JM, George SA, Wassink G, et al. Suppression of post hypoxic-ischemic EEG transients with dizocilpine is associated with partial striatal protection in the preterm fetal sheep. *Neuropharmacology* 2006; **50**: 491–503.
49. Bennet L, Booth L, Gunn AJ. Potential biomarkers for hypoxic-ischemic encephalopathy. *Semin Fetal Neonatal Med* 2010; **15**: 253–60.
50. Jensen EC, Bennet L, Hunter CJ, et al. Post-hypoxic hypoperfusion is associated with suppression of cerebral metabolism and increased tissue oxygenation in near-term fetal sheep. *J Physiol* 2006; **572**: 131–9.
51. Elstad M, Whitelaw A, Thoresen M. Cerebral resistance index is less predictive in hypothermic encephalopathic newborns. *Acta Paediatr* 2011; **100**: 1344–9.
52. Laptook AR, Corbett RJ, Sterett R, et al. Quantitative relationship between brain temperature and energy utilization rate measured in vivo using ^{31}P and ^{1}H magnetic resonance spectroscopy. *Pediatr Res* 1995; **38**: 919–25.
53. Lotgering FK, Bishai JM, Struijk PC, et al. Ten-minute umbilical cord occlusion markedly reduces cerebral blood flow and heat production in fetal sheep. *Am J Obstet Gynecol* 2003; **189**: 233–8.
54. Hunter CJ, Bennet L, Power GG, et al. Key neuroprotective role for endogenous adenosine A1 receptor activation during asphyxia in the fetal sheep. *Stroke* 2003; **34**: 2240–5.
55. Mortola JP. Implications of hypoxic hypometabolism during mammalian ontogenesis. *Respir Physiol Neurobiol* 2004; **141**: 345–56.
56. Guan J, Bennet L, Gluckman PD, Gunn AJ. Insulin-like growth factor-1 and post-ischemic brain injury. *Prog Neurobiol* 2003; **70**: 443–62.
57. Clawson TF, Vannucci SJ, Wang GM, et al. Hypoxia-ischemia-induced apoptotic cell death correlates with

IGF-I mRNA decrease in neonatal rat brain. *Biol Signals Recept* 1999; **8**: 281–93.

58. Guan J, Bennet L, George S, et al. Insulin-like growth factor-1 reduces postischemic white matter injury in fetal sheep. *J Cereb Blood Flow Metab* 2001; **21**: 493–502.
59. George SA, Bennet L, Weaver-Mikaere L, et al. White matter protection with insulin like-growth factor 1 (IGF-1) and hypothermia is not additive after severe reversible cerebral ischemia in term fetal sheep. *Dev Neurosci* 2011; **33**: 280–7.
60. Cao Y, Gunn AJ, Bennet L, et al. Insulin-like growth factor (IGF)-1 suppresses oligodendrocyte caspase-3 activation and increases glial proliferation after ischemia in near-term fetal sheep. *J Cereb Blood Flow Metab* 2003; **23**: 739–47.
61. Corley SM, Ladiwala U, Besson A, Yong VW. Astrocytes attenuate oligodendrocyte death in vitro through an alpha(6) integrin-laminin-dependent mechanism. *Glia* 2001; **36**: 281–94.
62. Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2006; **3**: CD004863.
63. Digicaylioglu M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-κB signalling cascades. *Nature* 2001; **412**: 641–7.
64. Statler PA, McPherson RJ, Bauer LA, et al. Pharmacokinetics of high-dose recombinant erythropoietin in plasma and brain of neonatal rats. *Pediatr Res* 2007; **61**: 671–5.
65. Robertson NJ, Tan S, Groenendaal F, et al. Which neuroprotective agents are ready for bench to bedside translation in the newborn infant? *J Pediatr* 2012; **160**: 544–52.
66. Nadam J, Navarro F, Sanchez P, et al. Neuroprotective effects of erythropoietin in the rat hippocampus after pilocarpine-induced status epilepticus. *Neurobiol Dis* 2006; **2**: 412–26.
67. Drury PP, Davidson JO, van den Heuij LG, et al. Status epilepticus after prolonged umbilical cord occlusion is associated with greater neural injury in fetal sheep at term-equivalent. *PLoS One* 2014; **9**: e96530.
68. Fang AY, Gonzalez FF, Sheldon RA, Ferriero DM. Effects of combination therapy using hypothermia and erythropoietin in a rat model of neonatal hypoxia-ischemia. *Pediatr Res* 2013; **73**: 12–7.
69. Fan X, van Bel F, van der Kooij MA, et al. Hypothermia and erythropoietin for neuroprotection after neonatal brain damage. *Pediatr Res* 2013; **73**: 18–23.
70. Traudt CM, McPherson RJ, Bauer LA, et al. Concurrent erythropoietin and hypothermia treatment improve outcomes in a term nonhuman primate model of perinatal asphyxia. *Dev Neurosci* 2013; **35**: 491–503.
71. Wang H, Zhang L, Jin Y. A meta-analysis of the protective effect of recombinant human erythropoietin (rhEPO) for neurodevelopment in preterm infants. *Cell Biochem Biophys* 2015; **71**: 795–802.
72. Zhu C, Kang W, Xu F, et al. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 2009; **124**: e218–26.
73. Elmahdy H, El-Mashad AR, El-Bahrawy H, et al. Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. *Pediatrics* 2010; **125**: e1135–42.
74. Yawno T, Castillo-Melendez M, Jenkin G, et al. Mechanisms of melatonin-induced protection in the brain of late gestation fetal sheep in response to hypoxia. *Dev Neurosci* 2012; **34**: 543–51.
75. Drury PP, Davidson JO, Bennet L, et al. Partial neural protection with prophylactic low-dose melatonin after asphyxia in preterm fetal sheep. *J Cereb Blood Flow Metab* 2014; **34**: 126–35.
76. Welin AK, Svedin P, Lapatto R, et al. Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. *Pediatr Res* 2007; **61**: 153–8.
77. Robertson NJ, Faulkner S, Fleiss B, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. *Brain* 2013; **136**: 90–105.
78. Gitto E, Romeo C, Reiter RJ, et al. Melatonin reduces oxidative stress in surgical neonates. *J Pediatr Surg* 2004; **39**: 184–9; discussion 189.
79. Bennet L, Tan S, Van den Heuij L, et al. Cell therapy for neonatal hypoxia-ischemia and cerebral palsy. *Ann Neurol* 2012; **71**: 589–600.
80. Drobyshevsky A, Cotten CM, Shi Z, et al. Human umbilical cord blood cells ameliorate motor deficits in rabbits in a cerebral palsy model. *Dev Neurosci* 2015; **37** (4–5): 349–62.
81. Park WS, Sung SI, Ahn SY, et al. Hypothermia augments neuroprotective activity of mesenchymal stem cells for neonatal hypoxic-ischemic encephalopathy. *PLoS One* 2015; **10**: e0120893.
82. Min K, Song J, Kang JY, et al. Umbilical cord blood therapy potentiated with erythropoietin for children with cerebral palsy: a double-blind, randomized, placebo-controlled trial. *Stem Cells* 2013; **31**: 581–91.
83. Bae SH, Lee HS, Kang MS, et al. The levels of pro-inflammatory factors are significantly decreased in cerebral palsy patients following an allogeneic umbilical cord blood cell transplant. *Int J Stem Cells* 2012; **5**: 31–8.
84. Dickinson R, Peterson BK, Banks P, et al. Competitive inhibition at the glycine site of the *N*-methyl-D-

aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modeling and electrophysiology. *Anesthesiology* 2007; **107**: 756–67.

85. Lobo N, Yang B, Rizvi M, Ma D. Hypothermia and xenon: novel noble guardians in hypoxic-ischemic encephalopathy? *J Neurosci Res* 2013; **91**: 473–8.
86. Chakkarapani E, Dingley J, Liu X, et al. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. *Ann Neurol* 2010; **68**: 330–41.
87. Faulkner S, Bainbridge A, Kato T, et al. Xenon augmented hypothermia reduces early lactate/*N*-acetylaspartate and cell death in perinatal asphyxia. *Ann Neurol* 2011; **70**: 133–50.
88. Faulkner SD, Downie NA, Mercer CJ, et al. A xenon recirculating ventilator for the newborn piglet: developing clinical applications of xenon for neonates. *Eur J Anaesthesiol* 2012; **29**: 577–85.
89. Galinsky R, Bennet L, Groenendaal F, et al. Magnesium is not consistently neuroprotective for perinatal hypoxia-ischemia in term-equivalent models in preclinical studies: a systematic review. *Dev Neurosci* 2014; **36**: 73–82.
90. Doyle LW, Crowther CA, Middleton P, Marret S. Antenatal magnesium sulfate and neurologic outcome in preterm infants: a systematic review. *Obstet Gynecol* 2009; **113**: 1327–33.
91. Doyle LW, Anderson PJ, Haslam R, et al. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. *JAMA* 2014; **312**: 1105–13.
92. Thornton JS, Ordidge RJ, Penrice J, et al. Temporal and anatomical variations of brain water apparent diffusion coefficient in perinatal cerebral hypoxic-ischemic injury: relationships to cerebral energy metabolism. *Magn Reson Med* 1998; **39**: 920–7.
93. Davidson JO, Green CR, Bennet L, Gunn AJ. Battle of the hemichannels: connexins and pannexins in ischemic brain injury. *Int J Dev Neurosci* 2014; **45**: 66–74.
94. Orellana JA, Hernandez DE, Ezan P, et al. Hypoxia in high glucose followed by reoxygenation in normal glucose reduces the viability of cortical astrocytes through increased permeability of connexin 43 hemichannels. *Glia* 2010; **58**: 329–43.
95. O'Carroll SJ, Alkadhi M, Nicholson LF, Green CR. Connexin 43 mimetic peptides reduce swelling, astrogliosis, and neuronal cell death after spinal cord injury. *Cell Commun Adhes* 2008; **15**: 27–42.
96. Davidson JO, Green CR, Nicholson LF, et al. Connexin hemichannel blockade improves outcomes in a model of fetal ischemia. *Ann Neurol* 2012; **71**: 121–32.
97. Davidson JO, Drury PP, Green CR, et al. Connexin hemichannel blockade is neuroprotective after asphyxia in preterm fetal sheep. *PLoS One*. 2014; **9**: e96558.
98. Davidson JO, Green CR, Nicholson LF, et al. Connexin hemichannel blockade is neuroprotective after, but not during, global cerebral ischemia in near-term fetal sheep. *Exp Neurol* 2013; **248**: 301–8.
99. Gunn AJ, Thoresen M. Animal studies of neonatal hypothermic neuroprotection have translated well in to practice. *Resuscitation* 2015; **97**: 88–90.
100. Dean JM, Gunn AJ, Wassink G, et al. Endogenous α (2)-adrenergic receptor–mediated neuroprotection after severe hypoxia in preterm fetal sheep. *Neuroscience* 2006; **142**: 615–28.
101. Guan J, Bennet L, George S, et al. Selective neuroprotective effects with insulin-like growth factor-1 in phenotypic striatal neurons following ischemic brain injury in fetal sheep. *Neuroscience* 2000; **95**: 831–9.

Chapter

42

Neonatal Seizures

Evaluation, Treatment, and Prognosis

Fiona M. Baumer and Courtney J. Wusthoff

Introduction

Neonatal seizures are a common clinical concern for neonatologists and neurologists alike. The risk of seizures is higher in the neonatal period than at any other point in the lifespan. Depending on the method for identifying seizures, reported incidence has ranged from 1% to 5%, with a lower gestational age and lower birth weight significantly increasing the risk [1].

Neonatal seizures have different etiologies, clinical expressions, and electrographic appearances compared with seizures that emerge later in life. The vast majority of neonatal seizures are secondary to an acute insult to the CNS, such as hypoxia or infection. Neonatal seizures not only signal CNS dysfunction but also likely cause further brain damage, thus making them neurologic emergencies. At the same time, diagnosis is difficult because the majority of neonatal seizures have no or only very subtle outward manifestations; most neonatal seizures are subclinical. Further complicating diagnosis, critically ill neonates often have unusual movements that may be confused with seizures but are not ictal. These issues can lead to both over- and underdiagnosis of neonatal seizures. Though treatment of seizures is generally considered necessary, antiepileptic medications themselves are not without risk; there is controversy regarding choice and duration of treatment.

This chapter reviews current knowledge on

1. Types and causes of neonatal seizures
2. Appropriate evaluation when seizures are suspected
3. Evidence behind current treatment strategies
4. Prognosis for patients with neonatal seizures

Definitions: Seizures, Epileptiform Discharges, and EEG Background

Seizures

The terminology used in discussing neonatal seizures warrants clarification because it sometimes can be the source of clinical miscommunication. Intuitively, most clinicians think of seizures as events consisting of abnormal electrical discharges in the brain manifesting as an abrupt change in clinical state, such as sudden rhythmic motor activity, a dramatic alteration in consciousness, or a quick change in vital signs. However, seizures can also consist of abnormal electrical activity without obvious outward clinical manifestations. An *electrographic seizure* is a paroxysmal abnormality in cortical electrical activity that evolves over time. This is defined by findings on electroencephalogram (EEG). When electrographic seizures are associated with clinical signs, they are *electroclinical seizures*. These are further subclassified based on a combination of clinical and EEG features. Electrographic seizures without obvious clinical manifestations are alternately called *subclinical* or *nonconvulsive seizures* [2]. Other terms sometimes used for these subclinical seizures include *occult, EEG-only*, or *subtle seizures* (Tables 42.1 and 42.2).

The "gold standard" for diagnosis of neonatal seizures is EEG [3]. The electrographic criteria for neonatal seizure are "a sudden abnormal EEG event defined by a repetitive and evolving pattern with minimum amplitude of 2 μV (peak to peak) and duration of at least 10 seconds" (Figure 42.1) The minimum duration of 10 seconds is a unique requirement of neonatal seizures (compared with seizures in older children and adults), as is the requirement that electrographic seizures must occur at least 10 seconds apart to be considered distinct seizures [4].

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Table 42.1 Definition of Neonatal Seizures: Electrographic Criteria

Sudden change in EEG
Repetitive waveforms that evolve in morphology, frequency, and/or location over time
Amplitude: at least 2 μV
Duration: at least 10 seconds
Seizures must be separated by at least 10 seconds to be considered separate
Clinical signs may or may not be present

Table 42.2 Types of Neonatal Seizures

Electrographic seizure: A paroxysmal abnormality in cortical electrical activity that evolves over time. To be considered a seizure, an event must meet all the criteria described in Table 42.1.
Electroclinical seizure: Electrographic seizure with associated clinical signs.
Subtypes are defined by the appearance of the associated clinical signs (i.e., tonic seizures, myoclonic seizure).
Subclinical/nonconvulsive/EEG-only seizures: Electrographic seizures with no or only very subtle clinical signs.

Epileptiform Discharges

Neonatal seizures should be distinguished from other types of abnormalities seen on EEG, such as *epileptiform activity* or *discharges*. While a seizure on EEG is comprised of an evolving pattern of epileptiform discharges, not all epileptiform discharges are seizures; the terms are not synonymous. Epileptiform discharges are brief abnormalities that stand out from the EEG background, usually due to a peaked or sharp appearance. They are sometimes referred to as *sharp waves* or *spikes* due to this EEG appearance. Not every patient with sharp waves on EEG also has seizures; in fact, it is normal and expected for term neonates to have at least some sharp waves present on EEG. Similarly, excessive multifocal sharps are a nonspecific indicator of brain dysfunction in neonates and do not necessarily indicate an increased risk of seizures. However, when sharp waves or spikes occur in runs or trains or are clustered in one brain region, this is associated with an increased risk of seizure [5].

One pattern of epileptiform discharges has a particularly high coincidence with neonatal seizures. *Brief rhythmic discharges* (BRDs) are EEG patterns that meet all criteria for neonatal seizures (i.e., sudden, abnormal, evolving) but are shorter in duration than 10 seconds. BRDs historically have also been referred to by several other names, including *brief intermittent/ictal/interictal rhythmic discharges* (BIRDs) or *brief electroencephalographic rhythmic discharges* (BERDs). BRDs have occasionally [6] but not consistently [7] been associated with clinical symptoms (e.g., focal clonic activity) in up to 15% of neonates, thus calling into question the diagnostic criteria for neonatal seizures. In general, BRDs are considered an ominous sign suggestive of underlying brain pathology because they have been associated with a concurrent risk of true seizures, as well as a risk of future developmental delay, cerebral palsy (CP), and death [6,7].

EEG Background Abnormalities

The EEG provides important information regarding the *background* electrical activity in the child's brain during wakefulness and sleep. Neonatal EEG is discussed more fully in Chapter 17. *Continuity* describes the persistence of electrical activity from second to second, and *excessive discontinuity* is associated with encephalopathy. The most severe form of discontinuity is *burst suppression*, a pattern of suppressed activity alternating with bursts of abnormal epileptiform discharges correlating with severe neuronal dysfunction. *Symmetry* and *synchrony* describe how similar electrical activity appears between the left and right hemispheres of the brain; differences can suggest structural problems. The backgrounds of premature and term infants are markedly different than that of an older child or adult and change significantly week to week with brain development. Because of this, interpretation of the neonatal EEG requires great familiarity with these developmental stages as well as knowledge of the gestational age of the patient.

Seizure Classification

The International League against Epilepsy (ILAE) updated its recommendations on seizure classification in 2010. In previous guidelines, neonatal seizures were considered a distinct entity; in the 2010 update, neonatal seizures are classified by the same scheme used for seizures in older patients (Table 42.3) [8]. Because of this relatively recent change, clinicians may see

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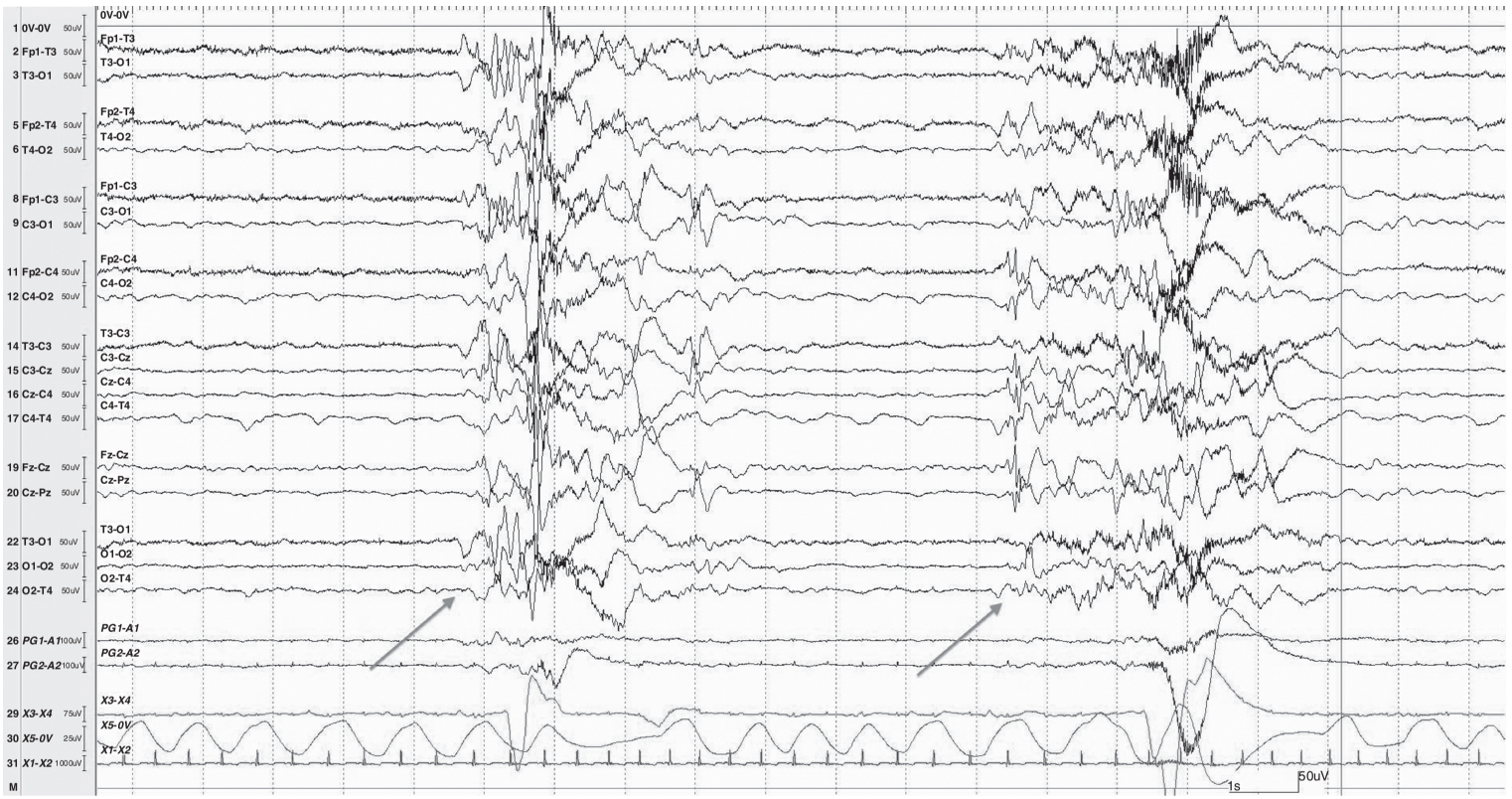


Figure 42.1 EEG showing the abnormal pattern of burst suppression. Arrows indicate abnormal bursts of high-amplitude sharp activity. The EEG in between bursts is of very low amplitude and hence suppressed. This pattern is seen in severe brain dysfunction, including severe hypoxic-ischemic injury, certain metabolic disorders, and in other causes of early-onset epileptic encephalopathy (sensitivity 7 μV, time constant 0.1 second, high-frequency filter 70 Hz, duration 20 seconds).

Table 42.3 International League against Epilepsy Seizure Classification

Generalized seizures	Focal seizures
Tonic-clonic	Focal sensory
Clonic	**Focal motor**
Typical absence	**Elementary clonic motor**
Atypical absence	**Asymmetric tonic motor**
Myoclonic absence	**Temporal lobe automatisms**
Tonic	**Hyperkinetic automatisms**
Spasms	**Inhibitor motor seizures**
Myoclonic seizures	Gelastic
Eyelid myoclonia (with or without absences)	Hemiclonic
Myoclonic atonic	**Secondarily generalized**
Negative myoclonus	Reflex seizures in focal epilepsy
Atonic	
Reflex seizures in generalized epilepsy	

Note: As of 2010, the ILAE began using the same classification system for all seizures regardless of age of the patient. The bolded seizure types are those likely to be seen in neonates. Neonates rarely have primarily generalized seizures, though some rare epileptic syndromes can have generalized myoclonic or tonic seizures or spasms.

neonatal seizures described by either classification standard.

In general, seizures are classified by both their clinical appearance (semiology) and by their EEG characteristics. A key distinction in seizure classification is between a focal and generalized mechanism of onset. Clinically apparent seizures are then classified by a number of features including motor signs (clonic, tonic, or myoclonic movements), autonomic changes, and automatisms (lip smacking, sucking movements, bicycling). Autonomic changes and automatisms are often quite subtle and frequently nonspecific, making these seizures difficult to recognize through clinical observation alone; EEG monitoring is highly useful in confirming that these events are seizures. Finally, subclinical seizures are those seen only on EEG without any reproducible clinical correlate. The vast majority of neonatal seizures are subclinical, without any clinically apparent signs. Even so, there is value in careful observation of clinical events because such a practice can facilitate timely and appropriate treatment.

General versus Focal Onset

The most important initial distinction in classifying a seizure is whether it has a generalized or focal mechanism of onset. Generalized seizures may begin from a specific point but almost immediately involve bilateral neural networks such that electrical activity appears on both sides of the brain simultaneously on EEG. Generalized seizures do not necessarily involve the entire cortex, and their appearance can be asymmetric (Figure 42.2). Focal seizures have a defined region of onset that is the same for every event, and electrical activity initially spreads through neural networks in that region (Figure 42.3), though the seizure may spread within the hemisphere or to the contralateral hemisphere with time [8]. Neonates can also have multiple focal seizures arising from different areas; these are classified as *multifocal seizures*.

In the vast majority of neonatal seizures, onset is focal or multifocal. Spread of the seizure within one hemisphere [9] and secondary generalization to the contralateral hemisphere [9,10] are less common in newborns than in older children because the network connections in the newborn brain are not as fully developed. Lack of myelination and immature synapses hinder transmission of seizures. Thus, while it is not impossible for a neonate to have a "generalized seizure," such labels are often misnomers, carried over from the terminology typically used to describe seizures in older patients. In neonates, focal seizures that always originate from the same location are suspicious for an underlying focal area of injury, such as a stroke. Multifocal seizures tend to reflect a more diffuse process, such as a hypoxic-ischemic brain injury or infection [4]. In general, children with multifocal seizures [11] and those with seizures that generalize to the contralateral hemisphere [12] have worse developmental outcomes.

Clonic Seizures

A *clonic seizure* is defined by clinical signs: "rhythmic movements of muscle groups in a focal distribution which consists of a rapid phase followed by a slow return movement" [13]. Clonic seizures appear as repetitive and rhythmic jerking movements. They can affect

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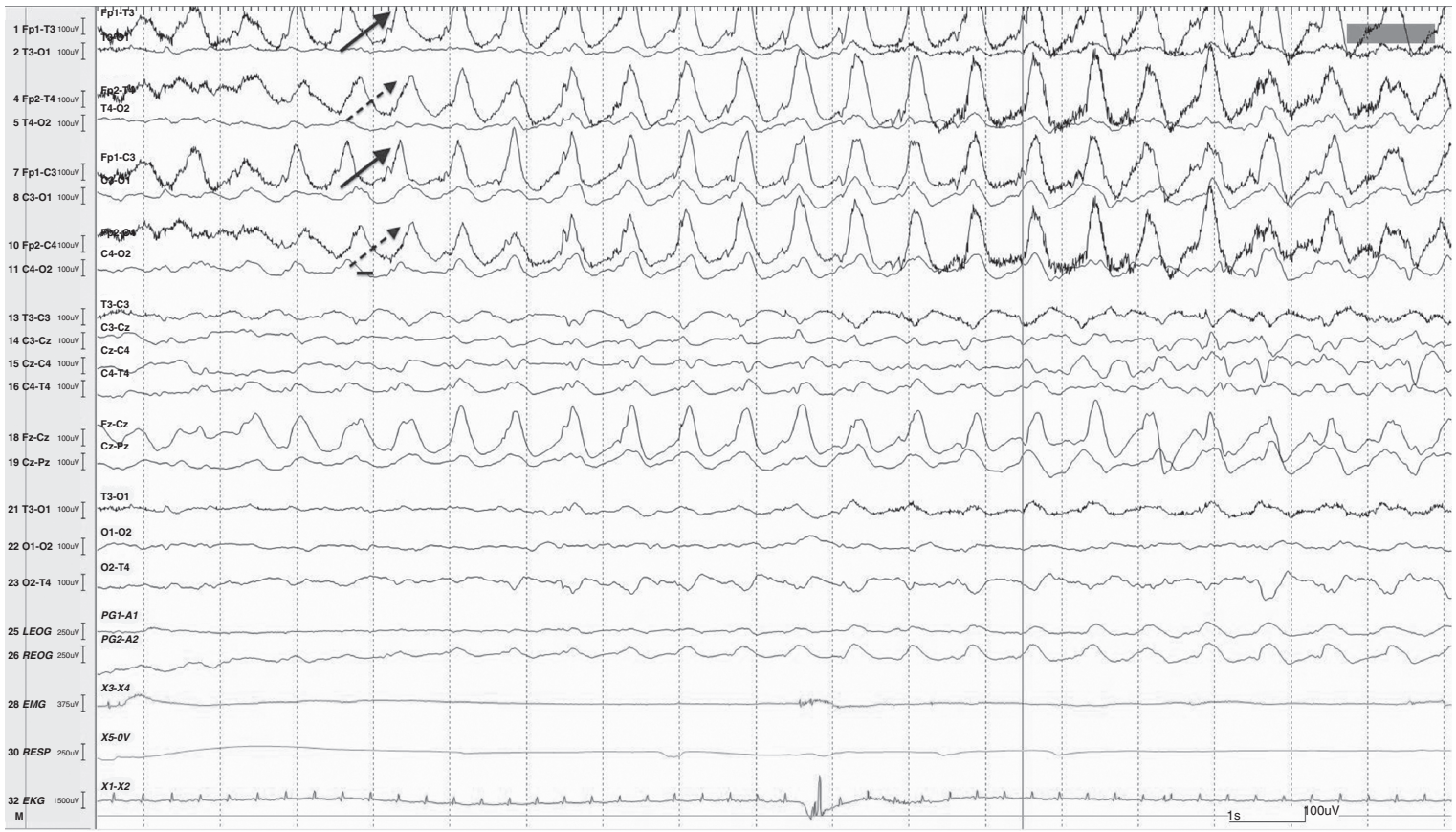


Figure 42.2 EEG showing a generalized neonatal seizure. The solid arrows show spike activity in the left frontal leads (FP1–T3 and FP1–C3), whereas the dashed arrow synchronized shows spike discharges in the right frontal leads (FP2–T4, FP2–C4). Note that the seizure does not have to be present throughout the entire cortex to be generalized, and in the first half of this recording, seizure is not seen in the centrotemporal or occipital leads (sensitivity 20 μV, time constant 0.1 second, high-frequency filter 70 Hz, duration 20 seconds).

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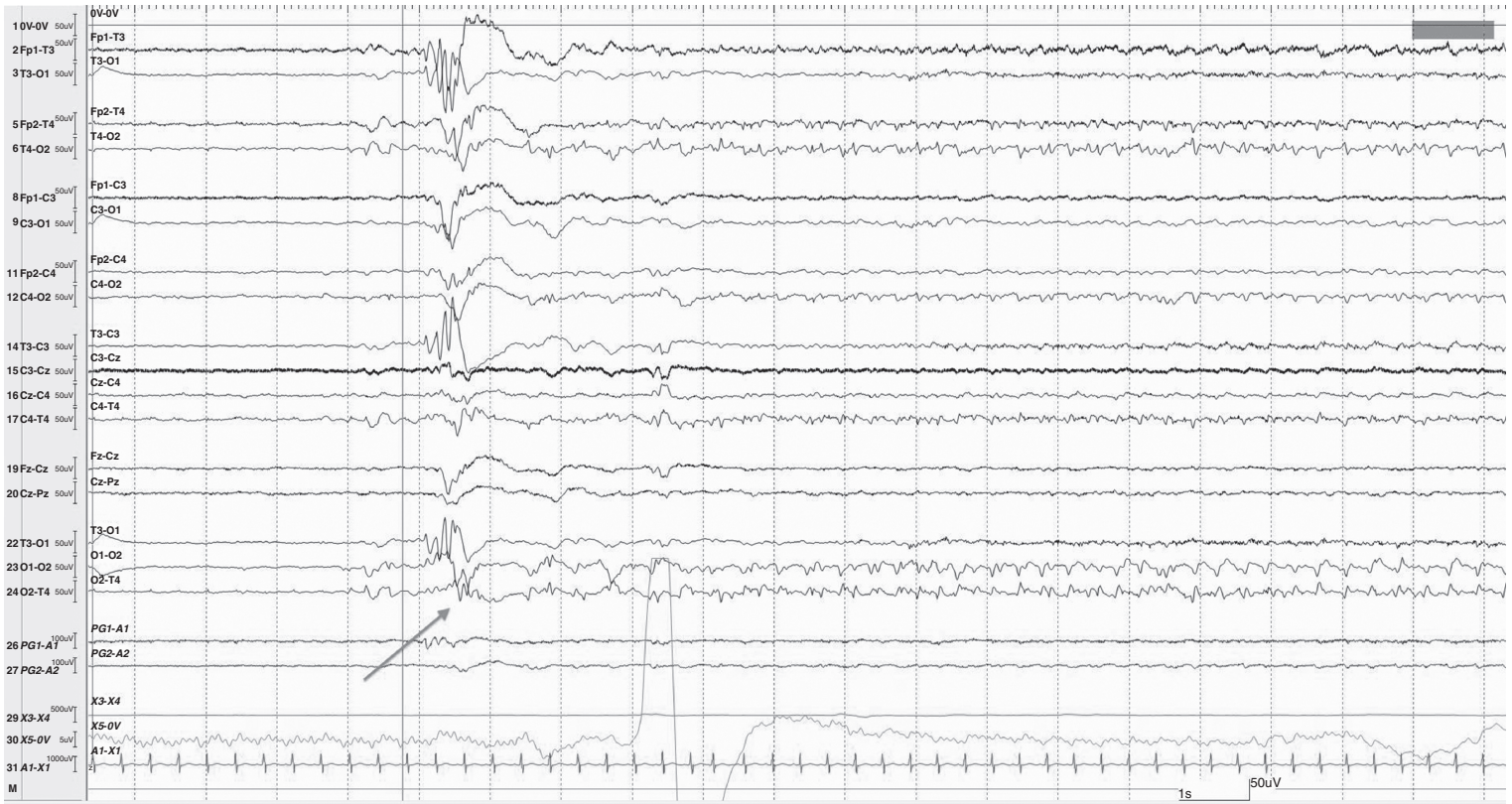


Figure 42.3 This image shows a focal neonatal seizure emerging from the right occipital leads (O2). The arrow points to the time of seizure onset. The sharp waves can be seen at all electrode pairs that contain O2 (i.e., T4–O2, C4–O2) and also less dramatically in some of the other right-hemisphere leads (i.e., FP2–T4, C4–T4) (sensitivity 7 μV, time constant 0.1 second, high-frequency filter 70 Hz, duration 20 seconds).

any part of the body, including the face, extremities, and even diaphragmatic or pharyngeal muscles. Among neonatal seizures with associated motor signs, clonic seizures are the most common, affecting about 20% of monitored neonates [14]. There is evidence that neonates with only focal clonic seizures have better outcomes than those with other seizures types [15,16].

While focal clonic seizures in neonates can spread to affect other parts of the body – for example, involving first only the fingers but then moving to the wrist – they do not tend to spread as dramatically as clonic seizures in older individuals. Generalized clonic activity involving the entire body at once is exceedingly rare in neonates.

Clonic seizures are the seizure type most easily and reliably recognized by clinical observation, but they still can be confused with other repetitive movements such as jitteriness or myoclonus. Table 42.4 presents a comparison of these movements. Unlike jitteriness or tremulousness, the muscle twitches of a clonic seizure cannot be suppressed or distracted with gentle pressure, though the movement itself may be overpowered with enough force. Distinction between clonus and myoclonus is described below in the section "Myoclonic Seizures."

Tonic Seizures

Tonic seizures are defined as a "sustained flexion or extension of axial or appendicular muscle groups" [13]. Tonic seizures can affect any body part and commonly appear as stiffening of a limb, torsion of the neck, or fixed eye deviation. In one study, tonic seizures were noted in only 8% of infants monitored on EEG [14]. Importantly, up to 30% of clinically observable "tonic" activity does not have an EEG correlate and is actually not seizure. For some of these infants, severe cortical damage leads to *brainstem release* and uninhibited extensor posturing that appears similar to tonic stiffening but is not seizure and thus cannot be treated with antiepileptic drugs. This is discussed further below.

Table 42.4 A Comparison of Clonic Seizure, Myoclonus, and Jitteriness

	Clonic seizure	Myoclonus	Jitteriness
Seizures?	Yes	Sometimes (can represent a benign variant, a seizure type, or a release phenomenon indicating CNS damage)	No
Semiology	Repetitive movements consisting of a rapid phase followed by slow return phase	Very rapid, monophasic movements without a return phase; can be isolated or repetitive	Repetitive movements, in which both the movement and return phase are rapid; usually low amplitude and high frequency
Location	Tends to affect one area of the body at a time; can spread to other areas over course of seizure	Can be focal, multifocal, or generalized	Tends to be multifocal or affect parts of the body that are not restrained by blankets
Rhythmic?	Yes	No	Yes
Suppressible with light touch?	No	Benign myoclonus can be suppressed with pressure but myoclonic seizures cannot	Yes, especially with flexion of joint
Stimulus induced	No	Sometimes	Yes
Diagnosis	Clinical picture is highly suggestive, but EEG confirms diagnosis	Benign sleep myoclonus can be diagnosed clinically; EEG often required to distinguish epileptic from nonepileptic myoclonus	Clinical picture is usually adequate to diagnose

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Table 42.5 Selected Differential Diagnosis of Neonatal Seizures

Acute brain injury
Hypoxic-ischemic injury
Cerebrovascular insult (arterial, venous)
Intraventricular hemorrhage
Extraparenchymal hemorrhage (epidural, subdural, subarachnoid)
Infections
Viral (HSV, enterovirus)
Bacterial (group B *Streptococcus, Escherichia coli*)
Congenital/TORCH infections
Metabolic disturbances
Hypoglycemia
Hypocalcemia/hypomagnesaemia
Hypo/hypernatremia
Brain malformations
Polymicrogyria
Lissencephaly
Hemimegalencephaly
Heterotopias
Tubers
Other cortical dysplasias
Brain malformations associated with inborn errors of metabolism (see below)
Inborn errors of metabolism with systemic complications/encephalopathy
Disorders of carbohydrate metabolism (e.g., galactosemia)
Aminoacidopathies (e.g., phenylketonuria)
Organic acidurias (e.g., maple syrup urine disease)
Urea cycle disorders (e.g., ornithine transcarbamylase deficiency)
Inborn errors of metabolism that may present primarily with seizures
Disorders of neurotransmitter metabolism (e.g., nonketotic hyperglycinemia, pyridoxine- and pyridoxyal-5-phosphate-dependent epilepsy, folinic acid–dependent epilepsy, GABA disorders)
Disorders of energy metabolism (e.g., GLUT-1, biotinidase deficiency, pyruvate dehydrogenase disorder, sulfite oxidase deficiency, purine disorders, creatine synthesis and transporter defects, Menkes disease, fumarase deficiency, respiratory chain disorders)
Biosynthesis defects that cause malformations or dysfunction (e.g., peroxisomal disorders, congenital disorders of glycosylation, disorders of cholesterol synthesis, disorders of homocysteine and folate, disorders of serine and glutamine metabolism, congenital neuronal ceroid lipofuscinosis, disorders of glycolipid synthesis)
Genetic disorders: Several dozen genetic causes of epilepsy have been identified; some of the more common genes include:
ARX
CDKL5
STXBP1
MECP2
PNKP
Channelopathies (*KCNQ2, KCNQ3, SCN1A, SCN2A*)
Tuberous sclerosis

Myoclonic Seizures

Myoclonus is defined as a rapid, isolated jerk. It can affect only one muscle group and appears focal or, alternatively, affects multiple muscles and is multifocal or generalized. Unlike clonic movements, there is no slow return phase, and the movements are irregular rather than rhythmic. A myoclonic jerk can occur in isolation or be a series of repetitive (though not rhythmic) movements. Myoclonus can arise from any level in the nervous system, including the cortex, subcortical white matter, brainstem, spinal cord, and peripheral nerve.

Interestingly, myoclonus can be a normal phenomenon in neonates, whereas myoclonic seizures can indicate various pathologies. Myoclonic seizures, in which motor activity correlates with abnormal electrographic activity, are an uncommon seizure subtype. Unlike other forms of myoclonus, myoclonic seizures are not induced by stimuli and cannot be suppressed by pressure or palpation of the affected body part. Furthermore, neonates with myoclonic seizures almost always have very abnormal neurologic examinations, whereas neonates with benign myoclonus are otherwise normal. In general, neonates with myoclonic seizures develop severe early-onset epilepsy syndromes. EEG can be extremely helpful in distinguishing normal myoclonus from myoclonic seizures in ill neonates, as discussed further below.

Subtle and Subclinical Seizures

Up to 80–90% of neonatal seizures have no obvious outward manifestation [9,17–19] or only very subtle and nonspecific signs. Subtle signs that may be concerning for neonatal seizures include repetitive facial or lingual movements (lip smacking), unusual eye movements, cycling of the legs or swimming of the arms, or unexplained vital sign changes [3]. When these movements are found to have EEG correlates, they are considered subtle electroclinical seizures. In contrast, such movements without EEG correlates are not considered true seizures. It can be very difficult to identify subtle electroclinical seizures. In a recent study, experienced healthcare professionals distinguished subtle epileptic events from other paroxysmal movements accurately in 20–50% of cases; furthermore, the interrater reliability between professionals was quite poor [20]. Of note, about half the events suspected to be seizures by clinicians in the NICU environment had no electrographic correlate; they were not seizures [19]. It is more common for subtle clinical events to have an electrographic correlate (to be seizures) if the neonate has other types of seizures; these events are less likely to be seizures when they are the only behavior of clinical concern [21]. Ultimately, it is not possible to accurately classify whether or not such signs are seizures by clinical examination alone; therefore, video-EEG monitoring is warranted for accurate diagnosis.

Even in neonates who undergo EEG for suspicion of seizures, only the minority (10–34%) of seizures found on EEG have an associated clinical change [10,19]. A particular challenge to neonatal seizure diagnosis is the phenomenon of *uncoupling*, in which a neonate with electroclinical seizures progresses to have only subclinical seizures after treatment with antiepileptic medication. Uncoupling affects up to 58% of newborns treated with antiepileptics [22,23]. Therefore, clinical observation alone is unreliable, and thus EEG is required to determine whether all seizures have resolved after antiepileptic drugs are given.

Epileptic Encephalopathies

Though not a specific seizure semiology, *epileptic encephalopathy* describes the clinical presentation of encephalopathy caused by the presence of epileptic abnormalities. The term *early onset epileptic encephalopathy* (EOEE) describes this clinical syndrome as it arises in neonates and infants. There are multiple specific causes of EOEE, including genetic, metabolic, and structural problems. While neonates with acute seizures secondary to brain injury may also have both seizures and encephalopathy, this is not a true epileptic encephalopathy because in these cases the brain injury is the underlying cause of both seizures and encephalopathy. In contrast, in epileptic encephalopathy, the seizures themselves are thought to cause, or at least contribute strongly to, the encephalopathy.

Nonepileptic Movements

Various neonatal movements can be difficult to distinguish from seizures by appearance alone. Some of these are benign events, whereas others, although not seizures, are nonetheless abnormal and warrant investigation. Some seizure mimics are particularly common in neonates.

Tremulousness or Jitteriness

Tremors may be misidentified as clonic seizures; both are characterized by rhythmic oscillatory movements. Distinguishing features include that in tremor, both phases are of the same amplitude and speed. This is in

contrast to clonic seizures, which manifest as a fast jerking movement with a slow rebound movement. Tremors are often higher frequency (faster) and lower amplitude (smaller, fine movements). Tremors are typically suppressible by flexion or repositioning of the affected body part. Though often spontaneous, tremors may be elicited by stimuli, whereas seizures arise spontaneously. *Jitteriness* refers to recurrent tremors.

Tremors are very common, with up to two-thirds of healthy newborns having some degree of fine tremoring the first days of life and up to 44% of newborns being jittery [24]. Benign tremor is hypothesized to be due to immaturity of inhibitory neurons [25] or elevated levels of catecholamines [26] and tends to resolve with soothing or sucking. Excessive, pathologic tremors can be caused by systemic problems, including hypoglycemia, hypocalcemia, infection, drug withdrawal, or thyroid disease. Excessive tremor is also seen primary neurologic disease, such as in mild hypoxic-ischemic encephalopathy (HIE) or intraventricular hemorrhage (IVH). Fine tremors are more likely to be benign or related to an electrolyte disturbance, whereas higher-amplitude tremors are more likely to be secondary to nervous system compromise [27].

Nonepileptic Myoclonus

In neonates, myoclonus can be benign or pathologic. Healthy premature babies often demonstrate occasional spontaneous myoclonus. *Benign neonatal myoclonus*, alternately termed *benign neonatal sleep myoclonus*, can manifest as quite pronounced myoclonus, typically most prominent in sleep, lasting up to several minutes. Benign neonatal myoclonus may be differentiated from pathologic myoclonus in that benign myoclonus can be stopped by rousing the infant and typically does not involve the face [28,29]. Benign neonatal myoclonus can be distinguished from clonic seizures in that benign myoclonus typically migrates from limb to limb and is suppressible. In contrast, seizures are stereotyped – affecting one limb or one side of the body each time – and are not suppressible. Benign neonatal myoclonus is a self-limited movement disorder; while it may last up to several months, most children outgrow it in the first year.

Nonepileptic but still pathologic myoclonus is attributed to a brainstem release phenomenon from loss of cortical inhibition of lower circuits. It is frequently seen in infants with global brain injury from hypoxia-ischemia, severe IVH, and toxic-metabolic disturbances, including drug withdrawal and glycine encephalopathy. Such patients have abnormal neurologic examinations and EEGs, even though the myoclonus itself is not a seizure [21,30,31]. These accompanying abnormalities distinguish pathologic myoclonus from benign myoclonus.

Hyperekplexia

Hyperekplexia is a rare neurologic disorder characterized by exaggerated abnormal movements that look like a hyperactive startle response but do not extinguish with repeated stimuli. Clinically, hyperekplexia should be suspected if a neonate has a startle response easily elicited by glabellar tap, and the response does not habituate over time. The "minor" form of hyperekplexia only involves excessive startle, whereas the "major" form is associated with additional problems, including generalized stiffness while awake, nocturnal myoclonus, and an increased risk of sudden infant death syndrome (SIDS) from central and obstructive apnea. *Of note, forced flexion of the head or lower extremities toward the trunk can occasionally abort spells of respiratory distress and be lifesaving maneuvers.* Hyperekplexia is thought to be caused by mutations in the glycine receptor gene, and clonazepam is the treatment of choice for excessive startle [21,32].

Brainstem Release Phenomena/Motor Automatisms

Some stereotyped movements of the newborn – including repetitive facial or lingual movements, eye movements, cycling of the legs, and swimming of the arms –may be either normal behaviors (such as leg cycling) or abnormal motor patterns indicating brain injury, although not seizure (such as abnormal jerking eye movements). EEG is critical to help distinguish these nonseizure behaviors and automatisms from true seizures in order to guide appropriate treatment.

Causes of Neonatal Seizures

Neurophysiology of Neonatal Seizures

On a cellular level, seizures occur when there is excessive depolarization and hence electrical discharges of neurons. Depolarization is caused by influx of sodium – bringing the membrane potential from negative to positive – while repolarization is established by efflux of potassium. Movement of these ions depends on their concentration as well as the electrical charge on either side of the membrane. The sodium-potassium-ATP pump maintains the correct concentration of ions on either side of the membrane to allow for rapid depolarization of the membrane; this pump requires significant energy expenditure to function.

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Other ions, including calcium and magnesium, can affect the flow of sodium and potassium. Finally, in order to propagate to surrounding neurons, the electrical signal is turned into a chemical one at the synapse by release of neurotransmitters that can either be excitatory or inhibitory to neighboring cells.

Developmental differences in neurophysiology and anatomy at each of these steps make the neonatal brain more susceptible to generating seizures. Neonatal brains have increased excitatory activity and relatively decreased inhibitory activity compared with older individuals. Glutamate is the primary excitatory neurotransmitter of the CNS, and there are increased concentrations of glutamate receptors (specifically *N*-methyl-D-aspartate [NMDA] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors) in the perinatal period compared with later in life. Additionally, in the neonatal period, the behavior of these receptors is slightly different from later in life, allowing for more neuroexcitation. The predominant inhibitory neurotransmitter, GABA, typically works by allowing influx of the negative chloride ion into the cell, thus hyperpolarizing it and preventing a discharge. In neonates, however, the chloride concentrations are altered due to differences in chloride channels such that activation of the $GABA_A$ receptor can actually lead to efflux of chloride and depolarization of the neuron.

Due to this relative excess of excitation, many pathologic states – both systemic and specific to the CNS – are more likely to result in seizures in the neonate. Over 80% of neonatal seizures are symptomatic of acute illness or brain injury. Some of the more common causes of symptomatic seizures are discussed here [33]. Less often, seizures are due to congenital brain malformations, metabolic epilepsies, and genetic epilepsy syndromes.

Neonatal Brain Injury

Hypoxic-Ischemic Injury

Hypoxic-ischemic injury is the most common cause of neonatal seizures in term infants in high-income countries, causing 40–60% of cases [34]. The hypoxic-ischemic event most often occurs antenatally or intrapartum, though up to 10% of cases occur postpartum due to problems such as lung or heart disease. Infants who have had perinatal hypoxic-ischemic brain injury often present with an encephalopathy at birth, exhibiting alterations in alertness, tone, and movements. Seizures in HIE usually begin by 24 hours after birth but may start at any point in the first 96 hours, particularly in neonates receiving therapeutic hypothermia [35,36]. There is frequently explosive onset of subclinical, focal, or multifocal seizures, with many children developing status epilepticus. The seizures usually stop by 5–7 days after injury [33]. Treatment is recommended because multiple animal and human studies suggest that seizures exacerbate existing cerebral injury [37–41].

Literature predating the use of therapeutic hypothermia suggested that approximately 22–64% of neonates with HIE developed seizures in the neonatal period [42–44]. In children with moderate to severe HIE who have undergone therapeutic hypothermia, the rate of neonatal seizures is approximately 30–65% [35,36,45], with 10–30% experiencing status epilepticus. The similar incidence in the pre- and posthypothermia literature may be secondary to the fact that video-EEG was used in the latter studies, whereas the former often relied on clinical observation. One single-center study did note a significant reduction in seizure burden in infants receiving hypothermia compared with those who did not receive this treatment after controlling for degree of injury seen on MRI [46]; interestingly, this benefit only applied to those with moderate but not with severe encephalopathy.

Cerebrovascular Disorders

Ischemic stroke is the second most common cause of neonatal seizures in full-term infants in high-income countries, accounting for up to 18% of cases [47]. The incidence of perinatal arterial stroke is approximately 1/1,600–5,000 [48]. When perinatal arterial stroke is identified in the neonatal period, it is overwhelmingly because a newborn has developed clinical seizures that trigger evaluation. At least half of cases of neonatal stroke go unrecognized until later in childhood, but for those that are diagnosed in the neonatal period, up to 97% present with seizures and 50% have seizures as the only recognized symptom [49]. Compared with neonates with more diffuse brain injury such as in HIE, those with neonatal stroke as a cause of seizures are more likely to appear active and alert between seizures. Poststroke seizures typically do come under control in the neonatal period, but there is a risk of developing epilepsy later in life. The reported incidence ranges from approximately 10% to 50% depending on time to follow-up and inclusion criteria [49–52].

Cerebral sinus venous thrombosis (CSVT) occurs less frequently than arterial stroke in neonates, affecting approximately 1/ 8,000–38,000 children per year; 42–78% of these neonates experience a venous infarct

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[53,54]. Seizures are the presenting symptom or a complication of CSVT in 55–80% of the cases, but affected neonates also manifest diffuse and focal neurologic deficits.

Intraventricular Hemorrhage

IVH is the most common cause of neonatal seizures in preterm infants, particularly in infants under 30 weeks' gestational age [1]. In one older series, 45% of preterm infants with seizures were found to have an underlying IVH [55]. More severe IVH carries a higher risk of seizures [56]. Seizures from IVH are more likely to present several days to a week after birth.

Extraparenchymal Hemorrhage

Subarachnoid and subdural hemorrhages can occur during the birth process. Rarely, such bleeds can lead to seizures, often occurring after the first day of life [33]. Usually no neurosurgical intervention is required, and following resolution of the acute, symptomatic seizures, these children have an excellent prognosis [57].

Other Provoked Seizures

Infections

CNS infections are the cause of neonatal seizures in approximately 5–10% of cases, with a suspected higher incidence in low- and middle-income countries. There is an equal incidence in preterm and term infants [1,47,57]. These can include congenital infections (such as TORCH infections) or acute CNS infections (such as group B *Streptococcus* or *E. coli* meningitis). Neonates who develop seizures without a clear cause warrant a full sepsis evaluation and lumbar puncture to assess for such infections.

Transient Metabolic Disturbances

Hypoglycemia

Hypoglycemia is thought to be responsible for approximately 3% of neonatal seizures, though the incidence has been falling with improved neonatal care [47]. The risk is greater in premature and low-birth-weight infants as well as infants of diabetic mothers. Hypoglycemia significant enough to trigger seizures is often associated with adverse neurodevelopmental outcomes [58].

Hypocalcemia and Hypomagnesemia

Hypocalcemia is thought to account for 1% of neonatal seizures. Early-onset hypocalcemia, occurring on days 2–3 of life, is usually seen in infants with very low birth weight or born to diabetic mothers. Late-onset hypocalcemia, occurring in the first to second week of life, is seen in endocrinopathies such as maternal hyperparathyroidism or DiGeorge syndrome. Hypomagnesemia rarely occurs in isolation but is often associated with hypocalcemia [57].

Hyper- and Hyponatremia

Metabolic disturbances that affect sodium are common in preterm and low-birth-weight infants and can be a cause of seizures in a minority of these patients. Sodium alterations as an etiology for seizures should especially be considered in children on parenteral nutrition because errors in the formula can cause significant shifts. Rarely, severe hypernatremia can also arise in neonates not receiving adequate breast milk; in these children, seizures are most likely to arise in the setting of overly rapid correction with hyptonic fluids [33,57].

Brain Malformations

In aggregate, malformations of cortical development account for 5–9% of neonatal seizures [1,47]. More common malformations include tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, schizencephaly, and polymicrogyria. Though these disorders may be the cause of a substantial percentage of neonatal seizures, most patients with these malformations do not have seizures in the neonatal period. Instead, most of these malformations are not detected until later in infancy or childhood. In tuberous sclerosis – one of the few conditions diagnosed prenatally due to the presence of cardiac rhabdomyomas seen on prenatal ultrasound – only 5% of children develop seizures in the neonatal period [59]. In general, malformations of cortical development causing neonatal seizures are also associated with poor neurodevelopmental outcomes, including severe developmental delay.

Inborn Errors of Metabolism

Inborn errors of metabolism describe a group of varied disorders that can present across the lifespan. Dysfunction of metabolic pathways can lead to inappropriate buildup of a by-product that causes "intoxication"; affected neonates often present with lethargy and poor feeding. In some disorders, such as maple syrup urine disease and urea cycle disorders, seizures may be secondary to cerebral swelling. In this sense, the seizures are symptomatic of the underlying metabolic condition.

At the same time, many metabolic disorders are associated with lifelong epilepsy and thus are typically classified as neonatal-onset epilepsies. These disorders are often detectable by basic metabolic screens, including chemistries, lactate, ammonia, serum amino acids, and urine organic acids.

Other metabolic disorders can present with seizures as their primary symptom and may not have obvious abnormalities on first-pass metabolic testing. One classification scheme divides such disorders into (1) disturbances of neurotransmitter metabolism, (2) disorders of energy production, and (3) biosynthetic defects [60]. Clues that neonatal seizures are secondary to one of these disorders include seizures beginning in utero (often experienced by the mother as excessive hiccoughs), seizure refractory to traditional antiepileptic medications, progressive worsening of the clinical and electrographic abnormalities, a pattern of burst suppression on neonatal EEG, and imaging suggestive of brain atrophy or hypoxic-ischemic injury without a clear insult [61]. In some cases, accurate diagnosis can lead to effective treatment options, as in the case of vitamin-responsive epilepsies (i.e., pyridoxine-dependent epilepsy).

Single-Gene Disorders

Knowledge of the genetics underlying epilepsy syndromes has grown exponentially in the last decade. Emerging reports describe both new mutations and new phenotypes associated with previously known genetic defects. While individual genetic epilepsies are rare, collectively they comprise a clinically relevant percentage of neonates with seizures. While an exhaustive inventory of genetic epilepsies is beyond the scope of this text, benign familial neonatal epilepsy merits specific mention.

Benign Familial Neonatal Epilepsy (BFNE)

This syndrome is an autosomal dominant condition manifesting with seizures in the first week of life. Typically seizures are clonic or apneic spells, though occasionally tonic seizures are also seen. Seizures usually resolve by 1 year of age, though approximately 10–15% of children develop epilepsy later in life [62]. For more than 80% of patients, the syndrome is caused by mutations in genes for potassium channels subunits (*KCNQ2* and *KCNQ3*), but BFNE has also been reported in patients with mutations in *PRRT2* and genes coding for a sodium channel subunit (*SCN2A*). Recent research has shown that mutations in several of these genes is associated with a spectrum of diseases, including neonatal epileptic encephalopathies [63].

BFNE is distinct from the clinical diagnosis of benign nonfamilial neonatal convulsions or "fifth day fits." In fifth-day fits, onset of clonic and/or apneic seizures typically occurs on the fourth to sixth day of life with resolution of events by 2 weeks. Examination and workup are negative, as is family history of seizures. The etiology of this syndrome remains unknown, although decreasing incidence suggests at least some patients who previously would have been considered to have fifth-day fits are now diagnosed with a specific genetic epilepsy, such as BFNE [57,64].

Early-Onset Epileptic Encephalopathies

Early-onset epileptic encephalopathies (EOEEs) typically have a metabolic or structural etiology, but approximately 15–20% may be secondary to a gene defect [63]. Epileptic encephalopathies are more common in older infants than in neonates, but there are two well-known syndromes with an early onset.

Early Myoclonic Epilepsy

Early myoclonic epilepsy (EME) is a very severe epilepsy that typically begins in the first month of life. Clinically, patients demonstrate several seizure types including myoclonic seizures, focal motor seizures, and tonic spasms. The EEG initially shows a pattern of high-amplitude bursts followed by short periods of suppression; this evolves into hypsarrhythmia later in infancy in many cases. Seizures are extremely difficult to control, and prognosis is poor, with half of children dying before 1 year of life and the rest having severe developmental delay. This syndrome can have various etiologies but most frequently is caused by inborn errors of metabolism.

Early Infantile Epileptic Encephalopathy

Early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome is another epilepsy syndrome with onset within the first 3 months of life, sometimes presenting in the neonatal period. Affected children have frequent clusters of tonic spasms as well as focal motor seizures. Seizures are intractable and accompanied by clinical encephalopathy. The EEG shows a true burst-suppression pattern. Survivors usually have severe developmental delay. Cortical malformations are a common cause of EIEE [23,65,66], though genetic mutations in over a dozen single genes have been reported to cause EIEE [67].

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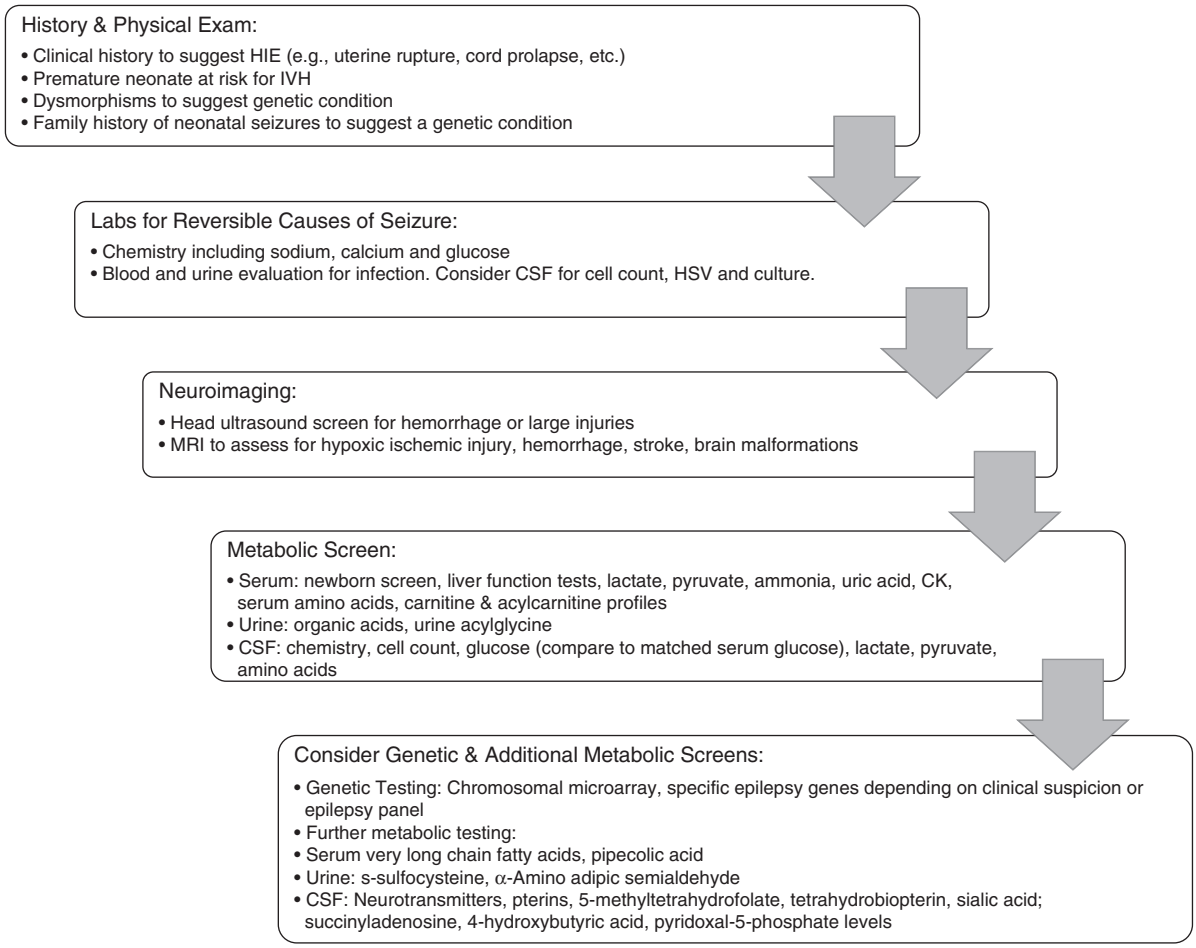


Figure 42.4 A suggested approach to the evaluation of neonatal seizures. Initial assessment should focus on evaluating for causes of acute neonatal brain injury – such as hypoxic-ischemic injury or intraventricular hemorrhage – because these are the most common causes of seizures. Special attention should be paid early to screening for reversible causes. Imaging is a crucial step for all patients. Metabolic and genetic tests should be considered in neonates without a clear etiology identified by the first few steps of testing.

Evaluation of Neonatal Seizures

The goal of the diagnostic workup in infants with suspected seizures is twofold: (1) to confirm the diagnosis and, in those with seizures, (2) to determine the underlying cause in order to guide management and prognosis.

Diagnosis

As described earlier, clinical diagnosis of seizures is limited by the fact that the majority of neonatal seizures have no outward manifestation, and neonates have many behaviors that may be mistaken for seizures but which are not. Therefore, measurement of cortical activity by EEG is the "gold standard" for diagnosis of seizures; the World Health Organization (WHO) and various international guidelines recommend such monitoring in any center where it is available [3,68].

Continuous EEG (cEEG)

The American Clinical Neurophysiology Society recommends that neonates at high risk for seizures be monitored by cEEG for at least 24 hours and that for those found to have seizures, the monitoring should be continued for at least 24 hours after the final seizures [3]. This longer recording is recommended because 35% of high-risk neonates will not have seizures in the first hour of recording but will go on to have seizures within the first day [35]. In infants with HIE, recording is recommended throughout the

cooling protocol and rewarming because approximately 50% of patients have their first seizure after 24 hours of life, and 5% have onset of seizures during rewarming [41]. In addition, assessment of the EEG background provides important information regarding the severity of neonatal brain dysfunction that correlates with the degree of injury and neurologic prognosis of the infant. cEEG is discussed more fully in Chapter 17.

Amplitude-Integrated EEG (aEEG)

There are several technical factors that can make obtaining a full EEG difficult, especially when resources are limited. A full neonatal EEG montage typically consists of 11 leads and requires an experienced technologist to apply as well as an experienced neurophysiologist to interpret. Many NICUs do not have these personnel available around the clock. Though not painful or invasive, placement of the electrodes can take time and repositioning of the patient, which can be physiologically stressful for unstable neonates. Furthermore, the electrodes can lead to skin breakdown over time, limiting the feasible duration of EEG monitoring, particularly in preterm infants.

aEEG is an alternate screening technique for measuring cortical activity that addresses some of these challenges. Rather than 10–12 electrodes, aEEGs only require three to four electrodes, which can be placed and monitored by any properly trained staff. The primary output is an integrated channel representing the overall amplitudes of cortical signals over time and hence can be screened much more quickly than a regular EEG. Studies comparing aEEG as interpreted by NICU personnel with cEEG interpreted by epileptologists have found that aEEG identifies 60–90% of patients with seizures as well as 12–80% of individual seizures [69–71]. There is limited evidence that aEEG may lead to earlier detection and treatment of seizures than cEEG, with a trend toward reduced injury on MRI [18]. Table 42.6 provides a comparison between cEEG and aEEG. aEEG is discussed further in Chapter 17.

Table 42.6 Amplitude-Integrated EEG (aEEG) versus Conventional EEG

aEEG	Conventional EEG
Readily available	Requires technologist
Identifies most seizures	"Gold standard" for seizure detection
No localization	Localization possible
Clear trends over time	Better for short time periods
Less background detail	Rich background detail
Quick interpretation	Delay to interpretation
Expertise needed	Expertise needed

Assessment of Etiology

Because most neonatal seizures are symptomatic of acute brain injury, assessment for etiology should focus on this possibility. In the immediate evaluation, laboratory investigations for evidence of infection and electrolyte abnormalities are appropriate. Following this, urgent neuroimaging is needed.

Head Ultrasound

Head ultrasound is often first-line neuroimaging when evaluating for acute brain injury. While resolution of images is not as precise as other modalities, ultrasound has the advantage of being a bedside technique that requires no sedation and involves no radiation exposure. Particularly when other imaging might not be possible for one or more days, head ultrasound is valuable as a first initial imaging screen for acute brain injury.

Computed Tomography (CT)

Head CT has a very limited role in the evaluation of neonates with seizures. While it can offer superior image resolution to head ultrasound, it remains inferior to MRI. Most urgent, treatable issues identified by head CT – such as large hemorrhages – can be picked up by ultrasound. Other types of injury that might be seen on head CT but not on ultrasound – such as stroke – usually do not have the possibility of acute intervention; therefore, waiting for MRI is reasonable. In addition, head CT requires transport off the unit to perform and exposes the developing neonatal brain to radiation. Given these issues, head CT is rarely indicated for evaluation of neonatal seizures.

Magnetic Resonance Imaging (MRI)

Ultimately, almost all neonates with seizures will require MRI. MRI provides the best image quality and offers the potential to include additional sequences (such as diffusion-weighted imaging) for superior detection of acute injury. In cases where stroke or thrombosis is suspected, MR angiography (MRA) and/or MR venography (MRV) may be included. Consistent use of MRI to evaluate neonatal seizures allows diagnosis of etiology in over 90% of cases [72].

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Other Tests

In cases where MRI does not identify a cause of neonatal seizures, it is appropriate to pursue additional metabolic and genetic testing. This includes a screen for inborn errors of metabolism, which may be tailored based on the patient's clinical presentation. Typically, such a screen would include lactate, pyruvate, ammonia, and a basic metabolic panel including liver function tests, serum amino acids, urine organic acids, and acylcarnitine and carnitine profiles. These tests along with the newborn screen can provide evidence for amino acidopathies, organic acidurias, urea cycle disorders, and mitochondrial disease. A lumbar puncture is required not only to rule out infection but also to expediently assess for certain metabolic disorders. In particular, workup should focus on treatable causes of neonatal seizures. These include disorders of the glucose transporter (GLUT-1), which can be diagnosed by comparing simultaneously drawn serum and CSF glucose levels; these patients require treatment with the ketogenic diet. In addition, vitamin-dependent epilepsies, such as pyridoxine or pyridoxal-5-phosphate-dependent disorders, can be identified with a combination of serum, urine, and CSF studies; often response to an empirical trial of vitamins is also important in making the diagnosis. CSF studies may also be helpful in the diagnosis of more rare metabolic causes of neonatal epilepsy [60].

Similarly, genetic panels are now commercially available to investigate the most common genetic etiologies of neonatal seizures. Though initially such panels took weeks to months to return, there are options now that return within several days to a week. Diagnosis of a genetic syndrome can be helpful in limiting other investigations, in understanding prognosis, in counseling families regarding the potential for recurrence in future pregnancies, and, for select conditions, in guiding management. Certain conditions are known to respond to specific treatments or to be exacerbated by others.

Treatment

Goals of Treatment

Neonatal seizures require emergent treatment because increasing evidence suggests that they can exacerbate underlying brain injury [73]. While there remains controversy as to what degree treating neonatal seizures improves long-term outcomes and how aggressively seizures should be treated, most clinicians do treat neonatal seizures [74]. Indeed, the WHO recommends treatment of all electrographic seizures [68]. The first steps in caring for a neonate with seizures are confirming the diagnosis with EEG and initiating evaluation of the etiology, as described earlier. In rare cases, reversible causes (i.e., electrolyte disturbances or infection) will be identified, and treatment of these may lead to cessation of seizures. For most neonates, however, antiseizure (typically called *antiepileptic*) medications will be required.

The goal of treatment should be clearly identified and communicated to all members of the care team. For most neonates, the initial goal will be complete resolution of all electrographic seizures, as recommended in the WHO guidelines. As care progresses, this goal may be adjusted based on individual circumstances. For example, a neonate with cardiovascular instability may not tolerate multiple antiseizure medications; in such a case, the goal may be to reduce the seizure burden as much as possible without compromising cardiovascular function. Similarly, if a diagnosis of brain malformation or other neonatal-onset epilepsy is made, the goal of treatment might be to reduce the number of seizures as much as possible while maintaining acceptable alertness on a medication regimen that can be continued after hospital discharge.

Early treatment of neonatal seizures is recommended in the acute period, with evidence that early treatment combined with a coordinated, consistent approach prevents overadministration of antiseizure medication [75]. While medication is typically continued at least until seizures have been controlled for 24 hours, and often for a few days following the acute period of injury, there is less evidence to support long-term continuation of antiseizure medications in the weeks or months following acute symptomatic neonatal seizures. Animal data have shown that chronic use of antiseizure medications can be associated with neuronal apoptosis [76]. The medications may affect normal brain development by affecting cell proliferation, neurogenesis, neuronal migration, normal apoptosis, and synaptic plasticity [77]. Therefore, an equally important though often overlooked step in the management of neonatal seizures is withdrawal of medications in a timely fashion, often before hospital discharge.

Choice of Treatment

There are minimal data comparing different treatment options for neonatal seizures. A Cochrane review [78] concluded that there is not adequate evidence to support one medication over others. The WHO and ILAE, however, recommend use of

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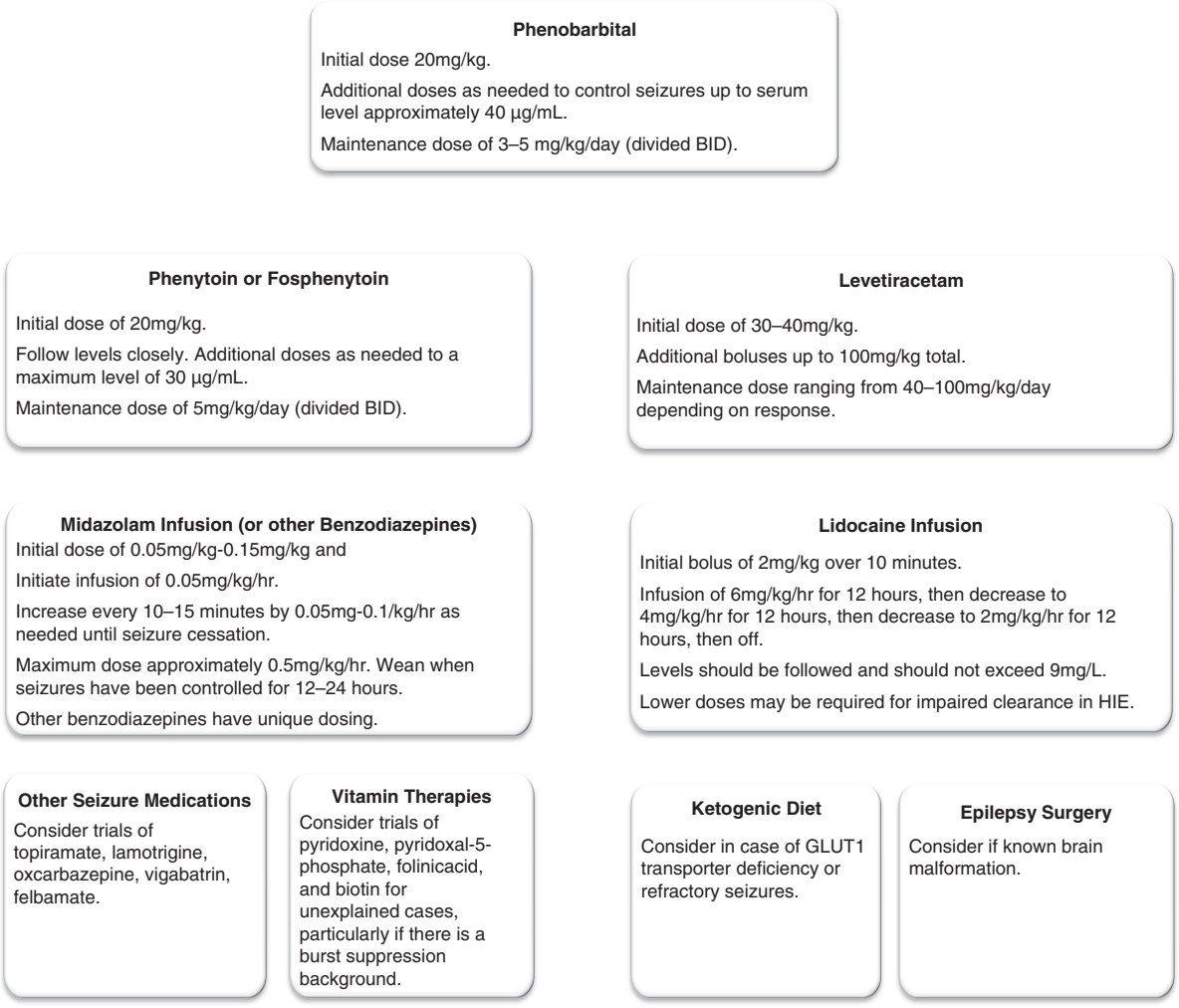


Figure 42.5 A suggested approach to the treatment of neonatal seizures. Phenobarbital should be tried first. After the level has been maximized, second-line agents can be considered. Some clinicians prefer to use levetiracetam before infusions and even before phenytoin. If infusions fail or the infant cannot be weaned without relapse of seizures, then alternative therapies should be considered.

phenobarbital as the first agent [68], and internationally, this is the most frequent initial treatment for neonatal seizures. With regard to second-line agents, the WHO recommends the use of phenytoin, a benzodiazepine, or lidocaine. There is varying familiarity and availability of these agents between institutions and countries, so preference is largely hospital specific. There is growing evidence that levetiracetam is safe and effective in the treatment of neonatal seizures, and this agent is now being used by some hospitals much earlier in their treatment algorithms. In cases where seizures continue despite these initial steps in treatment, neurologists often start other seizure medications typically used in older children and adults, such as topiramate (Figure 42.5).

There are several other treatments that should be considered depending on clinical context. For infants with refractory seizures and evidence of a severely abnormal background EEG, vitamin trials can be considered. If there is concern for a glucose transporter problem or several other metabolic disorders, then the ketogenic diet is the treatment of choice. There have also been case reports of successful use of the ketogenic diet for refractory neonatal seizures of unclear etiology [79]. Finally, if there is a known brain malformation causing refractory seizures, epilepsy

surgery can be considered even in the neonatal period if the child fails medication trials.

Phenobarbital

In practice, phenobarbital is the first-line agent for most neonatal seizures. It has generally been thought to have a reasonable safety profile, though it may have long-term adverse effects on neural development [33]. Bolus doses of phenobarbital (15–20 mg/kg) leading to levels of 20–25 μg/mL have been shown to control approximately 33–43% of neonatal seizures [80–83]. More recent studies indicate that higher phenobarbital levels around 40 μg/mL may achieve seizure control in up to 77% of patients [80–83], so it is recommended that such levels be achieved before addition of a second agent. A single randomized, controlled trial of term infants showed that phenobarbital and phenytoin were equally effective as initial therapy for neonatal seizures but that at least half the children treated with either agent continued to have seizures [80]. Seizure severity was more predictive of response in these children than was choice of first-line seizure drug.

Advantages of phenobarbital include availability of an intravenous (IV) formulation and extensive experience with the drug in neonates. Common challenges with phenobarbital include sedation, including respiratory depression that may necessitate intubation and ventilation when loading doses are given. In maintenance dosing, sedation may persist, which can confound the clinical examination of the neonate being evaluated for encephalopathy.

Of note, phenobarbital is a barbiturate drug that works by increasing the amount of time that a neuronal chloride channel is open. Theoretically, this allows for entry of chloride into the cell, causing hyperpolarization and decreasing excitability. In the premature brain, however, activation of immature chloride channels leads to egress of chloride from the cell and therefore causes depolarization and hyperexcitability. There has been much interest in combining phenobarbital with the loop diuretic bumetanide because preclinical studies have shown that it can reverse this depolarizing effect of the immature chloride channel by depleting intracellular chloride concentrations. The results of several studies have been mixed, but the largest trial to date has suggested no improvement in seizure frequency as well as an increase in ototoxicity when bumetanide was used to treat seizures [84].

Phenytoin

Historically, phenytoin and its less alkaline prodrug formulation fosphenytoin have been popular second-line agents for neonatal seizures, particularly in North America. One randomized, controlled trial has shown the efficacy of phenytoin to be the same as that of phenobarbital [80], with up to 45% of neonatal seizures being controlled with monotherapy. Advantages include the availability of an IV formulation and significant experience with its use in neonatal seizures. Additionally, it blocks sodium channels, which represent an alternative mechanism of action to barbituates and benzodiazepines (which both act on chloride channels).

Unfortunately, phenytoin has complicated pharmacokinetics that make its use in the newborn challenging. It is highly protein bound, so free levels can be difficult to achieve in newborns with renal or hepatic issues. It also causes hepatic induction of metabolism of many other medications. Finally, it is extremely difficult to maintain adequate drug levels in infants using oral dosing; therefore, it is of special importance to withdraw this medication before discharge from the hospital. Furthermore, phenytoin carries a risk of severe injection-site reactions, particularly if the vein is infiltrated. While fosphenytoin does not carry the same risk, it is much more expensive and also not readily available in some hospitals or countries [74].

Phenytoin and fosphenytoin are typically initiated with a 20 mg/kg bolus, with goal levels of 15–20 μg/mL. If seizures are refractory, extra bolus doses to achieve levels of 30 μg/mL can be given. Maintenance doses of 5 mg/kg per day divided b.i.d. (for IV formulations) or t.i.d. (for enteral formulations) are recommended. In neonates, levels should be followed closely because they can fluctuate significantly, particularly with enteral dosing. In addition, levels of other hepatically metabolized medications may need to be monitored because phenytoin can cause hepatic induction.

Benzodiazepines

Benzodiazepines are frequently used as a second- or third-line agent for seizures refractory to phenobarbital and phenytoin. Many different benzodiazepines are used for neonatal seizures. Midazolam is a very short-acting benzodiazepine administered as a drip that offers the advantages of rapid and relatively precise titration. Its metabolites are active, however, so it

can take a long time to clear. Clonazepam and other longer-acting agents can be dosed IV or enterally several times per day; they are often less sedating than midazolam. Like barbiturates, benzodiazepines act on the GABA receptor and its chloride channel, thus hyperpolarizing the neuron. They therefore share similar adverse effects as phenobarbital – including respiratory and, more rarely, cardiovascular depression – often necessitating medical support of these functions.

The dosing of benzodiazepines is medication specific. Midazolam should be started with a loading dose of 0.05–0.2 mg/kg and a maintenance dose of 0.05mg/kg per hour. The maintenance should be up-titrated by 0.05–0.1 mg/kg per hour as needed until seizure cessation, with maximum doses of 0.5 mg/kg per hour. While it can be given IV, clonazepam is often administered orally at doses of 0.03–0.05 mg/kg per day divided t.i.d. [74]. In general, when seizure medications are being withdrawn, benzodiazepines should be the first agent stopped, given their sedating effects. This should occur even if it seems that benzodiazepines were the only medication that stopped the seizures. Because benzodiazepines are often reserved as a third-line agent, the timing of their administration often coincides (sometimes uncannily so) with the natural waning of acute symptomatic seizures.

Lidocaine

Lidocaine can also be used as a second- or third-line agent for refractory neonatal seizures. It is used much more frequently in Europe than in North America; one study has shown it to be the third-line agent of choice at multiple major European medical centers [85]. Lidocaine is an amine derivative of cocaine that has good CNS penetration. It acts as a CNS depressant, though its precise mechanism of action as an antiepileptic is unclear. Small studies have found that when added to other antiseizure medications, lidocaine has a 70–92% response rate [74]. Lidocaine can cause arrhythmias and bradycardia, and therefore, it should only be administered in the NICU setting. The risk of such side effects can be significantly reduced by carefully following therapeutic levels; the presumed threshold for cardiac and nervous system toxicity is more than 9 mg/L [74]. It should not be given to neonates who have congenital heart issues or have received other proarrhythmic drugs such as phenytoin [86]. In general, lidocaine is started as a bolus dose followed by a continuous infusion based on the infant's weight; the infusion is decreased every several hours until it is stopped 24–36 hours after initiation [74,86]. Because of the cumulative risk of toxicity, the infusion must be stopped within 36 hours, even if seizures are responsive only to lidocaine. Furthermore, the dose must be adjusted if the infant is undergoing therapeutic hypothermia because clearance decreases during this time period.

Levetiracetam

Since its introduction in the 1990s, levetiracetam has quickly become an agent used for the treatment of refractory neonatal seizures. In some centers, it is used as a second-line agent over phenytoin, benzodiazepines, or lidocaine. Levetiracetam likely has a novel mechanism of action from other antiseizure medications. While the details are still not well understood, it may prevent neurotransmitter release by binding to a presynaptic vesicle protein, SV2a [87]. There has been particular interest in levetiracetam because animal data suggest that it may have fewer neurodevelopmental consequences than other seizure medications. Such effects have yet to be proven in humans, however.

Attempts to measure levetiracetam's efficacy as a first-line medication for neonatal seizures have been quite limited. Several retrospective trials have reported that levetiracetam has a 52–80% rate in terminating or decreasing the frequency of neonatal seizures when it is used as adjunctive therapy [88,89]. Overall, better studies with standardized dosing regimens and more consistent exposure to other medications are necessary to better approximate the efficacy of levetiracetam. Based on available data, levetiracetam does seem to have a reasonable safety profile. The most pronounced advantage of levetriacetam is that it has relatively few side effects and few drug-drug interactions. It is also available in an IV formulation.

Dosing strategies are still not clearly established, though neonates usually need higher doses than older children and adults. In general, an initial bolus dose of 30–40 mg/kg should be tried, with several repeat 10–20 mg/kg bolus doses administered as needed to control seizures; usually a maximum of 80–100 mg/kg should be tried before declaring the drug ineffective. For neonates who respond, maintenance doses of 40–100 mg/kg per day divided b.i.d. or t.i.d. can be initiated. Levels are typically not followed because they often take several days to return.

Other Antiseizure Medications

In addition to the medications just described, various other drugs approved for the treatment of seizures in children or adults are being trialed in newborns with refractory seizures. Introduction of such medications can be especially important in children with recognized neonatal epileptic encephalopathies because seizures are highly likely to return without continued treatment. Such agents include topiramate, oxcarbazepine, lamotrigine, felbamate, and vigabatrin. Unlike the medications described earlier, these do not come in IV formulations and therefore can be more difficult to administer in critically ill neonates. Furthermore, all these medications must be up-titrated over several days to weeks, so they are not adequate for the rapid treatment of seizures [74].

Vitamin Trials

Vitamin-dependent epilepsies are extremely rare. Pyridoxine-dependent epilepsy, the best described of these disorders, affects only 1/396,000 neonates [68]. In some patients with neonatal seizures, empirical trials of several vitamins are indicated even before a genetic or metabolic diagnosis has been made because the vitamins are relatively inexpensive, and appropriate replacement can lead to better neurocognitive outcomes for affected children. In general, trials of pyridoxine, pyridoxal-5-phosphate, folinic acid, and biotin are considered in neonates who have persistent seizures without a history of acute injury of other metabolic, infectious, or structural etiologies. Trials are particularly warranted if a burst-suppression pattern is present on EEG because many of these syndromes present with this finding.

Pyridoxine is typically given at 100 mg IV once, with monitoring of the EEG for improvement in the background during this bolus. Alternatively, enteral doses of 15 mg/kg per day given for at least 1 week can be tried. High doses of pyridoxine can cause hypotonia and respiratory depression in neonates for the 24 hours after administration, sometimes necessitating respiratory support; therefore, infants should be monitored closely in this time period. In infants with pyridoxine-dependent epilepsy, lifelong treatment with pyridoxine is required. *Pyridoxal-5-phosphate* (PLP) is an active metabolite of pyridoxine, and some neonates with refractory epilepsy respond to PLP even if they did not respond to pyridoxine. In general, a dose of 100 mg/kg divided six times per day is administered at least for a 3- to 5-day trial. PLP is only available in enteral forms and has side effects similar to pyridoxine [90]. A *folinic acid* (leucovorin) trial should also be considered, with 3–5 mg/kg per day administered for at least 3–5 days. CSF folate levels are important for making this diagnosis. Seizures associated with biotinidase deficiency tend to present slightly later, often in the second month of life, and there are often other symptoms such as an eczematous rash to suggest the diagnosis. In addition, the newborn screen catches at least some of these cases. Treatment with *biotin* 10 mg/day, however, can lead to quite good neurologic outcomes and so could be considered in neonates with intractable epilepsy of unclear etiology [60].

Withdrawal of Seizure Medications

In the vast majority of cases, neonatal seizures are symptoms of an acute injury. Many children with neonatal seizures do not go on to develop epilepsy, and for those who do, recurrence of seizures is typically months to years later. Given this, the WHO currently recommends seizure medications be weaned after 72 hours of seizure freedom. For children who have been controlled with one agent, it is considered safe to stop this medication abruptly. For those who required multiple agents for control, medications should be weaned individually, with phenobarbital being the last to be stopped [68].

Prognosis/Risk of Epilepsy in the Future

Current Limitations and Overview

Long-term follow-up data on the neurodevelopmental outcomes of children with a history of neonatal seizures is unfortunately lacking. There are several factors of study design that have made gathering such information quite difficult. Foremost, studies with the longest follow-up data have typically relied on a clinical diagnosis of seizures, which, as discussed earlier, is likely to lead to both inappropriate inclusion of some patients and exclusion of others. Second, follow-up data are often collected from visits in NICU follow-up or neurology clinics, thus potentially missing children with more positive outcomes who may not attend such visits. Conversely, children with genetic or epileptic syndromes are almost always excluded from these studies, thereby removing an important,

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albeit smaller segment of the population with neonatal seizures. Choice, administration, and timing of outcome measures represent a third challenge because there are many potential standardized tools to assess neurodevelopmental outcomes requiring different levels of expertise but no great consistency across studies; some studies have also used more subjective clinical impressions as their outcome measure. Duration of follow-up traditionally has been limited to 18–22 months, thus providing relatively limited "long-term" follow-up.

Despite these challenges, several important patterns have emerged regarding outcome of patients with neonatal seizures. Approximately 50% of survivors experience adverse neurodevelopmental outcomes, including epilepsy, intellectual disability, and cerebral palsy [15]. The most robust predictor of neurodevelopmental outcomes has been the initial etiology of the seizures. Those with transient or reversible causes are likely to do well, whereas those with structural or genetic etiologies have a much more guarded prognosis. Furthermore, several aspects of the neonatal course – including prematurity, high seizure burden, and abnormal background patterns on EEG – are predictive of poorer outcomes at a group level. Finally, and most important for the neonatologist, there is growing evidence that appropriate management of neonatal seizures, not only in terms of rapid recognition and treatment of the seizures but also in terms of appropriate withdrawal of antiepileptic medications in a timely fashion, is a modifiable risk factor that may have an impact on developmental outcome.

Specific Neurodevelopmental Outcomes

Mortality

Data collected from the 1990s and forward indicate that approximately 10–30% of children with neonatal seizures die in the neonatal period or early childhood. The highest risk of death is in the preterm population [15,16,91]. The variability in mortality likely reflects both advances in neonatal care and cultural differences in the practice of withdrawing care from severely affected infants across centers

Morbidity

As mortality of neonates with seizures has decreased, the incidence of significant neurologic morbidity in survivors has increased. A population study between 1990 and 1994 found that up to 65% of those with neonatal seizures had some degree of cerebral palsy, intellectual disability, and/or epilepsy [34,92]. Many survivors have more than one of these conditions.

Cerebral Palsy (CP)

CP is defined as a nonprogressive disorder of motor activity caused by an injury to the fetal or infant brain. CP is often associated with other neurologic problems, including disturbances in sensory, perceptual, cognitive, language, and/or behavioral function [93]. Approximately 25–45% of children with neonatal seizures develop CP [94]. One study found the risk to be substantially higher in surviving preterm (63%) compared with full-term (25%) neonates [15].

Intellectual Disability

Intellectual disability is generally defined as a full-scale IQ (FSIQ) of less than 70. In a recent long-term follow-up study of infants with neonatal seizures, Ronen et al. found that among survivors, 25% of term infants and 53% of preterm infants had intellectual disability [15]. In addition, another 23% of survivors in this study had learning disabilities.

Epilepsy

The ILAE defines epilepsy as (1) two or more unprovoked seizures separated by at least 24 hours, or (2) one unprovoked seizure with a risk of further seizures of at least 60%, or (3) a clear "epilepsy syndrome" [95]. Most neonatal seizures are secondary to an acute injury or metabolic disturbance and therefore are considered acute symptomatic (or "provoked") seizures and not epilepsy. Neonates with a known genetic epilepsy syndrome or seizures in the setting of a brain malformation are an exception, and they can be diagnosed with epilepsy in the neonatal period.

Acute symptomatic neonatal seizures typically stop in the newborn period, but unfortunately, approximately one-third of children with neonatal seizures go on to have unprovoked seizures at some point in their life, consistent with "postneonatal" epilepsy. For most children, epilepsy develops in the first 4 years of life, with a median age of onset of 9 months [15]. These patients are at high risk of developing severe epilepsy syndromes, with up to 10–16% developing West syndrome (infantile spasms with hypsarrhythmia and developmental delay) [94] and difficult-to-control seizures [96].

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Risk Factors for Poor Neurodevelopmental Outcomes

Clinical Factors

Prematurity

There are limited data regarding the prevalence of EEG-confirmed electrographic seizures in premature infants. Studies of preterm and term infants with *clinically* diagnosed seizures, however, have consistently shown that prematurity is a risk factor for death, CP, and developmental delays. Those with extremely low birth weights and neonatal seizures are also at higher risk for abnormal outcomes at 18–22 months [97] than those with higher birth weights.

Degree of Encephalopathy

Clinical variables typically associated with degree of HIE – including neonatal examination, Apgar scores, and need for prolonged resuscitation – have also been associated with poorer outcomes in neonates with seizures [98].

Etiology

The neurologic prognosis of neonates with seizures is most strongly affected by the underlying etiology of the seizures. A brief overview is presented in Table 42.7.

Seizure Burden

High seizure burden is associated with development of postneonatal epilepsy as well as poor neurocognitive function. With regard to epilepsy, frequent seizures and particularly status epilepticus (defined as greater than 50% of an hour with electrographic seizure activity) increase the risk of future epilepsy. One study found, even after adjusting for degree of injury visible on MRI, that neonates with HIE who experienced status epileptics had a 50–80% chance of

Table 42.7 Prognosis by Etiology of Neonatal Seizures

Pathology	Outcome	Notes
Transient metabolic disturbances (hypercalcemia, hypoglycemia)	Good	Prolonged hypoglycemia can cause permanent damage and a more guarded prognosis [94].
Hypoxic ischemic encephalopathy (HIE)	Variable depending on severity of injury	Neonatal seizures in patients with HIE predict poorer outcomes. Imaging data help to further prognosticate.
Intraventricular hemorrhage (IVH)	Variable depending on severity	Evidence is still emerging regarding incidence of seizures in preterms with IVH.
Arterial stroke	Variable depending on size of stroke but frequently favorable	The incidence of later epilepsy is 10–50% [49–52].
Venous stroke (from venous thrombosis)	Variable but generally favorable	Minimal follow-up data exist. Studies estimate that 45–77% of neonates with venous thrombosis are neurologically normal at 2 years [53,54,102].
Subarachnoid hemorrhage	Generally favorable	
Infection	Variable depending on type and extent of infection	Bacterial meningitis presenting with seizures is usually associated with poor outcomes.
Inborn errors of metabolism	Often poor but variable depending on specific disease	Care should focus on evaluation and rapid intervention of treatable metabolic disorders (e.g., phenylketonuria, urea cycle disorders, pyridoxine dependency).
Brain malformations	Almost always poor but variable based on malformation	Most brain malformations do not present with seizures in the neonatal period; those that do tend to cause severe epilepsies.
Genetic epilepsy syndromes	Highly variable depending on mutation	

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developing epilepsy compared with the typical risk of 15–30% in children with isolated seizures [99].

In addition to the risk of future epilepsy, a high neonatal seizure burden is also a risk for neurocognitive dysfunction. One study of 4-year-old children with a history of neonatal HIE found that those with the highest neonatal electrographic seizure burden had a full-scale IQ 2 standard deviations (33 points) below those without neonatal seizures, even after correcting for MRI-visible brain injury. Even children with a mild neonatal seizure burden had IQs 1 standard deviation below those without seizures. Overall, this study implies that neonatal seizures cause further neuronal injury above the initial insult in the encephalopathic infant [41]. The literature on children with congenital cardiac anomalies probably provides the longest follow-up of neonatal seizures. In this group, clinical and electrographic seizures were both associated with significantly lower IQs at 4 years of age and with worse scores across cognitive domains, including in reading, math, general memory, executive function, visual-spatial function, and social awareness at 16 years of age [100].

EEG Characteristics

Some information gathered from the EEG can be relevant to prognosis. Most important, a normal EEG background suggests a good prognosis, whereas a moderate or severely abnormal background (i.e., with burst suppression or very low voltage) correlates with poor neurologic outcomes [12,101], especially if these abnormalities persist across serial recordings. In addition, children with multifocal onset of their seizures or with spread of the electrographic seizure activity from one hemisphere to the other during a seizure are more likely to develop epilepsy later in life [12].

Summary

Neonatal seizures are a common problem for preterm and term infants. In the vast majority of cases, neonatal seizures indicate acute brain injury, but they can also be due to structural, metabolic, or genetic problems. Neonatal seizures can be difficult to diagnose based on clinical observations alone because the majority of neonatal seizures are subclinical, with no consistent outward manifestations, and infants have many unusual movements that can be mistaken for seizures. Given this, video-EEG is necessary to make an appropriate diagnosis and to monitor treatment response.

With regard to treatment, evidence suggests that neonatal seizures exacerbate underlying injury and lead to worse neurodevelopmental outcomes. Current guidelines recommend treating infants until all seizures have ceased. Reversible causes, such as infection or hypoglycemia, should be addressed expediently. Unfortunately, the antiseizure medications currently available likely have adverse effects on the developing brain. Furthermore, individual medications have limited efficacy. Currently, there is no strong evidence guiding treatment choice, but rather recommendations are based on clinical experience.

Prognosis of infants with neonatal seizures largely depends on the etiology of the spells. Infants with reversible problems – such as a transient metabolic disturbance, rapidly treated infection, or mild subarachnoid hemorrhage – often have resolution of seizures and normal developmental outcomes. Children with more significant problems – such as HIE, a large stroke, or a significant structural or genetic problem – are at much higher risk for early death or significant morbidity.

With improving neonatal care, including more rapid identification and treatment of seizures, children with neonatal seizures have a better long-term prognosis. However, there is a clear need for more research into this area. Important questions regarding choice and duration of treatment require prospective trials to be addressed. More inclusive and consistent studies of infant follow-up could provide better prognostic information.

References

1. Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. *J Perinatol* 1999; **19**(1): 40–3.
2. Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. *Lancet Neurol* 2013; **12**(12): 1170–9.
3. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol* 2011; **28**(6): 611–7.
4. Wusthoff CJ. Diagnosing neonatal seizures and status epilepticus. *J Clin Neurophysiol* 2013; **30**(2): 115–21.

5. Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. *J Clin Neurophysiol* 2013; **30**(2): 161–73.
6. Oliveira AJ, Nunes ML, Haertel LM, et al. Duration of rhythmic EEG patterns in neonates: new evidence for clinical and prognostic significance of brief rhythmic discharges. *Clin Neurophysiol* 2000; **111**(9): 1646–53.
7. Nagarajan L, Palumbo L, Ghosh S. Brief electroencephalography rhythmic discharges (BERDs) in the neonate with seizures: their significance and prognostic implications. *J Child Neurol* 2011; **26**(12): 1529–33.
8. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010; **51**(4): 676–85.
9. Bye AM, Flanagan D. Spatial and temporal characteristics of neonatal seizures. *Epilepsia* 1995; **36**(10): 1009–16.
10. Clancy RR. The contribution of EEG to the understanding of neonatal seizures. *Epilepsia* 1996; **37**(Suppl 1):S52–9.
11. Bye AM, Cunningham CA, Chee KY, Flanagan D. Outcome of neonates with electrographically identified seizures, or at risk of seizures. *Pediatr Neurol* 1997; **16**(3): 225–31.
12. Pisani F, Copioli C, Di Gioia C, et al. Neonatal seizures: relation of ictal video-electroencephalography (EEG) findings with neurodevelopmental outcome. *J Child Neurol* 2008; **23**(4): 394–8.
13. Scher MS. Neonatal seizures: an expression of fetal or neonatal brain disorders. In Stevenson DK, Benitz WE, Sunshine P, et al., eds., *Fetal and Neonatal Brain Injury*, 4th edn. Cambridge University Press, 2009:499–526.
14. Nagarajan L, Palumbo L, Ghosh S. Classification of clinical semiology in epileptic seizures in neonates. *Eur J Paediatr Neurol* 2012; **16**(2): 118–25.
15. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. *Neurology* 2007; **69**(19): 1816–22.
16. Garfinkle J, Shevell MI. Prognostic factors and development of a scoring system for outcome of neonatal seizures in term infants. *Eur J Paediatr Neurol* 2011; **15**(3): 222–9.
17. Clancy RR. Prolonged electroencephalogram monitoring for seizures and their treatment. *Clin Perinatol* 2006; **33**(3): 649–65.
18. Lawrence R, Mathur A, Nguyen T, et al. A pilot study of continuous limited-channel aEEG in term infants with encephalopathy. *J Pediatr* 2009; **154**(6): 835–41.
19. Murray DM, Boylan GB, Ali I, et al. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**(3): F187–91.
20. Malone A, Ryan CA, Fitzgerald A, et al. Interobserver agreement in neonatal seizure identification. *Epilepsia* 2009; **50**(9): 2097–101.
21. Orivoli S, Facini C, Pisani F. Paroxysmal nonepileptic motor phenomena in newborn. *Brain Dev* 2015; **37**(9): 833–9.
22. Connell J, Oozeer R, de Vries L, et al. Clinical and EEG response to anticonvulsants in neonatal seizures. *Arch Dis Child* 1989; **64**(4): 459–64.
23. Scher MS, Alvin J, Gaus L, et al. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol* 2003; **28**(4): 277–80.
24. Parker S, Zuckerman B, Bauchner H, et al. Jitteriness in full-term neonates: prevalence and correlates. *Pediatrics* 1990; **85**(1):17–23.
25. Shuper A, Zalzberg J, Weitz R, Mimouni M. Jitteriness beyond the neonatal period: a benign pattern of movement in infancy. *J Child Neurol* 1991; **6**(3): 243–5.
26. Sims M, Artal R, Quach H, Wu PY. Neonatal jitteriness of unknown origin and circulating catecholamines. *J Perinat Med* 1986; **14**(2): 123–6.
27. Rosman NP, Donnelly JH, Braun MA. The jittery newborn and infant: a review. *J Dev Behav Pediatr* 1984; **5**(5): 263–73.
28. Coulter DL, Allen RJ. Benign neonatal sleep myoclonus. *Arch Neurol* 1982; **39**(3): 191–2.
29. Resnick TJ, Moshé SL, Perotta L, Chambers HJ. Benign neonatal sleep myoclonus: relationship to sleep states. *Arch Neurol* 1986; **43**(3): 266–8.
30. Scher MS. Pathologic myoclonus of the newborn: electrographic and clinical correlations. *Pediatr Neurol* 1985; **1**(6): 342–8.
31. Huntsman RJ, Lowry NJ, Sankaran K. Nonepileptic motor phenomena in the neonate. *Paediatr Child Health* 2008; **13**(8): 680–4.
32. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. *Lancet Neurol* 2006; **5**(6): 513–24.
33. Volpe JJ. *Neurology of the Newborn*, 5th edn. Philadelphia: Saunders Elsevier Health Sciences, 2008.
34. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. *J Pediatr* 1999; **134**(1): 71–5.

35. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. Electrographic seizures during therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Child Neurol* 2011; **26**(6): 724–8.
36. Glass HC, Wusthoff CJ, Shellhaas RA, et al. Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. *Neurology* 2014; **82**(14): 1239–44.
37. Isaeva E, Isaev D, Holmes GL. Alteration of synaptic plasticity by neonatal seizures in rat somatosensory cortex. *Epilepsy Res* 2013; **106**(1–2): 280–3.
38. Miller SP, Weiss J, Barnwell A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology* 2002; **58**(4): 542–8.
39. McCabe BK, Silveira DC, Cilio MR, et al. Reduced neurogenesis after neonatal seizures. *J Neurosci* 2001; **21**(6): 2094–103.
40. Lynch M, Sayin U, Bownds J, et al. Long-term consequences of early postnatal seizures on hippocampal learning and plasticity. *Eur J Neurosci* 2000; **12**(7): 2252–64.
41. Glass HC, Glidden D, Jeremy RJ, et al. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J Pediatr* 2009; **155**(3): 318–23.
42. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**(15): 1574–84.
43. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**(9460): 663–70.
44. Murray DM, Ryan CA, Boylan GB, et al. Prediction of seizures in asphyxiated neonates: correlation with continuous video-electroencephalographic monitoring. *Pediatrics* 2006; **118**(1): 41–6.
45. Glass HC, Nash KB, Bonifacio SL, et al. Seizures and magnetic resonance imaging–detected brain injury in newborns cooled for hypoxic-ischemic encephalopathy. *J Pediatr* 2011; **159**(5): 731–5.
46. Srinivasakumar P, Zempel J, Wallendorf M, et al. Therapeutic hypothermia in neonatal hypoxic ischemic encephalopathy: electrographic seizures and magnetic resonance imaging evidence of injury. *J Pediatr* 2013; **163**(2): 465–70.
47. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics* 2006; **117** (4): 1270–80.
48. Lynch JK. Epidemiology and classification of perinatal stroke. *Semin Fetal Neonatal Med* 2009; **14**(5): 245–9.
49. Grunt S, Mazenauer L, Buerki SE, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. *Pediatrics* 2015; **135**(5):e1220–8.
50. Golomb MR, Garg BP, Carvalho KS, et al. Perinatal stroke and the risk of developing childhood epilepsy. *J Pediatr* 2007; **151**(4): 409–13.
51. Suppiej A, Mastrangelo M, Mastella L, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev* 2015; **38**(1):27–31.
52. Wusthoff CJ, Kessler SK, Vossough A, et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics* 2011; **127**(6): e1550–7.
53. deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001; **345**(6): 417–23.
54. Berfelo FJ, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke* 2010; **41**(7): 1382–8.
55. Scher MS, Aso K, Beggarly ME, et al. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. *Pediatrics* 1993; **91**(1): 128–34.
56. Davis AS, Hintz SR, Van Meurs KP, et al. Seizures in extremely low birth weight infants are associated with adverse outcome. *J Pediatr* 2010; **157**(5): 720–5.
57. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med* 2013; **18**(4): 185–91.
58. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: features associated with adverse outcomes. *Biol Neonate* 2006; **90**(2):74–86.
59. Kotulska K, Jurkiewicz E, Domańska-Pakieła D, et al. Epilepsy in newborns with tuberous sclerosis complex. *Eur J Paediatr Neurol* 2014; **18**(6): 714–21.
60. Van Hove JL, Lohr NJ. Metabolic and monogenic causes of seizures in neonates and young infants. *Mol Genet Metab* 2011; **104**(3): 214–30.
61. Ficicioglu C, Bearden D. Isolated neonatal seizures: when to suspect inborn errors of metabolism. *Pediatr Neurol* 2011; **45**(5): 283–91.
62. Wusthoff C. Benign familial neonatal epilepsy. *J Pediatr Epilepsy* 2012; **2012**(1): 143–9.
63. Olson HE, Poduri A, Pearl PL. Genetic forms of epilepsies and other paroxysmal disorders. *Semin Neurol* 2014; **34**(3): 266–79.
64. Pryor DS, Don N, Macourt DC. Fifth day fits: a syndrome of neonatal convulsions. *Arch Dis Child* 1981; **56**(10): 753–8.
65. Kato M, Saitoh S, Kamei A, et al. A longer polyalanine expansion mutation in the *ARX* gene causes early

.043

infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome). *Am J Hum Genet* 2007; **81**(2): 361–6.

66. Yamamoto H, Okumura A, Fukuda M. Epilepsies and epileptic syndromes starting in the neonatal period. *Brain Dev* 2011; **33**(3): 213–20.
67. Tavyev Asher YJ, Scaglia F. Molecular bases and clinical spectrum of early infantile epileptic encephalopathies. *Eur J Med Genet* 2012; **55**(5):299–306.
68. WHO, ILAE, IRCCS. *Guidelines on Neonatal Seizures*. Geneva: World Health Organization, 2011.
69. Shellhaas RA, Clancy RR. Characterization of neonatal seizures by conventional EEG and single-channel EEG. *Clin Neurophysiol* 2007; **118**(10): 2156–61.
70. Frenkel N, Friger M, Meledin I, et al. Neonatal seizure recognition: comparative study of continuous-amplitude integrated EEG versus short conventional EEG recordings. *Clin Neurophysiol* 2011; **122**(6): 1091–7.
71. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007; **120**(4): 770–7.
72. Osmond E, Billetop A, Jary S, et al. Neonatal seizures: magnetic resonance imaging adds value in the diagnosis and prediction of neurodisability. *Acta Paediatr* 2014; **103**(8): 820–6.
73. van Rooij LG, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. *Pediatrics* 2010; **125**(2):e358–66.
74. van Rooij LG, Hellström-Westas L, de Vries LS. Treatment of neonatal seizures. *Semin Fetal Neonatal Med* 2013; **18**(4): 209–15.
75. Wietstock SO, Bonifacio SL, McCulloch CE, et al. Neonatal neurocritical care service is associated with decreased administration of seizure medication. *J Child Neurol* 2015; **30**(9): 1135–41.
76. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci USA* 2002; **99**(23): 15089–94.
77. Ikonomidou C, Turski L. Antiepileptic drugs and brain development. *Epilepsy Res* 2010; **88**(1):11–22.
78. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. *Cochrane Database Syst Rev.* 2004; **4**: CD004218.
79. Cobo NH, Sankar R, Murata KK, et al. The ketogenic diet as broad-spectrum treatment for super-refractory pediatric status epilepticus: challenges in implementation in the pediatric and neonatal intensive care units. *J Child Neurol* 2015; **30**(2): 259–66.
80. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341**(7): 485–9.
81. Painter MJ, Pippenger C, MacDonald H, Pitlick W. Phenobarbital and diphenylhydantoin levels in neonates with seizures. *J Pediatr* 1978; **92**(2): 315–9.
82. Van Orman CB, Darwish HZ. Efficacy of phenobarbital in neonatal seizures. *Can J Neurol Sci* 1985; **12**(2): 95–9.
83. Gilman JT, Gal P, Duchowny MS, et al. Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989; **83**(5): 674–8.
84. Pressler RM, Boylan GB, Marlow N, et al. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. *Lancet Neurol* 2015; **14**(5): 469–77.
85. Vento M, de Vries LS, Alberola A, et al. Approach to seizures in the neonatal period: a European perspective. *Acta Paediatr* 2010; **99**(4):497–501.
86. Glass HC. Neonatal seizures: advances in mechanisms and management. *Clin Perinatol* 2014; **41**(1): 177–90.
87. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. *J Pediatr Pharmacol Ther* 2015; **20**(2):76–89.
88. Khan O, Chang E, Cipriani C, et al. Use of intravenous levetiracetam for management of acute seizures in neonates. *Pediatr Neurol* 2011; **44**(4): 265–9.
89. Abend NS, Gutierrez-Colina AM, Monk HM, et al. Levetiracetam for treatment of neonatal seizures. *J Child Neurol* 2011; **26**(4): 465–70.
90. Pearl PL, Gospe SM. Pyridoxal phosphate dependency, a newly recognized treatable catastrophic epileptic encephalopathy. *J Inherit Metab Dis* 2007; **30**(1):2–4.
91. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. *Neurology* 2007; **69**(23): 2177–85.
92. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology* 2000; **55**(4): 506–13.
93. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; **109**:8–14.
94. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. *Semin Fetal Neonatal Med* 2013; **18**(4): 224–32.
95. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014; **55**(4): 475–82.

96. Sillanpää M, Camfield P, Camfield C. Predicting long-term outcome of childhood epilepsy in Nova Scotia, Canada, and Turku, Finland: validation of a simple scoring system. *Arch Neurol* 1995; **52**(6): 589–92.

97. Teune MJ, van Wassenaer AG, van Dommelen P, et al. Perinatal risk indicators for long-term neurological morbidity among preterm neonates. *Am J Obstet Gynecol* 2011; **204**(5):396.

98. Pisani F, Spagnoli C. Neonatal seizures: a review of outcomes and outcome predictors. *Neuropediatrics* 2015; **47**(1):12–19.

99. Glass HC, Hong KJ, Rogers EE, et al. Risk factors for epilepsy in children with neonatal encephalopathy. *Pediatr Res* 2011; **70**(5): 535–40.

100. Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation* 2011; **124**(12): 1361–9.

101. Legido A, Clancy RR, Berman PH. Neurologic outcome after electroencephalographically proven neonatal seizures. *Pediatrics* 1991; **88**(3): 583–96.

102. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2000; **15**(5): 316–24.

Chapter

43 Nutritional Support of the Asphyxiated Infant

John A. Kerner and Kelly Haas

Routine Nutritional Support of the Premature Infant

Optimal nutritional support is critical in helping to obtain a successful outcome for the ever-increasing number of surviving premature infants [1]. Although it is paramount to ensure that the infant receives an adequate caloric intake, the ability of the very low-birth-weight (VLBW) infant to digest, absorb, and metabolize enteral nutrients is limited. In addition, complications of prematurity, such as respiratory distress, cardiovascular instability, hemorrhagic diatheses, and an immature renal system, create a challenge to the provision of proper nutritional support.

To provide nutrition to the premature infant appropriately, one must have an understanding of the biochemical and physiologic processes that occur during the development of the gastrointestinal tract. By 28 weeks of gestation, the anatomic development of the gastrointestinal tract in humans is nearly complete. Yet, as an organ of nutrition, the gut is functionally immature. Details of gastrointestinal tract development have been described previously [2–4] and are summarized in Table 43.1. Further, complications due to the incomplete development of the gastrointestinal tract in the low-birth-weight infant have been well delineated by Sunshine (Table 43.2).

Enteral Feeding

Gastric Feeding: Intermittent Gavage or Continuous Infusion

Nasogastric (NG) feeds may be given continuously or intermittently. Intermittent feeding, also known as *gavage feeding*, is easy to administer and allows one to evaluate the gastric emptying time by checking the gastric residual before each meal. The stomach takes less time to empty with human milk than with formula and when in the prone or lateral position [5,6].

Premature infants are predisposed to developing gastroesophageal reflux (GER) because of their incompetent lower esophageal sphincter, small stomach capacity, and delayed gastric emptying. Hence, to prevent GER and subsequent risk of aspiration and apnea, it is necessary to feed these infants smaller volumes on a more frequent basis [7]. Also, gastric distension may interfere with respiratory function [8]. For these reasons, premature infants may benefit from continuous NG feeds.

Toce et al. demonstrated that infants whose birth weight was between 1,000 and 1,249 g had better weight gain when fed via continuous NG infusion rather than via gavage feeds [9]. A reduction in stool weight was also reported. Both observations were presumed to be secondary to less stimulation of the gastrocolic reflex with a resulting longer transit time that allowed for better absorption.

Continuous feeding is not without disadvantages. Nutrients, especially fat, may be lost within the tubing during continuous infusion of breast milk [10]. Preterm formulas with a high mineral content may precipitate and clog the tubing [11]. Further, intermittent feeding may be important in the induction of metabolic and endocrine changes that occur in early postnatal life [12].

Transpyloric Feeding

Transpyloric feeding is defined as instilling the nutrients directly into the small intestine. The advantages of this method are minimal gastric distension, lower risk of aspiration, and, at least during the first 10 days of life, potentially greater volume tolerance with less initial weight loss than with NG feeding [13]. Two prospective studies compared continuous NG and transpyloric feeding [14,15], but only one [14] concluded that there was an advantage to transpyloric feeding during the first 2–3 weeks of life. Roy et al. compared every-2-hour bolus NG feeds versus nasojejunal (NJ) feeds in healthy low-birth-weight infants

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Table 43.1 Development of the Human Gastrointestinal Tract

Age (weeks)	Crown-rump length (mm)	Stage of development
2.5	1.5	Gut not distinct from yolk sac
3.5	2.5	Foregut and hindgut present Yolk sac broadly attached at midgut Liver bud present Mesenteries forming
4	5.0	Intestine present as a single tube from mouth to cloaca Esophagus and stomach distinct Liver cords, ducts, and gallbladder forming Omental bursa forming Pancreatic buds appear as outpouching of gut
5.6	8.0–12.0	Intestine elongates into a loop, and duodenum begins to rotate under superior mesenteric artery Stomach rotates Parotid and submandibular buds appear Cloaca elongates and septum forms to divide cloaca
7	17.0	Circular muscle layer present Duodenum temporarily occluded Intestinal loops herniated into cord Villi begin to develop Pancreatic anlagen fuse
8	23	Villi lined by single layer of cells Small intestine coiling within cord Taste buds appear Microvilli short, thick, and irregularly spaced Lysosomal enzymes detected Cloacal membrane that sealed the rectum begins to disappear
9–10	30–40	Auerbach's plexus appears Intestine reenters abdominal cavity Crypts of Lieberkühn develop Active transport of glucose appears aerobically and anaerobically Dipeptidases present Microvilli of enterocytes more regular and glycocalyx present Mitochondria numerous below microvilli
12	56	Parietal cells present in stomach Muscular layers of intestine present Alkaline phosphatase and disaccharidases detectable Active transport of amino acids present Mature taste buds present Enterochromaffin cells appear Pancreatic islet cells appear Bile secretions begin Colonic haustra appear Coelomic extension into umbilical cord obliterated Meconium first detected in ileum
13–14	78–90	Meissner's plexus appears Circular folds appear Peristalsis detected Lysosomes detected ultrastructurally

Table 43.1 (cont.)

Age (weeks)	Crown-rump length (mm)	Stage of development
16	112	Pancreatic lipase and tryptic activity detected Lymphopoiesis present Peptic activity present Swallowing evident: 2–7 mL/24 h
20	160	Peyer's patches present Muscularis mucosa present Mesenteric attachments complete Zymogen granules present and well developed in pancreas (22 weeks) Intestine has lost ability to transport glucose anaerobically
24	200	Paneth's cells appear Maltase and sucrase and alkaline phosphatase very active Ganglion cells detected throughout small and large intestine and in the rectum Amylase activity present in intestine
28	240	Enterokinase activity increases Esophageal glands present Frequency and intensity of duodenal peristaltic contractions increasing
32	270	Lactase activity increases Hydrochloric acid found in stomach
34	290–300	Sucking and swallowing become coordinated Esophageal peristalsis rapid, nonsegmental contraction occurs Small intestinal motility becomes coordinated
36–38	320–350	Maturity of gastrointestinal tract achieved

Source: Reproduced with permission from Sunshine [53].

Table 43.2 Complications Due to the Incomplete Development of the Gastrointestinal Tract in low-Birth-Weight Infants

Incomplete development of motility
Poor coordination of sucking and swallowing
Aberrant esophageal motility
Biphasic esophageal peristalsis
Decreased or absent lower esophageal sphincter pressure
Delayed gastric emptying time
Poorly coordinated motility of the small and large intestine
Stasis
Dilation
Impaired blood supply
Functional obstruction
Delayed ability to regenerate new epithelial cells
Decreased rates of proliferation
Decreased cellular migration rates
Shallow crypts
Shortened villi
Decreased mitotic indices

Table 43.2 (cont.)

Inadequate host resistance factors
Decreased gastric acidity
Decreased concentrations of immunoglobulins in lamina propria and intestinal secretions
Impaired humoral and cellular response to infection
Inadequate digestion of nutrients
Decreased digestion of protein
Decreased activity of enterokinase
Trypsin activity low prior to 28 weeks
Decreased concentration of gastric hydrochloric acid and pepsinogen
Decreased digestion of carbohydrates
Decreased hydrolysis of lactose
Decreased ability to transport glucose actively
Decreased activity of pancreatic amylase
Decreased digestion of lipids
Decreased production and reabsorption of bile acids
Decreased activity of pancreatic lipase
Increased incidence of other problems that may indirectly lead to poor gastrointestinal function
Hyaline membrane disease
Intraventricular hemorrhage
Patent ductus arteriosus
Hypoxemic–ischemic states

Source: Reproduced with permission from Sunshine [53].

and found no difference in growth or weight gain in the two groups [16]. Since the stomach was bypassed in the NJ group and fat digestion starts in the stomach, more fat malabsorption occurred in the NJ-fed babies. The fat malabsorption may be minimized by duodenal placement of the feeding tube [14].

Further, in two studies, transpyloric feeding was not recommended in infants requiring either ventilatory support via a face mask or nasopharyngeal suctioning [17,18] because of the risk of dislodgement and subsequent aspiration. Lucas evaluated seven randomized trials comparing transpyloric (nasoduodenal or NJ) with intragastric feeding [19]. None of the trials was large or conclusive, but collectively they argue against transpyloric feeding. Lucas stated, "There is no convincing evidence that transpyloric feeding improves enteral feed tolerance and growth, or reduces aspiration pneumonia" [19].

Polyvinyl chloride tubes were used initially for transpyloric feeding because they are relatively stiff and easily positioned. However, if left in the duodenum for several days, they harden and may perforate the intestine [20]. Silastic tubes are now commonly used, but they are more flexible and hence difficult to position. They are usually weighted at the tip and placed with the help of gravity. Being more flexible, they can curl back into the stomach. Perforation even with the Silastic tubes has been reported [21].

A change in the microbial flora of the upper intestine of infants fed via transpyloric feeds has been reported. The upper intestine of the normal infant is sterile or contains sparse gram-positive flora. However, Dellagrammaticus et al. have shown that the presence of a tube facilitates colonization with "fecal-type" flora, in which *Streptococcus faecalis* and gram-negative bacteria predominate [22]. Theoretically, a heavy resident flora of the upper intestine could lead to poorer assimilation of feeds. Conflicting data exist on the relationship of necrotizing enterocolitis (NEC) to transpyloric feeds [17,23]. As detailed later in this chapter, it is not the route of feeding that was responsible in the preceding studies for the NEC but rather the increased osmolality of the formula used. In controlled studies, NEC was proven not to be more frequent during transpyloric feeds compared to NG feeds [14,17,24]. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) issued guidelines for feeding the preterm infant [13].

ESPGHAN Guidelines

Enteral feeding should be introduced as soon as it is safe to do so.

1. Intermittent gastric tube feeding seems more physiologic than transpyloric feeding and whenever possible should be preferred.
2. When there are feeding difficulties such as regurgitation, poor gastric emptying, or gastric distension, continuous gastric feeding or even transpyloric feeding may be necessary because they are useful alternatives either to reduced oral feeding or total parenteral nutrition.
3. The success of any feeding technique is at least partly the result of the skill of the staff of the unit in following the unit's own practiced routines.
4. Nursery routines should encourage the mother to play an active role in feeding. This will help her to become confident in the care of her baby [13].

Schanler et al., in an elegant randomized trial in 171 premature infants, showed that bolus tube feeding was associated with significantly less feeding intolerance and greater rate of weight gain than the continuous-feeding method [25]. More important, this group demonstrated the benefit of early gastrointestinal priming [25].

Gastrointestinal priming is a practice with sound scientific rationale. Also known as *minimal feedings, gut stimulation, trophic feedings*, and *hypocaloric feedings*, this practice attempts to enable the premature infant's intestine to adapt to later advancement of full enteral feedings while preventing the known mucosal atrophy and unphysiologic gut hormone status noted in animals and humans kept NPO [26–28]. Schanler et al. were congratulated by Kliegman [29] for their large randomized, controlled trial that confirmed the overall safety of gastrointestinal priming (no increased incidence of NEC) while clearly demonstrating the positive effects of this novel feeding practice – better calcium and phosphorus retention; improved feeding tolerance; and reduced risk of physiologic jaundice, cholestasis, metabolic bone disease, and glucose intolerance [25]. Kliegman went on to state that "gastrointestinal priming must now become the standard of care for very low birth weight infants" [29]. In Schanler's study, the gastrointestinal priming group (prime continuous, prime bolus) received 20 mL/kg per day of milk (either formula or breast milk) from days 4 through 14 [25].

Early feeding of preterm infants has been shown to decrease intestinal permeability [30] and increase lactase activity [31]. Trophic feeding has been shown to

1. Shorten time to regain birth weight
2. Improve feeding tolerance
3. Reduce the duration of phototherapy
4. Reduce the duration of parenteral nutrition
5. Lower the incidence of cholestasis
6. Reduce metabolic bone disease
7. Improve gastrointestinal maturation, motility, and hormone responses
8. Improve mineral absorption
9. Enhance enzyme maturation
10. Reduce intestinal permeability
11. Be safe (the practice does not increase the incidence of NEC) [32]

Parenteral Feeding

Parenteral nutrition (PN) is an alternative for some premature infants who cannot be fed enterally due to illness or other circumstances. In a review by Moyer-Mileur and Chan, parenteral feeds in VLBW infants requiring assisted ventilation for more than 6 days led to a decrease in the percentage of weight loss from birth weight and a shorter time required for recovery of birth weight than in those fed enterally or by a combination of enteral and parenteral feeds [33]. A delay in enteral feeds increased the tolerance to subsequent enteral feeds in the infants. *Tolerance* was defined as absence of residuals, abdominal distension, or guaiac-positive reducing-substance-positive stools [33]. Another retrospective study presented inconclusive data regarding the benefits and risks of PN [34].

Limited data exist on the potential benefit of PN in the treatment of preterm infants. A controlled study of peripheral total parenteral nutrition (TPN) composed of casein hydrolysate, dextrose, and soybean emulsion in 40 premature infants with respiratory distress syndrome (RDS) showed that TPN neither favorably altered the clinical course of the syndrome nor worsened an infant's pulmonary status [35]. Among infants weighing less than 1,500 g, those who received TPN had a greater survival rate than a control group (71% versus 37%).

Yu et al. performed a controlled trial of TPN on 34 preterm infants with birth weights of less than 1,200 g [36]. Infants in the TPN group had a greater mean daily weight gain in the second week of life and regained birth weight sooner than did control infants.

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Four infants in the milk-fed control group developed NEC, whereas no infants developed NEC in the TPN group. The results of a more recent study conducted by Kerner et al. [37] of 40 infants who weighed less than 1,500 g at birth were in agreement with the two mentioned controlled studies [35,36]. No increased risk in using peripheral PN compared with conventional feeding techniques was found. Also, comparable growth was reported in the two groups.

In an early study, 59 infants weighing less than 1,500 g were randomly assigned either to a PN regimen via central catheter or a transpyloric feeding regimen (mother's milk or SMA Gold Cap [Wyeth Laboratories, Philadelphia, PA, USA]) via a Silastic nasoduodenal tube [38]. The authors postulated that some of the problems of enteral feeding in VLBW infants might be overcome if enteral nutrients were delivered beyond the pylorus [39]. The PN group had a higher incidence of bacterial sepsis. Conjugated hyperbilirubinemia occurred only in the PN group. Despite the observations that 34% (10/29) of the infants in the transpyloric group failed to establish full enteral feeding patterns by the end of the first week of life and therefore had achieved lower protein-energy intake than the PN group, no beneficial effect on growth or mortality was found in the PN group.

The authors concluded that "[p]arenteral nutrition does not confer any appreciable benefit and because of greater complexity and higher risk of complications should be reserved for those infants in whom enteral nutrition is impossible" [38]. Zlotkin et al. disagreed with this conclusion: "Had peripheral-vein feeding been used rather than central venous alimentation, or had nasogastric gavage feeding been used in preference to transpyloric feeding, the morbidity and mortality would have declined and the results comparing TPN with enteral feeds would have been quite different" [40].

A study that remains a model for nutritional support in VLBW infants was performed by Cashore et al. [41]. They described 23 infants who weighed less than 1,500 g in whom peripheral PN was begun on day 2 of life to supplement enteral feedings, thus allowing for adequate nutrition while avoiding overtaxing the immature gastrointestinal tract. These infants regained their birth weight by the age of 8–12 days and achieved growth rates that approximated intrauterine rates of growth. Interestingly, infants weighing less than 1,000 g were still not taking all their nutrients enterally by 25 days of age.

Premature infants, especially those who have RDS and are incapable of full oral feeds, often receive PN because of their extremely limited substrate reserve, very rapid growth rate, and perceived susceptibility to irreversible brain damage secondary to malnutrition [40]. A survey of 269 neonatal intensive care units (NICUs) showed that TPN was used exclusively during the first week of life in 80% of infants weighing 1,000 g or less at birth [42]. The others received a combination of parenteral and enteral feedings in the first week. Adamkin began PN by 72 hours of age in neonates with a birth weight of less than 1,000 g in whom respiratory disease and intestinal hypomotility limited the safety of feedings in the first 1–2 weeks of life [43].

In some nurseries, umbilical arterial catheters are used for infusing PN. Few studies exist regarding the safety of this practice. Yu et al. studied 34 infants with a birth weight of less than 1,200 g and randomly assigned them to TPN via umbilical arterial catheter or enteral feeds [36]. The TPN group had better nitrogen balance and weight gain, less NEC, and unchanged mortality compared with the enterally fed group. No data on catheter-related complications were presented, although bacterial or fungal septicemia did not occur in either group in the study period [36]. Higgs et al. described a controlled trial of TPN versus formula feeding by continuous nasogastric (NG) drip [44]. The study included 86 infants weighing 500–1,500 g. The TPN, including glucose, amino acids, and fat emulsion, was administered by umbilical artery catheter for the first 2 weeks of life. There was no difference in neonatal morbidity or mortality between the two groups. Specifically, there was no difference in septicemia, although 4 of the 43 TPN babies had "catheter problems," described in the text only as "blockage" of the catheter.

As in the study of Higgs et al., Hall and Rhodes found that morbidity, mortality, and common complications, such as infection and thrombosis, were similar in infants receiving umbilical lines for TPN compared with infants receiving tunneled jugular catheters for TPN [45]. These authors concluded that TPN by indwelling umbilical catheters presents no greater risk than infusion through tunneled jugular catheters. However, careful analysis of the authors' data raises questions about their conclusions. According to the authors, "Six deaths may

have been catheter-related" [45]. Five of those deaths occurred in the umbilical artery catheter group; death resulted from thrombosis of the aorta in one patient, candidal septicemia in two, streptococcal septicemia in one, and enterococcal septicemia in one. One death occurred in the jugular venous catheter group, with right atrial thrombosis, superior vena cava syndrome, and *Staphylococcus epidermidis* on blood culture.

Merritt cautions against the use of umbilical arterial catheters for TPN because this practice is associated with a high incidence of arterial thrombosis [46]. Coran, a pediatric surgeon, strongly recommends that PN not be given through either umbilical arteries or umbilical veins [47]. PN through umbilical veins causes phlebitis, which may lead to venous thrombosis and portal hypertension. He is especially concerned about infusing PN solutions into an umbilical arterial line because this practice can lead to thrombosis of the aorta or iliac vessels. Severe damage, such as thrombosis of the aorta, may occur to an artery without being recognized. Only over a period of time will the side effects of umbilical arterial catheter use, such as inappropriate growth of one limb [47], become clinically evident. Even the use of 12.5% dextrose infused through an umbilical arterial line has increased osmolality, which has been shown to cause thrombophlebitis [47]. Although the first three studies described earlier all claimed there were no short-term complications, they did not address the problem of long-term complications [48].

Coran stated that if PN is required and peripheral veins are not usable, or if peripheral vein delivery is inadequate to provide necessary calories, he would consider percutaneous subclavian vein catheterization, which he could perform successfully even in a 900-g infant [47]. In a study by Sadig, 52 Broviac catheters were inserted in 40 preterm and 8 term infants [49]. Sixty-nine percent of VLBW infants and 20% of those weighing more than 1,500 g experienced catheter-associated infections. Seventy-eight percent (14/18) of these infections were treated successfully with antibiotics without catheter removal. The rate of thrombosis was also higher in VLBW infants. A retrospective review compared TPN via umbilical catheters in 48 neonates (birth weight 1.7 ± 0.58 kg) versus administration via central venous catheters in 26 infants (birth weight 2.05 ± 0.89 kg) [50]. There was no difference in infection rate between the two groups when adjustment was made for the number of days of catheter life. Transient hypertension occurred in two (4%) of the umbilical arterial catheter group and in one (3.8%) of the central catheter group. There was one aortic thrombus noted on autopsy in the umbilical arterial catheter group. There was one vegetation on the tricuspid valve in the central catheter group. These authors concluded that umbilical arterial catheters are a reasonable route for PN solutions.

As nurseries become more comfortable with percutaneous central lines [51,52], hopefully umbilical arterial catheters will be used less frequently to provide nutrition.

Nutritional Support of the Asphyxiated Infant

Asphyxia may cause significant injury to the gastrointestinal tract. This injury may predispose an infant to develop NEC. During acute episodes of shock or hypoxemia, the "vital structures," which include the heart, brain, and adrenal glands, are preferentially perfused. Perfusion of the "nonvital organs," including the skin, muscle, lungs, kidney, and gastrointestinal tract, is decreased significantly. With limited periods of hypoxia, the newborn has some autoregulatory capabilities of maintaining blood flow to the intestine. However, if the ischemia is maintained for a prolonged period, perforation and significant mucosal hemorrhage may occur [53]. Coupled with asphyxia, feeding the premature infant heightens the risk for the development of neonatal NEC.

Most centers do not enterally feed an asphyxiated infant for the first 5 days to 2 weeks. During this period of time, the asphyxiated infant typically receives nutritional support from PN. This practice is extrapolated from animal data on cellular proliferation and migration. The intestinal mucosa of newborn and suckling rats has a very slow rate of cellular proliferation and migration compared with adult animals [54]. While the turnover of intestinal epithelia in the adult jejunum is 48–72 hours, the rate in the 10-day-old animal is at least twice as long, and in the 2- to 3-day-old animal it may be even longer [55]. In a study by Sunshine et al. in adult animals, labeled cells reached the tips of the villi within 48 hours [56]. During the same period, the labeled cells had migrated only one-eighth to one-fourth of the length of the villi in suckling animals. There are indications

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that this same slower rate of turnover of intestinal epithelia exists in newborn humans [57]. Thus a period of several days to 2 weeks without enteral nutrition in an asphyxiated infant is thought to allow sufficient time for intestinal epithelial turnover and intestinal healing.

Necrotizing Enterocolitis

NEC is a well-described and extensively investigated affliction of high-risk newborns. The etiology of this multifactorial disorder remains elusive, and currently there is no universally accepted theory of pathogenesis [58–61]. Risk factors include prematurity, low birth weight, congenital heart disease, perinatal asphyxia, bowel ischemia, abnormal colonization of the intestine, and indomethacin exposure [62].

Epidemiology

The incidence varies widely, with some centers reporting rare isolated cases [63] and others reporting an incidence of 3–5% of all neonatal admissions [64]. Among patients in whom NEC develops, the average birth weight is 1,400–1,500 g, and the mean gestational age is 30–32 weeks [65]. In one study by Stoll et al., the overall incidence was 3/1,000 live births, but this increased to 66/1,000 live births for infants weighing less than 1,500 g. Similarly, the mortality was 0% for infants weighing more than 2,500 g and increased to 40% for infants weighing less than 1,500 g [66]. A recent report described the incidence of NEC as approximately 1.1/1,000 live births, with an in-hospital mortality rate of 15% [67]. The age at diagnosis ranged from 2 to 44 days and was inversely related to gestational age. All babies of greater than 35 weeks' gestational age were diagnosed by 1 week of age. Stoll et al. felt that there may be two populations who develop NEC – an early population consisting of term and preterm infants and a later group of solely preterm babies who are smaller and sicker, who presumably have ongoing insults to their gastrointestinal tracts and therefore are at continued risk to develop the disease. These babies must be closely monitored for the possible development of NEC later in their hospital course [66]. It is important to appreciate that approximately 10% of all NEC cases occur in full-term neonates [58].

There are two distinct patterns of NEC: endemic and epidemic [68]. Superimposed on an endemic rate, epidemics (which refer to cases clustered in location and time) may be observed. No seasonal pattern of occurrence of these epidemics has been demonstrated. Patient characteristics appear to differ during epidemics – they are more mature, with fewer antecedent neonatal illnesses, acquire NEC later, and have been fed for a longer period than patients who develop NEC during nonepidemic times.

Clinical Picture

NEC may assume a broad spectrum of clinical severity. Some infants have little in the way of signs and symptoms, with a benign course, and others have fulminant disease characterized by extensive gangrene, perforation, shock, and death. The diagnosis of NEC is suspected when two or more typical gastrointestinal signs and symptoms occur simultaneously with nonspecific signs [64]. The initial signs and symptoms of 123 consecutive patients are presented in Table 43.3, as found by Walsh and Kliegman in a 9-year study [69]. Not all patients will have every symptom, and the signs will vary chronologically in their appearance depending on the severity of the illness (Table 43.4).

Table 43.3 Initial Signs and Symptoms of NEC

Signs	Percentage of patients[a]
Abdominal distension	73
Bloody stool	28
Apnea, bradycardia	26
Abdominal tenderness	21
Retained gastric contents	18
Guaiac-positive stool	17
"Septic appearance"	12
Shock	11
Bilious emesis	11
Acidosis	10
Lethargy	9
Diarrhea	6
Cellulitis of abdominal wall	6
Right lower quadrant mass	2

[a] Total exceeds 100% because many patients had more than one sign.

Source: Reproduced with permission from Walsh and Kliegman [69].

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Table 43.4 Unusual Manifestations of NEC

10% occur in term infants
10–12% occur in infants who have never been fed
10–15% of infants will not have pneumatosis intestinalis
10–15% of infants will have no blood in stools
10–15% of infants will develop intestinal strictures

Source: Reproduced with permission from Sunshine [53].

Because the initial symptoms of NEC are nonspecific and the findings on physical examination may be deceptively benign, radiographic findings are used to support the diagnosis. Radiographic examinations of the abdomen may show nonspecific findings of distension, ileus, and ascites [70]. The two diagnostic radiologic signs are pneumatosis intestinalis (intramural intestinal gas) and intrahepatic portal venous gas. One of these is essential to confirm the diagnosis. More severe disease will result in perforation and pneumoperitoneum. However, pneumatosis intestinalis may be subtle and fleeting. It is typically first seen in the ileocecal area but may be seen anywhere from the stomach to rectum. Two patterns are described: a curvilinear intramural radiolucency, probably representing subserosal gas, and a cystic form assuming a foamy or bubbly appearance, probably representing submucosal gas. Gas mixed with stool in the bowel, however, can be difficult to distinguish from pneumatosis intestinalis [66]. Pneumatosis may also be present in other clinical situations – intestinal gangrene secondary to vascular occlusion, Hirschsprung disease with enterocolitis, obstruction at the site of bowel atresia, pyloric stenosis, and meconium ileus.

Investigators have developed screening tests for NEC such as breath hydrogen analysis [71,72], urine analysis for D-lactate [73] (produced by enteric flora when fed excess carbohydrate), serum D-lactic acid (a bacterial fermentation product of unabsorbed carbohydrates) levels [74], and more recently, fecal calprotectin [155], but these tests have not become routine in clinical monitoring up to the present.

Treatment

Since NEC can manifest within a wide range of severity along a continuum of various stages of bowel disease, the true nature or clinical course that NEC will follow is usually not known until 48 hours after onset. Bell et al. proposed important clinical staging criteria for NEC that allowed accurate comparisons of patients with disease of similar severity [75]. Kliegman et al. modified Bell's staging criteria to include systemic, intestinal, and radiographic signs and suggested treatment regimens based on the stages (Table 43.5) [76].

In addition to the recommendations in Table 43.5, a large-bore, double-lumen NG tube should also be placed to decompress the stomach. The length of time the bowel is allowed to "rest" will depend on the progression or lack of progression of the disease and on the philosophy of the institution. PN is recommended in patients with documented NEC during the period of intestinal recovery. When prolonged parenteral feedings are required, a central venous line may need to be placed. PN allows for a slow return to enteral feedings – it is common for this transition to take 1–3 weeks to reestablish full enteral feedings. Infants requiring surgical resection of the bowel will have a more protracted course, especially with extensive resections, and may develop *short-bowel syndrome*. The specifics of such management are described elsewhere [77]. Immediate surgical management of NEC has been reviewed [78–80], and the preferred operation for VLBW infants was recently investigated in a multicenter randomized clinical trial [81]. Moss et al. compared the outcomes of primary peritoneal drainage with laparotomy and bowel resection in preterm infants with perforated NEC (n = 117, all <34 weeks' gestation). There were no differences between the two surgeries at 90 days postoperatively; length of hospital stay was also comparable between the two groups [81]. The study suggests that peritoneal drainage is a reasonable alternative to laparotomy [82].

Pathogenesis

There is no universal acceptance of a unifying theory regarding the pathogenesis of NEC. Numerous controlled studies have been performed to delineate the neonate at risk. Stoll et al. determined that affected infants were quite similar to controls and identified no risk factors [66]. Kliegman et al. failed to delineate any important risk factor. They therefore concluded that perinatal problems that precede NEC are equally common in all high-risk infants [76].

A unifying theory must explain the development of NEC in the enterally fed or fasted high-risk neonate and in the healthy term newborn [65]. It seems likely that NEC represents the final response of the

Table 43.5 Modified Bell's Staging Criteria for NEC

Stage	Systemic signs	Intestinal signs	Radiologic signs	Treatment
IA Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pregavage residuals, mild abdominal distension, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics × 3 days pending culture
IB Suspected NEC	Same as above	Bright red blood from rectum	Same as above	Same as above
IIA Definite NEC: mildly ill	Same as above	Same as above plus absent bowel sounds ± abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics × 7–10 days if examination is normal in 24–48 hours
IIB Definite NEC: moderately ill	Same as above plus mild metabolic acidosis, mild thrombocytopenia	Same as above plus absent bowel sounds and definite abdominal tenderness ± adominal cellulites or right lower quadrant mass	Same as IIA plus portal vein gas ± ascites	NPO, antibiotics × 14 days, $NaHCO_3$ for acidosis
IIIA Advanced NEC: severely ill, bowel intact	Same as IIB plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Same as above plus signs of generalized peritonitis, marked tenderness	Same as IIB plus definite ascites	Same as above plus as much as 200 mL/kg fluids, fresh frozen plasma, inotropic agents, ventilation therapy, paracentesis
IIIB Advanced NEC: severely ill, bowel perforated	Same as IIIA, sudden deterioration	Same as IIIA plus sudden increased distension	Same as IIB plus pneumoperitoneum	Same as above plus surgical intervention

Source: Reproduced with permission from Walsh and Kliegman [69].

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immature gastrointestinal tract to one or more unrelated stresses. Because there are many stressful factors, there may be a wide range in the severity of bowel injury and therefore a continuous spectrum of clinical disease. Perhaps in the mildly affected infant the stresses are not as injurious, and in the severely affected infant multiple stresses act synergistically to produce more severe damage [65].

Enteral Feeding

Conflicting opinions exist regarding the relationship of enteral feeding practices and the development of NEC. It is important to bear in mind that 5–10% of patients who develop NEC have never been fed [58]. Controlled studies comparing feeding techniques in infants with and without NEC fail to consistently support feeding as an important precursor, though controversy certainly persists.

There are numerous ways by which feedings might contribute to the pathogenesis or progression of NEC:

1. Direct mucosal injury by hypertonic feedings
2. Alteration of intestinal flora
3. Structural immaturity of the premature infant's intestine
4. Absence of breast milk's immunologically protective effect in formula-fed infants
5. The effect of early or large-volume feedings on an alimentary tract compromised by an adverse perinatal event

The pragmatic issues, such as timing of feedings, rate and volume of feedings, and the osmolality/osmolarity of feedings have been evaluated.

Timing of Enteral Feeding

There is a definite trend to delay enteral feedings in sick premature infants. In a survey of 269 NICUs by Churella et al., most units (80%) gave parenteral feedings during the first week of life to infants weighing less than1,000 g at birth [42]. None started enteral feeds alone, and 20% used a combination of enteral and parenteral feeds. Sixty-nine percent of those weighing 1,001–2,399 g received a combination of parenteral and enteral feeds. The first enteral feed was begun at a mean of 7 days after birth for infants weighing less than1,000 g at birth, 5 days after birth for those with a birth weight of 1,001–1,500 g, and 3 days after birth for those weighing more than 1,500 g [42].

In a prospective study by Eyal et al., delaying feedings in VLBW infants (<1,500 g) from 2–3 days to 2–3 weeks decreased the incidence of NEC from 18% to 3% [83]. It is interesting to note that in patients (3%) who developed NEC after delayed onset of enteral feeds, the time of the first symptoms ranged from 23 to 60 days compared with 7–23 days in those fed enterally within the first week of life. Hence infants in whom enteral feeds are delayed must be observed for a longer period for the development of NEC.

Brown and Sweet felt that NEC was virtually eliminated from their nursery with the initiation of an extremely cautious feeding protocol that fostered late initiation of enteral feeds, slow advancement to reach full feeds 2 weeks after onset of feeds, and prompt discontinuance of feeds when untoward signs suggesting that hypoxia, hypoperfusion, or gastrointestinal dysfunction developed (i.e., distension, guaiac-positive stools, or apnea) [63].

However, Ostertag et al. in a prospective study of 34 low-birth-weight infants (<1,500 g) who were fed on day 1 or day 7 did not find any significant increase in the incidence of NEC: 29% of those enterally fed on day 1 compared with 35% fed enterally on day 7 developed NEC. There were no differences in the perinatal risk factors in the two groups [84]. In a study by Unger et al., delayed initiation of enteral feedings was associated with a decreased incidence of NEC only among male infants with birth weights less than 775 g; hence this study did not support elective withholding of enteral feeds in other groups of low-birth-weight infants [34].

Rate and Volume of Enteral Feeds

Aggressive feeding practices were found to be associated with NEC by Krousop [85]. In his case material, infants who developed NEC received an average of 43 mL/kg during the initial day of enteral feeds and 72 mL/kg during the second day [85]. Book et al. did not find any difference in the incidence of NEC in a small prospective study comparing fast and slow feeding rates (increase of 20 versus 10 mL/day) designed to attain complete enteral feedings at 7 and 14 days, respectively [86]. However, in a retrospective uncontrolled study, Goldman found an increased incidence of NEC when feedings were advanced by large volumes (>40–60 mL/kg per day) [87]. He also found a higher percentage of disease in infants receiving volumes greater than 150 mL/kg per day. Anderson et al. noted an increased incidence of NEC among those low-birth-weight infants fed aggressively – advanced at a rate exceeding 20 mL/kg per day [88].

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The mechanism by which excessive feeding predisposes to NEC is uncertain. There may be relative mucosal ischemia due to an imbalance between mucosal blood flow and oxygen extraction due to an excessive load [65]. Alternatively, the already low concentration of lactase in preterm infants may be overwhelmed by the excessive lactose load. The excess lactose is then fermented by the microflora, resulting in H_2 production, initiating NEC [65]. Reducing substances are also a by-product of this bacterial fermentation. Book et al. found that 75% of infants who developed NEC had three to four or more reducing substances in their stools from 1–4 days prior to clinical manifestations of disease [89].

Walsh et al. recommended starting enteral feeds at 1 mL every 1–2 hours and advancing feeds slowly, no greater than 20 mL/kg per day. They successfully fed 1-kg infants who required ventilatory support [65]. However, the infants were continuously monitored for intolerance – increased residuals, distension, guaiac-positive stools, or reducing substances in the stool. Sweet recommended holding feeds if there were significant residuals in the stomach prior to a feed [90]. If residues persisted, then the bowel was rested for 5–7 days. If abdominal distension developed during feeds, appropriate cultures and radiographs were obtained. Even if they were inconclusive, Sweet would not feed the infant for 1–2 weeks. In his conservative approach, infants who developed sudden episodes of apnea, pallor, bradycardia, or poor skin perfusion were not fed for 1 week or more. Sweet had only one episode of NEC in 5 years out of 300 infants (89 infants weighing < 1,000 g and 211 weighing 1,000–2,500 g).

Two randomized, controlled trials have cast doubt on the role of rapid feeding advancement in the increased incidence of NEC. One randomized, controlled trial among 185 premature infants weighing 501–1,500 g comparing 15 mL/kg per day and rapid 35 mL/kg per day feeding advancement of Similac Special Care 20 kcal/oz did not show a statistically significant difference in the rate of NEC (Bell stage ≥ II) between the two groups [91]. A second randomized, controlled trial among 155 preterm infants weighing between 1,000 and 2,000 g comparing feeding advancement by 30 mL/kg per day with a control group with advancement by 20 mL/kg per day did not demonstrate any significant difference in the incidence of NEC between the two groups (3 of 72 infants in the intervention group and 2 of 83 infants in the control group developed NEC) [146]. However, infants in the rapid feeding advancement group achieved full-volume feedings, regained birth weight faster, and had fewer days of PN compared with the control group. Similarly, a Cochrane review demonstrated that infants who received a more rapid rate of feeding advancement had no significant increase in the development of NEC but had fewer days to full enteral feeds and regaining birth weight [92]. Indeed, the most recent American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines on nutrition support of infants at risk for NEC recommend that minimal enteral nutrition be initiated in the first 2 days of life with advancement by 30 mL/kg per day in infants weighing more than 1,000 g [156].

Osmolality/Osmolarity of Feeds

Both animal studies and clinical data have implicated hypertonic feeds in causing mucosal injury. DeLemos et al. produced enterocolitis in goats fed hypertonic formula [93]. Book et al. found that feeding infants weighing less than 1,200 g an elemental formula with an osmolarity of 650 mosmol/L resulted in an 87% incidence of NEC compared with 25% of neonates fed standard cow's milk–based formula (359 mosmol/L) [94]. Willis et al. noted a higher frequency of NEC among infants fed undiluted hypertonic calcium lactate than among those unsupplemented or supplemented with diluted calcium lactate [95]. The American Academy of Pediatrics has recommended that infant feedings have an osmolarity of less than 400 mosmol/L (equivalent to an osmolality of approximately 450 mosmol/kgH_2O) [96].

Hypertonic formulas may be the result of added oral medications. In an excellent review by White and Harkavy, the osmolalities of five oral preparations were studied: theophylline, calcium glubionate, digoxin, phenobarbital, and dexamethasone [97]. The osmolalities of all five were greater than 3,000 mosmol/kgH_2O, and hence they should be given undiluted orally with extreme caution. When mixed with formula, theophylline, calcium glubionate, and digoxin had acceptable osmolalities (<400 mosmol/kgH_2O), but dexamethasone and phenobarbital elixirs still had osmolalities of approximately 1,000 mosmol/kgH_2O when 3.8 and 1 mL, respectively, were mixed with 15 mL of formula [97]. Ernst et al. showed that 1 mL of Polyvisol added to 30 mL of a standard formula increased the osmolality from 375 to 744 mosmol/kgH_2O [98]. If an intravenous

line is required for other reasons, then the intravenous route of drug administration may be preferred over the oral route.

Immunologic Considerations

The newborn protects its mucosa by secretory immunoglobulin A (sIgA). sIgA inhibits bacterial adherence to mucosal cells in addition to preventing other toxins and antigenic material from binding to the epithelial cells. However, in term infants, sIgA is not demonstrable in intestinal fluids until 1 week of age, and adult values are not reached until 1 month of age [99]. However, nature has its way of protecting the newborn. sIgA-producing plasma cells in the maternal gut are antigenically stimulated and migrate to the breast, where specific antibodies are secreted into the colostrum. Thus the breastfed newborn receives some passive protection against the bacteria he or she is most likely to harbor (i.e., his or her mother's).

The possibility of improving gut defenses has been explored extensively [100]. Eibl et al. reported their results using an oral immunoglobulin preparation (73% IgA and 26% IgG) in reducing the incidence of NEC in low-birth-weight infants (800–2,000 g) [101]. These were infants for whom breast milk was not available. In 88 infants fed the oral IgA-IgG, there were no cases of NEC compared with 6 cases among the 91 control infants. The IgA-IgG preparation was made from human serum. In a meta-analysis, the oral administration of IgG or IgG-IgA did not reduce the incidence of definite NEC, suspected NEC, need for surgery, or death from NEC [102].

Benefits of Human Milk

The possibility that breast milk (containing IgA) offers similar immunoprotective benefit has also been studied. In nonbreastfed premature infants with immature intestinal development, there is no protection against bacteria when microbial colonization occurs. Hence maternal milk has potential importance in protecting the newborn. The work of Barlow et al. in rats substantiates the importance of breast milk in preventing NEC [103]. These authors consistently produced a disease similar to NEC by producing a hypoxic insult in rats fed artificial formula. All breastfed asphyxiated rats were protected from disease. In the rat model, live milk leukocytes appeared to be prophylactic. The authors concluded that breast milk induced protective enteric immunity for newborn rats, and it may similarly protect premature infants [103]. However, NEC has been reported in neonates exclusively fed fresh, frozen, or pasteurized human milk [104].

In the past, many nurseries fed premature infants pooled frozen human milk. Kliegman et al. found that there was no difference in the incidence of NEC among these infants and those fed commercial formula [105]. The reason for this, despite the theoretical advantages of breast milk, could include the adverse affects of storage on the viability and functional integrity of the cellular components of milk, in addition to the possibility of contamination. In a study by Stevenson et al., there was no difference in the intestinal flora of preterm hospitalized infants fed stored frozen breast milk and a proprietary formula. However, all the infants fed breast milk had been treated with parenteral antibiotics [106].

Lucas and Cole reported a large prospective multicenter study of 926 preterm infants formally assigned to their early diet [107]. The results argue strongly for a highly protective effect of human milk on the subsequent development of NEC. In exclusively formula-fed babies, confirmed NEC was 6–10 times more common than in those fed breast milk alone and three times more common than in those who received formula plus breast milk. Among babies born at more than 30 weeks' gestation, confirmed NEC was rare in those whose diet included human milk; it was 20 times more common in those fed formula only. Pasteurized donor milk seemed to be as protective as raw maternal milk. In formula-fed but not breastfed infants, delayed feeding was associated with a lower frequency of NEC. In babies fed breast milk (alone or with formula), there was a sharp decline in the incidence of NEC with length of gestation. Beyond 30 weeks' gestation, there was only one confirmed case of NEC among 376 babies receiving human milk. The authors concluded that early introduction of breast milk into the diets of preterm infants could make NEC beyond 30 weeks' gestation a rarity [107].

Schanler et al., in a randomized trial, confirmed the value of feeding human milk to VLBW infants [25]. In their study, independent of treatment group assignment, infants receiving the most human milk had a significantly lower incidence of NEC. Further, Schulman et al. showed that the feeding of human milk (versus formula) was associated with decreased intestinal permeability at 28 days of age ($p = 0.02$) [30]. Multiple more recent studies have continued to support the protective effect of human milk against

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the development of NEC. In one prospective study of 223 infants, enteral feedings containing at least 50% human milk in the first 14 days of life were associated with a sixfold decrease in the odds of NEC [109]. An analysis of two clinical trials among 260 premature infants weighing less than 1,250 g at birth comparing exclusive human milk, human milk–based fortifier, or cow's mild–based products demonstrated by linear regression analysis that for each 10% increase in the intake other than exclusive human milk diet, the risk of NEC increases by 11.8%, and the risk of surgical NEC increases by 21% [157]. A multicenter randomized, controlled trial of exclusive donor human milk and human milk fortifier compared with preterm formula among 53 extremely premature infants with birth weights of 500–1,250 g demonstrated lower rates of NEC (3% human milk compared with 21% receiving formula) and surgical NEC (0% human milk compared with 17% receiving formula) among infants fed exclusively human milk products [158]. These authors determined that for every six infants fed an exclusive human milk diet, one case of surgical NEC would be prevented [158]. Lastly, a multicenter randomized trial among 207 premature infants with birth weights of 500–1,250 g comparing exclusively human milk intake with bovine milk–based product intake demonstrated a 77% reduction in the risk of NEC when receiving an exclusive human milk diet [159].

Fresh human milk is composed of numerous immunoprotective factors, including neonatal antigen-specific antibodies (IgA, IgM, and IgG), macrophages, lymphocytes, neutrophils, enzymes, lactoferrin, lysozyme, growth factors (e.g., epidermal growth factor [EGF]), hormones, oligosaccharides, polyunsaturated fatty acids, nucleotides, and specific glycoproteins. Another potentially beneficial component of human milk that was more recently discovered is platelet-activating factor (PAF) acetyl hydrolase (PAF-AH). This enzyme inhibits the activity of PAF, which is likely to be a significant mediator in the pathophysiologic cascade of NEC [108]. Thus more recent evidence detailed earlier as well as the most recent ASPEN nutritional guidelines for infants at risk for NEC strongly support exclusive human milk rather than cow's milk–based products in premature infants at risk of NEC [156].

Ischemia and Hypoxia

Ischemia and subsequent damage to the intestinal mucosa have been hypothesized in the pathogenesis of NEC. Investigators developed an ischemic model of NEC in piglets and postulated a "diving reflex." This is a well-documented reflex in marine animals when there is arterial constriction in the vascular beds of the skin, kidney, and gastrointestinal tract in an attempt to preserve cardiac and cerebral blood flow during prolonged diving. Premature infants may respond in a similar manner to repeated episodes of gut ischemia. Factors implicated in the ischemia-hypoxia pathogenesis of NEC include prenatal asphyxia, hypotension, hypothermia, umbilical vessel catheterization, patent ductus arteriosus (PDA), polycythemia, and exchange transfusion. Nonetheless, NEC does not develop in the majority of infants with these risk factors [64,66], and NEC has been reported in premature infants with no risk factors [110].

Umbilical vessel catheterization has been widely implicated in the pathogenesis of mucosal ischemia; 80% of infants with umbilical artery catheters have been found to have distinct arterial thrombosis [111]. Plasticizer levels in tissues of neonates with NEC were found to be significantly higher than in those without catheters [112]. A significant increase in portal venous pressure was noted in newborn piglets undergoing exchange transfusion via umbilical venous catheter. The authors concluded that alterations in mucosal vascular pressures produced ischemia secondary to vascular congestion and hemorrhage [113].

The presence of a low umbilical catheter has been reported to increase the risk of NEC, especially if the infant is fed during the period of catheterization. However, a prospective randomized clinical trial did not support this association [114]. Kliegman's own experience reinforces the safety and value of feeding infants as small as 600 g who are on a ventilator while an umbilical catheter is in place [29]. In the study of Schanler et al., there was no association between the use of umbilical catheters, concomitant feeding, and either feeding intolerance or NEC [25].

Role of Vitamin E

Premature infants weighing less than 1,500 g maintained at high serum levels of vitamin E for retinopathy of prematurity (ROP) prophylaxis have been found to have a higher incidence of NEC. Johnson et al. found that premature infants weighing less than 1,500 g who received prophylactic vitamin E had a higher incidence of NEC and sepsis if maintained at pharmacologic levels (>3.0 mg/dL or 0.03 mg/mL) for

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more than 1 week [115]. Hence they recommended serum vitamin E levels be kept between 1.0 and 3.0 mg/dL. In another study, high serum vitamin E levels (>3.5 mg/dL) were found in premature infants weighing less than1,500 g when receiving the recommended dosage of MVI Pediatric [116]; hence weekly serum vitamin E is recommended in infants weighing between 1 and 3 kg. Further, infants with elevated vitamin E levels should have multivitamins held until serum vitamin E levels normalize; infants weighing less than 3 kg should receive 2 mL/kg (maximum 5 mL) of MVI Pediatric daily to avoid elevations in serum vitamin E and the increased NEC risk.

The most likely reason for the increased incidence of NEC is that pharmacologic serum vitamin E levels result in a decrease in oxygen-dependent intracellular killing ability, which leads to an increased susceptibility to infection in preterm infants.

Role of Infectious Agents

Many consider NEC to be an infectious disease because many infants are colonized with a resistant and invasive organism. These organisms are capable of producing hydrogen gas, which leads to pneumatosis. The most commonly encountered organisms have been *Escherichia coli, Klebsiella*, and *Clostridium*, and more recently *Staphylococcus epidermidis* has been implicated in a number of patients [53]. The premature infant has decreased resistance; coupled with the inability to mount an appropriate immune response, these infections can be overwhelming.

Prophylactic use of oral aminoglycosides was initially hailed as a means of either preventing NEC altogether or preventing perforation if NEC had already developed. Prospective studies have demonstrated that oral gentamicin does not prevent intestinal perforation or alter the course of the disease. Further, oral aminoglycosides can be absorbed across the damaged intestine and increase serum levels, possibly leading to drug toxicity [65]. In addition, Neu et al. showed that in animals who had been asphyxiated, the use of gentamicin significantly decreased jejunal lactase levels [117].

Maternal Cocaine Use

Maternal cocaine use has also been implicated in NEC in infants [80]. Cocaine compromises uterine blood flow and fetal oxygenation in pregnant ewes, thus potentially impairing fetal gut development [118]. Lopez studied 1,284 NICU admissions and found that 12% of exposed infants and 3% of nonexposed infants developed NEC [119]. In low-birth-weight or premature infants, the risk is two to three times higher during the first 2 weeks in exposed babies but rises to five times higher after 2 weeks, particularly in infants smaller than 1,500 g.

Role of Corticosteroids

In a large multicenter collaborative trial using antenatal corticosteroids to prevent RDS, a significantly decreased incidence of NEC was noted in infants treated with steroids [120]. Similar results have been shown prospectively in infants treated prenatally, with a trend in reduction of NEC even with postnatal treatment [121]. Additionally, corticosteroids stimulate PAF-AH and inhibit the PAF synthesis pathway [122]. In the study of Schulman et al., antenatal steroid administration was associated with decreased intestinal permeability at 28 days of age ($p = 0.017$) [30]. Corticosteroids are one of the growth factors implicated in the physiologic maturation of the intestinal barrier, and in animal studies they help to mature many components of the microvillous surface and enhance the intestinal barrier to the uptake of antigens [80]. Postnatal glucocorticoids are clearly not the ultimate answer to decrease NEC because their use is associated with a number of significant adverse effects, including growth retardation, hyperglycemia, hypertension, infections, hypertrophic cardiomyopathy, gastrointestinal bleeding, and intestinal perforation [123].

Newer Thoughts on Etiology

Enteral feeding composition, bacterial infection, and mesenteric ischemia appear to play significant roles in the pathogenesis of NEC but are likely secondary to the basic underlying defects of intestinal barrier immaturity. Contributing to this barrier of young (compared with more mature) intestine may be

1. Decreased mucus production or immature mucin composition
2. Increased susceptibility to disruption of the epithelial cell layer at the cell membrane and/or the basement membrane level
3. Decreased repair capacity of the epithelial cell layer
4. Decreased tissue antioxidant activity
5. Decreased ability to maintain tissue oxygenation secondary to immature regulation of blood flow and oxygenation

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6. Increased susceptibility to inflammatory mediators
7. Dysfunctional immune response
8. Abnormal motility [124]

One – or, more likely, several – of these factors contributing to gut immaturity may then result in mucosal injury that progresses to NEC [125,126].

NEC seems to involve a final common pathway that includes the endogenous production of inflammatory mediators involved in the development of intestinal injury. Endotoxin lipopolysaccharide, PAF, tumor necrosis factor (TNF), and other cytokines together with prostaglandins and leukotrienes are thought to be involved in the final common pathway of NEC pathogenesis [108].

PAF has emerged as a primary mediator of pathogenesis of NEC [127,128]. PAF exerts local paracrine effects and is rapidly hydrolyzed by PAF-AH. PAF binds to a specific receptor, leading to hypotension, increased vascular permeability, hemoconcentration, lysosomal enzyme release, and platelet and neutrophil aggregation [128]. Gonzalez-Crussi and Hsueh have shown that intraaortic injection of PAF resulted in experimental bowel necrosis in the adult rat that is similar to NEC [129]. Plasma levels of PAF-AH, the PAF-degrading enzyme, have been shown to be significantly lower in preterm neonates, and PAF levels in stools increase after the initiation of enteral feeding [127].

PAF receptor antagonists or PAF-AH mixed in the formula prevented the development of experimental NEC [127]. The bowel necrosis can be exacerbated by a nitric oxide synthase inhibitor [108]. Epithelial cells of the intestinal mucosa turn over naturally by the removal of some cells via programmed cell death (apoptosis) and by replacement of the dying cells with proliferating cells in the crypts. Abundant apoptosis might lead to a breach in the mucosal barrier, allowing bacterial translocation into the submucosa and triggering an inflammatory cascade. PAF is a potent stimulator of apoptosis in cultured intestinal epithelial cells [129].

Intestinal trefoil factor (ITF) is a cytoprotective peptide secreted by the intestinal goblet cells that has been shown to protect the gut mucosa against damage induced by several injurious agents. In an experimental rat model of NEC, ITF protected against PAF-mediated injury [130]. A proposed schematic of the etiology of NEC is shown in Figure 43.1.

Nitrous oxide is synthesized from arginine and is critical for intestinal barrier function. Inhibition of nitrous oxide synthesis increases intestinal damage. Glutamine and arginine serum levels have both been shown to be significantly lower in premature infants with NEC compared with controls [131]. However, glutamine supplementation is not recommended for infants at risk for NEC based on the most recent ASPEN nutrition support guidelines for infants at risk for NEC because there have not been sufficient studies to show any benefit [156].

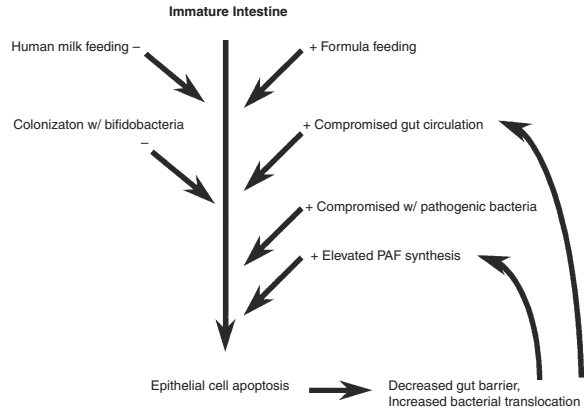


Figure 43.1 Proposed schematic of the etiology of NEC. PAF, platelet-activating factor; –, protective effect; +, damaging effect.

(Modified with permission from Caplan and Jilling [127].)

Salivary EGF has been shown to be decreased in NEC infants compared with controls. There is a question of whether a fall in EGF predicts the onset of NEC. If EGF were low, EGF supplementation could possibly be given, though more research is needed in this area [124].

Early colonization of the gut might have an important role in developing susceptibility to NEC. Probiotics are live microbial organisms that enhance mucosal IgA responses, increase the production of anti-inflammatory cytokines, and normalize gut ecology [135]. The use of probiotics may be a feasible strategy to reduce the incidence of NEC in high-risk populations and requires further investigation. Bifidobacterial supplementation reduced the incidence of NEC in a neonatal rat model [132]. Supplementation of formula with live bifidobacteria prevented the development of NEC in a quail model [133]. Further work from the laboratory of Butel et al. focused on the contribution of the prebiotic oligofructose to the protective role of bifidobacteria [134]. Thus the combination of a probiotic and prebiotic may offer a new therapeutic way of preventing NEC.

Early randomized prospective studies in human infants suggest that oral probiotics decrease the incidence of NEC without the development of other infectious complications such as sepsis [136,137]. Two recent studies investigating the use of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* [161] *or infantis* [162] demonstrated a similar reduction in the risk of NEC among VLBW infants given probiotics [161,162], though one study found this reduction only among infants fed human breast milk but not formula [161]. A multicenter randomized, double-blinded, placebo-controlled trial investigating the use of a probiotic combination (*B. infantis, Streptococcus thermophilus*, and *B. lactis*) among premature infants weighing less than 1,500 g determined that infants receiving the probiotic combination had a reduced incidence of NEC (Bell stage II or greater) compared with the control group (2% compared with 4.4%) [163]. This study had a low incidence of NEC in the control group, and there was a high rate of human breast milk feeding (96.9%) in both control and intervention groups [163]. A systematic review of the use of *L. reuteri* determined that there were no adverse events, and all studies showed a significant improvement in the incidence of NEC among premature infants [164]. However, there are several case reports of sepsis following the use of probiotics among preterm infants, including *Lactobacillus* [138], *Saccharomyces cerevisiae* [139], and *B. longum* [160]. Data are insufficient at this time to comment on the short- and long-term safety of probiotics for the prevention of NEC in preterm infants. The type of probiotics used and the timing and dosage are still to be optimized [140]. Therefore, until further studies on efficacy and safety are available, routine use of probiotic therapy in premature infants cannot be recommended [141,156].

If human milk is not available, altered premature formulas may lower the incidence of NEC. Delipidated formula (formula without fat) has been shown not to alter intestinal permeability, whereas premature formulas increase intestinal permeability [124]. Carlson et al. studied preterm infants fed on experimental formula with egg phospholipids (one or more of which may have enhanced immature intestinal function) in a randomized, double-blind clinical study. Infants fed the experimental formula developed significantly less stage II and stage III NEC compared with controls [142].

Outcome of NEC

In addition to post-NEC strictures, the most common complication is short-bowel syndrome – estimated to be 25% in one review [79]. Because patients with short-bowel syndrome depend on PN for varied periods of time, some patients progress to TPN-associated cholestasis, with subsequent cirrhosis and liver failure [79].

Neurodevelopmental outcome has also been studied in babies surviving NEC. Sonntag et al. studied 20 of 22 surviving VLBW infants diagnosed with NEC between 1992 and 1996. Severe developmental delay was especially frequent in the NEC group: it was found in 55% of the infants after NEC but only 22.5% of the infants without NEC at 20 months' corrected age [143]. In an additional study of 1,151 extremely low-birth-weight infants, factors significantly associated with increased neurodevelopmental morbidity included chronic lung disease, grades 3–4 intraventricular hemorrhage/periventricular leukomalacia, steroids for chronic lung disease, NEC, and male gender [144].

Prevention of NEC

Given the multitude of known beneficial effects of breast milk for feeding premature infants, administration of fresh breast milk should be given top priority as the most natural and safe way of lowering the risk of NEC [125,156]. Early gastrointestinal priming with human milk, using the bolus tube-feeding method, "may provide the best advantage for the premature infant" [25].

Because there will continue to be infants for whom breast milk feeding is not an option, investigation into the ideal nutrient composition for infant formulas and the administration of formula additives should be actively pursued [124]. Premature formulas must be altered to minimize adverse effects on intestinal barrier function. Omega-3 fatty acids and egg phospholipid–containing diets have been used in both animal and human studies [142,145]. These lipids seem to have an anti-inflammatory effect, with reduction of the levels of PAF and leukotrienes in the intestinal mucosa and a significant decrease in the incidence of stage III NEC in less-than-32-week premature infants [80].

As described previously, studies have shown that there is no difference in the incidence of NEC among premature infants receiving a slow versus fast feeding advancement [91,92,146] but improved time to regaining birth weight and fewer days on PN among the group

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who was advanced more quickly on feeds [146]. Indeed, the most recent ASPEN clinical guidelines for nutrition support of infants at risk for NEC recommend the initiation of enteral nutrition within the first 2 days of life with advancement by 30 mL/kg per day in infants weighing more than 1,000 g [156]. These findings suggest that VLBW infants may not require as much caution in their feeding regimens as previously suggested, but few neonatologists currently advance feedings rapidly in preterm infants [127]. Experience dictates a very slow regimen for increases in feeding, beginning early [147,148].

Future therapies potentially beneficial in preventing NEC include

1. Supplementation of feedings with probiotics (e.g., bifidobacteria) and possibly prebiotics (e.g., oligofructose)
2. PAF antagonists or recombinant PAF-AH
3. Dietary supplements with growth factors (e.g., EGF, glutamine)
4. Arginine supplementation of the preterm infant's diet – an amino acid essential to intestinal integrity
5. Promotion of intestinal mucus production and addition of mucin to commercially prepared infant formula
6. Antioxidant administration, especially glutathione and vitamin E [124]

A recent clinically oriented study examining multimodal prophylaxis (early trophic feeding with human breast milk, enteral antibiotic, antifungal agent, and probiotics) in a high-risk group has shown a low incidence of NEC, especially when treatment was started within the first 24 hours of life [149].

Our knowledge of optimal nutrition in premature infants is in a continuing state of evolution. Current recommendations for providing nutrition in the asphyxiated premature infant are discussed next.

Recommendations for Nutritional Management of Asphyxiated Infants

Several preventive measures can be proposed for at-risk infants. At-risk infants are those who are suspected to have had an intrauterine or neonatal episode of asphyxia or shock leading to poor bowel perfusion.

Late Introduction of Feedings

At-risk infants should receive nothing enterally for the first 5 days to 2 weeks of life; they should receive TPN. Enteral feedings are then initiated slowly, but at the first sign of abdominal distension, increasing gastric residuals, regurgitation, and guaiac- or Clinitest-positive (anhydrous Benedict's reagent) stools, enteral feedings should be stopped and not reintroduced for several days to weeks.

Slow Advancement of Feedings

At the end of 5 days to 2 weeks, or if feedings are to be initiated earlier than stated earlier (e.g., in tiny newborns on ventilators), one should begin with 1 mL every 1–2 hours and advance slowly to increase the total feedings by no more than 20 mL/kg per day.

Human Milk

While early studies suggested that human milk would be protective against NEC, NEC has been described even in infants receiving fresh human milk. However, the immune protection from fresh human milk is thought by many to be very important to the preterm infant, and the large study of 926 preterm infants by Lucas and Cole argues strongly for the protective effects of human milk [107]. Multiple studies among premature infants have shown that infants receiving human milk products have a lower incidence of NEC than infants receiving formula [30,109,157–159]. Exclusive use of human milk rather than cow's milk–based products or formula is recommended in the most recent ASPEN clinical guidelines for the nutritional support of infants at risk for NEC [156]. Because human milk may not meet the calcium, phosphorus, caloric, and protein needs of low-birth-weight infants, it can be supplemented with a human milk fortifier. In our laboratory, we have shown that such supplementation has no adverse effects on key anti-infective factors in human milk [150].

Route of Feeding

Intermittent gavage tube feeding appears more physiologic than transpyloric feeding and, wherever possible, is preferred. Schanler et al. confirmed the advantage of such bolus feedings [25]. Enteral nutrition may be the critical element that triggers postnatal gut maturation through release of gut peptide hormones [151]. If the patient has regurgitation, poor gastric emptying, or gastric distension, continuous NG feeding or even transpyloric feeding may be required [13].

Observe for Early Signs of NEC

Carefully monitor all high-risk infants for any early signs of NEC. These signs may occur for up to 60 days of life in infants whose first feed is delayed beyond the first week of life. If the diagnosis of NEC is suspected, feedings are stopped, and the infant receives nutrition by the parenteral route for several days to 2 weeks depending on the severity of symptoms.

Summary: Asphyxia and NEC

Asphyxiated infants may have experienced a significant insult to the gut, predisposing them to NEC. Enteral feedings are usually withheld for the first 5 days to 2 weeks after the insult and then advanced slowly. Prolonged bowel rest may arrest gut maturation, but maturation will resume when intraluminal nutrients are reintroduced [152]. Gut atrophy in the chronically parenterally fed infant may lead to increased intestinal permeability to bacteria [153,154].

References

1. Committee on Nutrition. Nutritional needs of low birth weight infants. *Pediatrics* 1985; **75**; 976–86.
2. Grand RJ, Watkins JB, Torti FM. Development of the human gastrointestinal tract. *Gastroenterology* 1976; **70**:790–810.
3. Lebenthal E, Le PC. Interactions of determinants in the ontogeny of the gastrointestinal tract: a unified concept. *Pediatr Res* 1983; **17**:19–24.
4. Milla PJ. Development of intestinal structure and function. In Tanner MS, Stocks RJ, eds., *Neonatal Gastroenterology: Contemporary Issues*. Newcastle upon Tyne: Scholium International, 1984:1–20.
5. Cavell B. Gastric emptying in preterm infants. *Acta Paediatr Scand* 1979; **68**: 725–30.
6. Yu VYH. Effect of body position on gastric emptying in the neonate. *Arch Dis Child* **975**; 50: 500–4.
7. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. *J Pediatr* 1979; **95**: 763–8.
8. Pitcher-Wilmott R, Shurack JG, Fox WW. Decreased lung volume after nasogastric feeding of neonates recovering from respiratory distress. *J Pediatr* 1979; **96**: 914–16.
9. Toce SS, Keenan WJ, Homan SM. Enteral feeding in very low-birth-weight infants: a comparison of two nasogastric methods. *Am J Dis Child* 1987; **141**: 439–44.
10. Narayanan I, Singh B, Harvey D. Fat loss during feeding of human milk. *Arch Dis Child* 1984; **59**: 475–7.
11. Moyer L, Chan GM. Clotted feeding tubes with transpyloric feeding of premature infant formula. *J Pediatr Gastroenterol Nutr* 1982; **1**: 55–7.
12. Lucas A, Bloom SR, Aynsley-Green A. Metabolic and endocrine events at the time of the first feed of human milk in preterm and term infants. *Arch Dis Child* 1978; **53**: 731–6.
13. Bremer HJ, Brooke OG, Orzalesi M, et al. *Nutrition and Feeding of Preterm Infants*. Oxford: Blackwell, 1987: 197–8.
14. Van Caillie M, Powell GK. Nasoduodenal versus nasogastric feeding in the very low birth weight infant. *Pediatrics* 1975; **56**: 1065–72.
15. Whitfield MF. Poor weight gain of the low birth weight infant fed nasojejunally. *Arch Dis Child* 1982; **57**:597–601.
16. Roy RN, Pollnitz RP, Hamilton JR, et al. Impaired assimilation of nasojejunal feeds in healthy low-birth-weight infants. *J Pediatr* 1977; **90**: 431–4.
17. Beddis I, McKenzie S. Transpyloric feeding in the very low birth weight (1500 gm and below) infant. *Arch Dis Child* 1979; **54**: 213–7.
18. Whittfield MF. Transpyloric feeding in infants undergoing intensive care. *Arch Dis Child* 1980; **55**:571.
19. Lucas A. Enteral nutrition. In Tsang RC, Lucas A, Uauy R, et al., eds., *Nutritional Needs of the Premature Infant*. Baltimore: Williams & Wilkins, 1993: 209–23.
20. Hayhurst EG, Wyman M. Morbidity associated with prolonged use of polyvinyl feeding tubes. *Am J Dis Child* 1975; **129**: 72–4.
21. Rodriguez JP, Guero J, Frias EG, et al. Duodenorenal perforation in a neonate by a tube of silicone rubber during transpyloric feeding. *J Pediatr* 1978; **92**: 113–16.
22. Dellagrammaticus HD, Duerden BI, Milner RDG. Upper intestinal bacterial flora during transpyloric feeding. *Arch Dis Child* 1983; **58**: 115–19.
23. Vazquez C, Arroyos A, Valls A. Necrotizing enterocolitis: increased incidence in infants receiving nasoduodenal feeding. *Arch Dis Child* 1980; **55**:826.
24. Pereira GR, Lemons JA. Controlled study of transpyloric and intermittent gavage feeding in the small preterm infant. *Pediatrics* 1981; **67**:68–72.
25. Schanler RJ, Schulman RJ, Lau C, et al. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. *Pediatrics* 1999; **103**: 434–9.
26. Lucas A, Bloom SR, Aynsley-Green A. Gut hormones and "minimal enteral feeding." *Acta Paediatr Scand* 1986; **75**: 719–23.
27. Dunn L, Hulman S, Weiner J, et al. Beneficial effects of early hypocaloric enteral feeding on neonatal

gastrointestinal function: preliminary report of a randomized trial. *J Pediatr* 1988; **112**: 622–9.

28. Slagle TA, Gross SJ. Effect of early low-volume enteral substrate on subsequent feeding tolerance in very low birth weight infants. *J Pediatr* 1988; **113**: 526–31.
29. Kliegman RM. Experimental validation of neonatal feeding practices. *Pediatrics* 1999; **103**: 492–3.
30. Schulman RJ, Schanler RJ, Lau C, et al. Early feeding, antenatal glucocorticoids, and human milk decrease intestinal permeability in preterm infants. *Pediatr Res* 1998; **44**: 519–23.
31. Schulman RJ, Schanler RJ, Laue C, et al. Early feeding, feeding tolerance, and lactase activity in premature infants. *J Pediatr* 1998; **133**: 645–9.
32. Schanler RJ. Feeding strategies in premature infants. Presented as a lecture at Advances in Perinatal and Pediatric Nutrition Conference, Stanford University, July 1999. Published in course syllabus, 1999: 454–61.
33. Moyer-Mileur L, Chan GM. Nutritional support of very-low-birth-weight infants requiring prolonged assisted ventilation. *Am J Dis Child* 1986; **140**: 929–32.
34. Unger A, Goetzman BW, Chan C, et al. Nutritional practices and outcome of extremely premature infants. *Am J Dis Child* 1986; **140**: 1027–33.
35. Gunn T, Reaman G, Outerbridge EW, et al. Peripheral total parenteral nutrition for premature infants with the respiratory distress syndrome: a controlled study. *J Pediatr* 1978; **92**: 608–13.
36. Yu VYH, James B, Hendry P, et al. Total parenteral nutrition in very low birthweight infants: a controlled trial. *Arch Dis Child* 1979; **54**: 653–61.
37. Kerner JA, Hattner JAT, Trautman MS, et al. Postnatal somatic growth in very low birth weight infants on peripheral parenteral nutrition. *J Pediatr Perinat Nutr* 1988; **2**:27–34.
38. Glass EJ, Hume R, Lang MA, et al. Parenteral nutrition compared with transpyloric feeding. *Arch Dis Child* 1984; **59**: 131–5.
39. Dryburgh E. Transpyloric feeding in 49 infants undergoing intensive care. *Arch Dis Child* 1980; **55**: 879–2.
40. Zlotkin SH, Stallings VA, Pencharz PB. Total parenteral nutrition in children. *Pediatr Clin North Am* 1985; **32**:381–400.
41. Cashore WJ, Sedaghatian MR, Usher RH. Nutritional supplements with intravenously administered lipid, protein hydrolysate, and glucose in small premature infants. *Pediatrics* 1975; **56**:8–16.
42. Churella HR, Bachhuber BS, MacLean WC. Survey: methods of feeding low-birth-weight infants. *Pediatrics* 1985; **76**: 243–9.
43. Adamkin DA. Nutrition in very very low birth weight infants. *Clin Perinatol* 1986; **13**: 419–43.
44. Higgs SC, Malan AF, Heese HDeV. A comparison of oral feeding and total parenteral nutrition in infants of very low birthweight. *S Afr Med J* 1974; **48**: 2169–73.
45. Hall RT, Rhodes PG. Total parenteral alimentation via indwelling umbilical catheters in the newborn period. *Arch Dis Child* 1976; **51**: 929–34.
46. Merritt RJ. Neonatal nutritional support. *Clin Consult Nutr Support* 1981; **1**:10.
47. Coran AG. Parenteral nutritional support of the neonate. Tele Session (a group telephone workshop, August 17), Tele Session Corporation, New York, 1981.
48. Kerner JA. The use of umbilical catheters for parenteral nutrition. In Kerner JA, ed., *Manual of Pediatric Parenteral Nutrition*. New York: Wiley, 1983: 303–6.
49. Sadig HF. Broviac catheterization in low birth weight infants: incidence and treatment of associated complications. *Crit Care Med* 1987; **15**:47–50.
50. Kanarek KS, Kuznicki MB, Blair RC. Infusion of total parenteral nutrition via the umbilical artery. *J Parenter Enteral Nutr* 1991; **15**: 71–4.
51. Nakamura KT, Sato Y, Erenberg A. Evaluation of a percutaneously placed 27-gauge central venous catheter in neonates weighing less than 1200 grams. *J Parenter Enteral Nutr* 1990; **14**: 295–9.
52. Abdulla F, Dietrich KA, Pramanik AK. Percutaneous femoral venous catheterization in preterm neonates. *J Pediatr* 1990; **117**: 788–91.
53. Sunshine P. Fetal gastrointestinal physiology. In Eden RD, Boehm FH, eds., *Assessment and Care of the Fetus: Physiological, Clinical and Medicolegal Principles*. East Norwalk, CT: Appleton & Lange, 1990:93–111.
54. Koldovsky O, Sunshine P, Kretchmer N. Cellular migration of intestinal epithelia in suckling and weaned rats. *Nature* 1966; **212**: 1389–90.
55. Herbst JJ, Sunshine P. Postnatal development of the small intestine of the rat. *Pediatr Res* 1969; **3**:27–33.
56. Sunshine P, Herbst JJ, Koldovsky O, et al. Adaptation of the gastrointestinal tract to extrauterine life. *Ann NY Acad Sci* 1971; **176**:16–29.
57. Herbst JJ, Sunshine P, Kretchmer N. Intestinal malabsorption in infancy and childhood. *Adv Pediatr* 1969; **16**:11–64.
58. Kliegman RM, Fanaroff AN. Necrotizing enterocolitis. *N Engl J Med* 1984; **310**: 1093–103.
59. Kosloske AM. Pathogenesis and prevention of necrotizing enterocolitis: a hypothesis based on personal observation and a review of the literature. *Pediatrics* 1984; **74**: 1086–92.

60. Neu J. Necrotizing enterocolitis:an update. *Acta Paediatr* 2005; **94**: 100–5.
61. Stevenson DK, Blakely ML. Historical perspectives: necrotizing enterocolitis: an inherited or acquired condition? *NeoReviews* 2006; **7**:e125–34.
62. Gephar SM, McGrath JM, Effken JA, Halpern MD. Nectrotizing enterocolitis risk: state of the science. *Adv Neotatal Care* 2012; **12**:77–89.
63. Brown E, Sweet AY. Preventing necrotizing enterocolitis in neonates. *JAMA* 1978; **240**: 2452–4.
64. Frantz ID, L'Heureux P, Engel RR, et al. Necrotizing enterocolitis. *J Pediatr* 1975; **56**: 259–63.
65. Walsh MC, Kliegman R, Fanaroff A. Necrotizing enterocolitis: a practitioner's perspective. *Pediatr Rev* 1988; **9**: 219–26.
66. Stoll BJ, Kanto WP, Glass RI, et al. Epidemiology of necrotizing enterocolitis: a case control study. *J Pediatr* 1980; **96**: 447–51.
67. Holman RC, Stoll BJ, Curns AT, et al. Enterocolitis hospitalizations among neonates in the United States. *Paediatr Perinat Epidemiol* 2006; **20**:498–506.
68. Moonijian AS, Peckham G, Fox W, et al. Necrotizing enterocolitis: endemic vs. epidemic. *Pediatr Res* 1978; **12**:530.
69. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986; **33**:179–200.
70. Mata AG, Rosenpart RM. Intraobserver variability in the radiographic diagnosis of necrotizing enterocolitis. *Pediatrics* 1980; **66**:68–71.
71. Kirschner B, Lahr C, Lahr D. Detection of increased breath hydrogen in infants with necrotizing enterocolitis. *Gastroenterology* 1980; **72**: A57/1080.
72. Stevenson DK, Shahin SM, Ostrander CR, et al. Breath hydrogen in preterm infants: correlation with changes in bacterial colonization of the gastrointestinal tract. *J Pediatr* 1982; **101**: 607–10.
73. Garcia J, Smith FR, Cucinelli SA. Urinary D-lactate in infants with necrotizing enterocolitis. *J Pediatr* 1984; **104**: 268–70.
74. Rivas Y, Solans C, Spivak W. Serum D-lactic acid level, a new marker for necrotizing enterocolitis. *J Pediatr Gastroenterol Nutr* 2000; **31**:S236.
75. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg* 1978; **187**:1–7.
76. Kliegman RM, Hack M, Jones P, et al. Epidemiologic study of necrotizing enterocolitis among low-birth-weight infants: absence of identifiable risk factors. *J Pediatr* 1982; **100**: 440–4.
77. Kerner JA, Hartman GE, Sunshine P. The medical and surgical management of infants with the short bowel syndrome. *J Perinatol* 1985; **5**: 517–21.
78. Raine PAM. Neonatal necrotizing enterocolitis. In Reed GB, Claireaux AE, Cockburn F, eds., *Diseases of the Fetus and Newborn*, 2nd edn. London: Chapman & Hall, 1995: 1485–91.
79. Dimmitt RA, Moss RL. Clinical management of necrotizing enterocolitis. *NeoReviews* 2001; **2**:e110–17.
80. Israel EJ, Morera C. Necrotizing enterocolitis. In Walker WA, Durie PR, Hamilton JR, et al., eds., *Pediatric Gastrointestinal Disease*, 3rd edn. Ontario: Decker, 2000: 665–76.
81. Moss RL, Dimmit RA, Barnhart DC, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. *N Engl J Med* 2006; **354**: 2225–34.
82. Flake AW. Necrotizing enterocolitis in preterm infants: is laparotomy necessary? *N Engl J Med* 2006; **354**:2275.
83. Eyal F, Sagi E, Avital A. Necrotizing enterocolitis in the very low birth weight infant: expressed breast milk feeding compared with parenteral feeding. *Arch Dis Child* 1982; **57**: 274–6.
84. Ostertag SG, LaGamma EF, Reisen CE, et al. Early enteral feeding does not affect the incidence of necrotizing enterocolitis. *Pediatrics* 1986; **77**: 275–80.
85. Krousop RW. The influences of feeding practices. In Brown EG, Sweet AY, eds., *Necrotizing Enterocolitis*. New York:Grune & Stratton, 1980:57.
86. Book LS, Herbst JJ, Jung AL. Comparison of fast and slow-feeding rate schedules to the development of necrotizing enterocolitis. *J Pediatr* 1976; **89**: 463–6.
87. Goldman HI. Feeding and necrotizing enterocolitis. *Am J Dis Child* 1980; **134**: 553–5.
88. Anderson DM, Rome ES, Kliegman RM. Relationship of endemic necrotizing enterocolitis to alimentation. *Pediatr Res* 1985; **19**:331A.
89. Book LS, Herbst JJ, Jung AL. Carbohydrate malabsorption in necrotizing enterocolitis. *Pediatrics* 1976; **57**: 201–4.
90. Sweet AY. Necrotizing enterocolitis: feeding the neonate weighing less than 1500 grams – nutrition and beyond. In Sunshine P, ed., *Report of the 79th Ross Conference on Pediatric Research*. Columbus, OH: Ross Products Division, 1980.
91. Caple J, Armentrout D, Huseby V, et al. Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. *Pediatrics* 2004; **114**: 1597–600.
92. Kennedy KA, Tyson JE, Chamnanvanikij S. Early versus delayed initiation of progressive enteral feeding for parenterally fed low birth weight or preterm infants. *Cochrane Database Syst Rev* 2000; **2**:CD001970.

93. DeLemos RA, Rogers JH, McLaughlin GW. Experimental production of necrotizing enterocolitis in newborn goats. *Pediatr Res* 1974; **8**:380.

94. Book LS, Herbst JJ, Atherton SO, et al. Necrotizing enterocolitis in low-birth-weight infants fed an elemental formula. *J Pediatr* 1975; **87**: 602–5.

95. Willis DM, Chabot J, Radde IC, et al. Unsuspected hyperosmolality of oral solutions contributing to necrotizing enterocolitis in very-low-birth-weight infants. *Pediatrics* 1977; **60**: 535–8.

96. AAP Committee on Nutrition. Commentary on breast feeding and infant formulas including proposed standards for formulas. *Pediatrics* 1976; **57**: 278–85.

97. White KC, Harkavy KZ. Hypertonic formula resulting from added oral medications. *Am J Dis Child* 1982; **136**: 931–3.

98. Ernst JA, Williams JM, Glick MR. Osmolality of substances used in the intensive care nursery. *Pediatrics* 1983; **72**: 347–52.

99. Barnard J, Greene H, Cotton R. Necrotizing enterocolitis. In Kretchmer N, Minkowski A, eds., *Nutritional Adaptation of the Gastrointestinal Tract of the Newborn. Nestle Nutrition*, vol. **3**. New York: Raven Press, 1983: 103–28.

100. Udall JN. Gastrointestinal host defense and necrotizing enterocolitis. *J Pediatr* 1990; **117**:33–43.

101. Eibl MM, Wolf HM, Furnkranz H, et al. Prevention of necrotizing enterocolitis in low-birth-weight infants by IgA-lgG feeding. *N Engl J Med* 1988; **319**:1–7.

102. Foster J, Cole M. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low-birth-weight neonates. *Cochrane Database Syst Rev* 2004; **1**:CD001816.

103. Barlow B, Santulli TV, Heird WC, et al. An experimental study of acute neonatal necrotizing enterocolitis: the importance of breast milk. *J Pediatr Surg* 1974; **9**: 587–95.

104. Reisner SH, Garty B. Necrotizing enterocolitis despite breast-feeding. *Lancet* 1977; **ii**:507.

105. Kliegman RM, Pittard WB, Fanaroff AA. Necrotizing enterocolitis in neonates fed human milk. *J Pediatr* 1979; **95**: 450–3.

106. Stevenson DK, Yang C, Kerner JA, et al. Intestinal flora in the second week of life in hospitalized preterm infants fed stored frozen breast milk or a proprietary formula. *Clin Pediatr* 1985; **24**: 338–41.

107. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* 1990; **336**: 1519–23.

108. Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. *Pediatr Clin North Am* 1996; **43**: 409–32.

109. Sisk PM, Lovelady CA, Dillard RG, et al. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol* 2007; **27**: 428–33.

110. Kliegman RM, Fanaroff AA. Neonatal necrotizing enterocolitis: a nine-year experience. Epidemiology and uncommon observations. *Am J Dis Child* 1981; **135**: 603–14.

111. Lehmiller DH, Kanto WF. Relationship of mesenteric thromboembolism, oral feeding and necrotizing enterocolitis. *J Pediatr* 1978; **92**:96–100.

112. Hillman LS, Goodwin SL, Sherman WR. Identification and measurement of plasticiser in neonatal tissues after umbilical catheters and blood products. *N Engl J Med* 1975; **292**: 381–6.

113. Touloukian RJ, Kadaw A, Spencer RP. The gastrointestinal complications of umbilical venous exchange transfusion: a clinical and experimental study. *Pediatrics* 1973; **51**:36–42.

114. Davey AM, Wagner CL, Cox C, et al. Feeding premature infants while low umbilical artery catheters are in place: a prospective, randomized trial. *J Pediatr* 1994; **124**: 795–9.

115. Johnson L, Bowen FW, Abbasi S, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1500 grams or less. *Pediatrics* 1985; **75**: 619–38.

116. Kerner JA, Poole RL, Sunshine P, et al. High serum vitamin E levels in premature infants receiving MVI-Pediatric. *J Pediatr Perinat Nutr* 1987; **1**:75–82.

117. Neu J, Masi M, Stevenson DK, et al. Effects of asphyxia and oral gentamicin on intestinal lactase in the suckling rat. *Pediatr Pharmacol* 1981; **1**: 215–20.

118. Czyrko C, Del Pin CA, O'Neill JA, et al. Maternal cocaine abuse and necrotizing enterocolitis: outcome and survival. *J Pediatr Surg* 1991; **26**: 414–18.

119. Lopez SL. Time of onset of necrotizing enterocolitis in newborn infants with known prenatal cocaine exposure. *Clin Pediatr* 1995; **34**: 424–9.

120. Bauer CR, Morrison JC, Poole WK, et al. A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. *Pediatrics* 1984; **73**: 682–8.

121. Halac E, Halac J, Begue EF, et al. Prenatal and postnatal corticosteroid therapy to prevent neonatal necrotizing enterocolitis: a controlled trial. *J Pediatr* 1990; **117**: 132–8.

122. Muguruma K, Gray PW, Tjoelker LW, et al. The central role of PAF in necrotizing enterocolitis development. *Adv Exp Med Biol* 1997; **407**: 379–82.

.044

123. Thebaud B, Lacaze-Masmonteil T, Watterberg K. Postnatal glucocorticoids in very preterm infants: "the good, the bad, and the ugly." *Pediatrics* 2001; **107**: 413–15.

124. Crissinger KD. Pathogenesis of necrotizing enterocolitis. Workshop presented at the 25th Clinical Congress of A.S.P.E.N. Chicago: Clinical Congress of the American Society for Parenteral and Enteral Nutrition, 2001: 203–4.

125. Crissinger K. Understanding necrotizing enterocolitis: promising directions. *Pathophysiology* 1999; **5**: 247–56.

126. Kliegman R, Walker W, Yolken R. Necrotizing enterocolitis research agenda for a disease of unknown etiology and pathogenesis. *Pediatr Res* 1993; **34**: 701–8.

127. Caplan MS, Jilling T. The pathophysiology of necrotizing enterocolitis. *NeoReviews* 2001; **2**:e103–9.

128. Rabinowitz SS, Dzakpasu P, Piecuch S, et al. Platelet-activating factor in infants at risk for necrotizing enterocolitis. *J Pediatr* 2001; **138**: 81–6.

129. Gonzalez-Crussi F, Hsueh W. Experimental model of ischemic bowel necrosis: the role of platelet activating factor and endotoxin. *Am J Pathol* 1983; **112**: 127–35.

130. Chang H, Gonzalez-Crussi F, Hsueh W, et al. Prevention of experimental necrotizing enterocolitis with intestinal trefoil factor (ITF). *Gastroenterology* 2000; **118**:A197.

131. Becker RM, Wue G, Galanko JA, et al. Reduced serum amino acid concentrations in infants with necrotizing enterocolitis. *J Pediatr* 2000; **137**: 785–93.

132. Caplan MS, Miller-Catchpole R, Kaup S, et al. Bifidobacterial supplementation reduces the incidence of necrotizing enterocolitis in a neonatal rat model. *Gastroenterology* 1999; **117**: 577–83.

133. Butel MJ, Roland N, Hilbert A, et al. Clostridial pathogenicity in experimental necrotizing enterocolitis in gnotobiotic quails and protective role of bifidobacteria. *J Med Microbiol* 1998; **47**: 391–9.

134. Catala I, Butel MJ, Bensaada M, et al. Oligofructose contributes to the protective role of bifidobacteria in experimental necrotizing enterocolitis in quails. *J Med Microbiol* 1999; **48**:89–94.

135. Garg P. Necrotizing enterocolitis: newer insights. *J Clin Diagn Res* 2007; **1**:90–103.

136. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; **115**:1–4.

137. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; **147**: 192–6.

138. Kunz AN, Noel JM, Fairchok MP. Two cases of *Lactobacillus* bacteremia during probiotic treatment of short gut syndrome. *J Pediatr Gastoenterol Nutr* 2004; **38**: 457–8.

139. Munoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis* 2005; **40**:1625.

140. Barclay AR, Stenson B, Simpson JH, et al. Probiotics for necrotizing enterocolitis: a systematic review. *J Pediatr Gastroenterol Nutr* 2007; **45**: 569–72.

141. Hunter CJ, Upperman JS, Ford HR, et al. Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). *Pediatr Res* 2008; **63**: 117–23.

142. Carlson SE, Montalto MB, Ponder DL, et al. Lower incidence of necrotizing enterocolitis in infants fed a preterm formula with egg phospholipids. *Pediatr Res* 1998; **44**: 491–8.

143. Sonntag J, Grimmer I, Scholz T, et al. Growth and neurodevelopmental outcome of very low birthweight infants with necrotizing enterocolitis. *Acta Paediatr* 2000; **89**: 528–32.

144. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Developmental Neonatal Research Network, 1993–1994. *Pediatrics* 2000; **105**: 1216–26.

145. Akisu M, Baka M, Coker I, et al. Effect of dietary n-3 fatty acids on hypoxia-induced necrotizing enterocolitis in young mice: n-3 fatty acids alter platelet-activating factor and leukotriene B4 production in the intestine. *Biol Neonate* 1998; **74**: 31–8.

146. Rayyis SF, Ambalavanan N, Wright L, et al. Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *J Pediatr* 1999; **134**: 293–7.

147. La Gamma E, Browne L. Feeding practices for infants less than 1500 grams at birth and the pathogenesis of necrotizing enterocolitis. *Clin Perinatol* 1994; **21**:271–306.

148. Brown E, Sweet A. Neonatal necrotizing enterocolitis. *Pediatr Clin North Am* 1982; **29**: 114–70.

149. Schmolzer G, Urlesberger B, Haim M, et al. Multi-modal approach to prophylaxis of necrotizing enterocolitis: a clinical report and review of literature. *Pediatr Surg Int* 2006; **22**: 573–80.

150. Quan R, Yang C, Rubinstein S, et al. The effect of nutritional additives on anti-infective factors in human milk. *Clin Pediatr* 1994; **33**: 325–8.

151. Aynsley-Green A. Metabolic and endocrine interrelation in the human fetus and neonate. *Am J Clin Nutr* 1985; **41**:399–417.

152. Feng JJ, Kwong LK, Kerner JA, et al. Resumption of intestinal maturation upon reintroduction of intraluminal nutrients: functional and biochemical correlations. *Clin Res* 1987; **35**:228A.

153. Mascarenhas MR, Kerner JA, Stallings VA. Parenteral and enteral nutrition. In Walker WA, Durie PR, Hamilton JR, et al., eds., *Pediatric Gastrointestinal Disease*, 3rd edn. Ontario: Decker, 2000: 1705–52.

154. Zenk KE, Sills JH, Koeppel RM. *Neonatal Medications and Nutrition: A Comprehensive Guide*, 2nd edn. Santa Rosa, CA: NICU Ink Book, 2000: 527–8.

155. Bin-Nun A, Booms C, Sabag N, et al. Rapid fecal calprotectin (FC) analysis: point of care testing for diagnosing early necrotizing enterocolitis. *Am J Perinatol* 2015; **32**(04):337–342.

156. Fallon EM, Nehra D, Potemkin AK, et al. A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for necrotizing enterocolitis. *J Parenteral Enteral Nutr* 2012; **36**(5):5–6-523.

157. Abrams, SA, Schanler RJ, Lee ML, et al. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeed Med* 2014; **9**(6): 281–5.

158. Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *J Pediatr* 2013; **163**(6): 1592–5.

159. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr* 2010; **156**(4): 562–7.

160. Bertelli C, Pillonel T, Torregrossa A, et al. *Bifidobacterium longum* bacteremia in preterm infants receiving probiotics. *Clin Infect Dis* 2015; **60**(6): 924–7.

161. Repa A, Thanhaeuser M, Endress D, et al. Probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) prevent NEC in VLBW infants fed breast milk but not formula. *Clin Invest* 2015; **77**(2): 381–8.

162. Hartel C, Pagel J, Rupp J, et al. Prophylactic use of *Lactobacillus acidophilus/Bifidobacterium infantis* probiotics and outcome in very low birth weight infants. *J Pediatr* 2014; **165**(2): 285–9.

163. Jacobs SE, Tobin JM, Opie GF et al. Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. *J Pediatr* 2013; **132**(6): 1055–62.

164. Athalye-Jape G, Rao S, Patole S. Lactobacillus reuteri DSM 17938 as a probiotic for preterm neonates: a strain-specific systematic review. *J Parenter Enteral Nutr* 2015; **40**(6): 783–94.

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Chapter 44

Early Outcomes after Extremely Preterm Birth

Susan R. Hintz

Epidemiology and Survival after Extremely Preterm Birth

Preterm birth, defined by the World Health Organization (WHO) as delivery before 37 completed weeks of pregnancy, continues to be a growing problem for countries across the world [1]. Preterm birth remains a substantial problem for developed nations as well, although the landscape of prematurity appears to be changing. According to the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics, in the United States in 2013, the preterm birth rate (proportion of live births at less than 37 weeks estimated gestational age [EGA]) was 11.39%, which was down very slightly from the 2012 preterm birth rate of 11.55% [2]. Nevertheless, this represents a considerable decline from the preterm birth rate peak of 12.8% in 2006. Furthermore, rates of preterm birth have declined for each of the largest race and Hispanic-origin groups and for 49 of the 50 United States over that period. However, the proportion of infants delivered very preterm (<32 weeks' EGA) stands at 1.92%, which, although down from a peak of 2.04% in 2006 and 2007, remains relatively unchanged. Similarly, the extremely preterm birth rate (<28 weeks' EGA) is remarkably stable; in 2013, the extremely preterm birth rate was 0.73%, exactly the same as 2012 and 2011 and minimally changed from a peak of 0.77% in 2005. Although a decrease in overall preterm birth rate has been realized, and the very preterm and extremely preterm birth rates seem to be miniscule, the impact in terms of total births is important. Given the nearly 4 million births annually, approximately 450,000 infants less than 37 weeks' EGA, 75,000 very preterm infants, and 30,000 extremely preterm were born in 2013 in the United States alone [3].

Survival after Extremely Preterm Birth: Recent Cohorts

With advances in perinatal and neonatal care and changes in the approach to resuscitation, survival for extremely preterm infants has improved significantly in developed nations over the past decades. This survival benefit has extended to the most premature among the extremely preterm, those of less than 25 + 6/7 weeks' gestation, recently referred to as periviable" births in an executive summary of a Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) workshop on the topic [4]. Several recent studies describing survival rates for extremely preterm cohorts are highlighted below, and findings are summarized in Table 44.1.

- Among infants 22 + 0/7 to 28 + 6/7 weeks' EGA born in the NICHD Neonatal Research Network, consisting of large, academic quaternary-care centers selected by competitive National Institutes of Health (NIH) peer review, overall survival to discharge increased from 70% in 1993 to 79% in 2012 [5]. Survival to discharge in 2012 for infants from all sites increased with increasing gestational age from 9% at 22 weeks' EGA, 33% at 23 weeks' EGA, 65% at 24 weeks, 81% at 25 weeks, 87% at 26 weeks, 94% at 27 weeks, and 94% at 28 weeks. Adjusted survival increased between 2009 and 2012 most markedly for infants at 23 weeks (adjusted relative risk [RR] 1.09; 95% confidence interval [CI] 1.05–1.14) and 24 weeks (1.05; 95% CI 1.03–1.07), with smaller relative increases in survival noted between 2009 and 2012 among those 25 and 27 weeks' EGA. No survival changes were demonstrated for those 22, 26, or 28 weeks' EGA over the same time period.

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Table 44.1 Extremely Preterm Survival: selected Recent Cohorts

Author	Birth period	Gestational age in weeks						
		22	23	24	25	26	27	28
Stoll (2015)	2012	5/79 (6%)	34/122 (28%)	85/163 (52%)	153/225 (68%)	208/250 (83%)	238/283 (84%)	284/311 (91%)
Ancel (2015)	2011	0/58 (0%)	1/89 (1.1%)	58/186 (31%)	182/308 (59%)	311/413 (75%)	329/400 (82%)	411/457 (90%)
Zegers (2016)	2007–11			110/197 (56%)	358/493 (73%)			
EXPRESS (2009)	2004–7	5/51 (10%)	53/101 (52%)	96/144 (67%)	167/205 (81%)	176/206 (85%)		
Costeloe (2012)	2006	3/152 (2%)	66/339 (19%)	178/442 (40%)	346/520 (66%)	448/580 (77%)		
Doyle (2010)	2005	1/20 (5%)	7/22 (22%)	22/43 (51%)	31/46 (67%)	47/57 (82%)	64/72 (89%)	
Ishii (2013)	2003–5	27/75 (36%)	154/245 (63%)	256/332 (77%)	345/405 (85%)			

Note:
Stoll [5]: Survival to discharge among infants live born and inborn at a NICHD NRN hospital in 2012, 401–1,500 g.
Zegers [6]: Survival to initial hospital discharge among those admitted to NICU weighing 500 g or more at birth, without known congenital infection or anomalies.
EXPRESS [10]: Survival to 365 days among live born at 22–26 weeks or less. Note that infants born at 22 weeks or less are reported for this cohort.
Costeloe [12]: EPICure 2; survival to discharge among live-born infants at 22–26 weeks.
Doyle [17]: Survival to 2 years corrected age among live-born infants in the state of Victoria, Australia, in 2005, free of lethal congenital anomalies.
Ishii [18]: Survival to 3 years among live-born infants at 22 + 0/7 to 25 + 6/7 weeks' gestation, inborn or transferred to one of 48 tertiary centers in the Neonatal Research Network, Japan.
Ancel [15]: EPIPAGE-2; survival to discharge among live births at 22–34 weeks in France (only one region of France did not participate, representing less than 2% of all births).

- In the Netherlands, data from the Netherlands Perinatal Registry were used to examine survival among extremely preterm infants between two periods (2000–5 and 2007–11) before and after a relatively restricted pregnancy and newborn management national guideline had been modified toward more active treatment by the Netherlands Association of Pediatrics and the Netherlands Association of Obstetrics and Gynaecology in 2006, particularly for those 25 + 0/7 to 25 + 6/7 weeks' EGA [6]. Among those admitted to the NICU with birth weights of 500 g or more, mortality rates before discharge decreased significantly in the more recent period across gestational age groups (24 weeks: 70.8% versus 44.2%; 25 weeks: 46.5% versus 27.4%; 26–29 weeks: 13% versus 7.9%). In addition, the number of live-born infants and those admitted to a NICU was higher at all gestational ages during the more recent period; thus the total number of infants discharged from NICUs was higher as well. From these data, the downward shift in mortality appeared to begin even before 2006, suggesting that practice approaches had already started to change prior to modification of the guideline. Also of note, previously published data in the

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Netherlands from the nationwide survey Project on Preterm and Small for Gestational Age Infants (POPS) suggested that survival to discharge for infants 22–27 weeks' EGA was on the rise even in the 1990s [7].

- In Sweden, changes in approach to perinatal management and routine neonatal intervention also appear to have contributed to improved survival among extremely preterm and periviable infants. In an extremely low-birth-weight (ELBW) Swedish birth cohort from 1990–2 [8], only half the infants were born at a level III hospital, one-fifth were exposed to antenatal steroids, and among 23 and 24 weeks' EGA infants who were born alive, 8% and 28% survived to 1 year, respectively. In 2001, the Swedish National Board of Health and Welfare published a guideline that substantively changed the national approach to centralization of perinatal services for threatened extremely preterm delivery and encouraged individualized evaluation of the mother and infant rather than a gestational age–based threshold for care. Soon thereafter, two large regional tertiary care centers in Sweden published their findings after implementing active perinatal management strategies, reporting that survival to discharge for live-born infants 23–25 weeks' EGA increased from 55% to 78% from 1992 to 1998 [9]. The Extremely Preterm Infants in Sweden Study (EXPRESS) was subsequently launched, including all live-born infants less than 27 weeks' EGA and stillborn infants at 22 + 0/7 to 26 + 6/7 weeks delivered in Sweden from April 2004 to March 2007 [10]. Among live-born infants 23 + 0/7 to 26 + 6/7 weeks' EGA in this more recent era, 85–95% received antenatal steroids, 78–90% were delivered at a level III hospital, and survival to 1 year was 52% at 23 weeks, 67% at 24 weeks, 81% at 25 weeks, and 85% at 26 weeks.
- The EPICure studies were population-based, time-limited studies in the United Kingdom and Ireland to assess perinatal and neonatal approaches and to determine survival and neonatal morbidity and neurodevelopmental outcomes for extraordinarily preterm babies. The EPICure 1 collected data for all births in the United Kingdom and Ireland among those 22–25 + 6/7 weeks' EGA during 10 months in 1995 [11], and the EPICure 2 cohort collected data in England among live births at 22–26 + 6/7 weeks' EGA in 2006 [12]. Comparisons between cohorts were limited to those born at 22–25 + 6/7 weeks' EGA in England. Survival to discharge from hospital for all babies 22–25 + 6/7 weeks in England increased from 40% (266/666) to 53% (593/1115) over the two epochs, an increase of 13% (95% CI, 8–18%). Survival also increased at each week of gestation: by 9.5% (−0.1–19%) at 23 weeks, 12% (4–20%) at 24 weeks, and 16% (9–23%) at 25 weeks.
- The EPIPAGE-2 cohort study is a national population-based prospective study of infants born in France at 22–34 weeks' gestation during 2011 [13]. Only one region, representing less than 2% of all births in France, did not participate. Data were collected on all births, including live births and stillbirths. Among live births at 22–23 weeks, only one infant survived to discharge (1/147; 0.7%). However, survival to discharge among live births was 31% at 24 weeks, increasing to 75% by 26 weeks. For the entire 22–26 weeks' gestation group, survival to discharge among live births was 52.4% (552/1,054). Comparing EPIPAGE-2 to EPIPAGE-1 (1997 birth year) in similar regions, survival to discharge among live births did not improve at 22–24 weeks; however, there was significant improvement in survival at 25–29 weeks. Furthermore, survival without severe neonatal morbidity also increased from the 1997 to 2011 birth cohorts by 14%, indicating that 1/7 infants in this gestational age range had a more favorable in-hospital outcome in the more recent period. Follow-up for the EPIPAGE-2 cohort is planned through 12 years, which will provide a crucial longitudinal picture for the neurodevelopmental, behavioral, and functional outcomes through late childhood.
- In the state of Victoria, Australia, a series of population-based extremely preterm birth cohorts have been followed over the past three decades by the Victoria Infant Collaborative Study (VICS) Group, including 1991–2, 1997, and 2005 [14–17]. Survival to 2 years' corrected age for infants born 22 + 0/7 to 27 + 6/7 weeks' gestation increased from 56% for the 1991–2 to 70% for the 1997 cohorts and remained stable at 64% for the 2005 cohort. Survivals to 2 years for 1997 and 2005 were 45% and 22% at 23 weeks, 41%, and 51% at 24 weeks, and 77% and 67% at 25 weeks, although the absolute numbers are very small for the lowest gestational age groups (I). Of note, survival rates

for the 1997 ELBW birth cohort was quite high already compared with contemporary cohorts and increased significantly from 1985–7 and 1991–2 [15], reflective of a more consistently active management approach [14].

- The Neonatal Research Network of Japan reported the results of a 48 tertiary center study of 3-year survival and outcomes among live-born infants at 22 + 0/7 to 25 + 6/7 weeks' gestation born January 1, 2003 through December 31, 2005 [18]. Survival to 3 years for this group overall was 74% (782/1057), with survival rates of 36% at 22 weeks, 63% at 23 weeks, 77% at 24 weeks, and 85% at 25 weeks.

Evolution of Perinatal and Neonatal Approach

Over the full breadth of neonatal intensive care history from the 1950s, certainly some of the most substantial factors contributing to the remarkably improved survival rates for extremely preterm infants have been related to enormous scientific progress leading to development of perinatal and neonatal treatments and technologies. However, it is difficult to point to any specific paradigm-shifting advance in therapies that could explain the more recently reported improvements in survival rates among the most extremely preterm infants. Nonetheless, the stance toward active antepartum, intrapartum, and neonatal intervention and the accompanying counseling approach with expectant mothers and families may be increasingly influential. The shifts and variations in decision making around application of perinatal and neonatal advanced treatment options, particularly among those in the "periviable" gestational age range, may at least in part explain observed regional and national differences in survival rates and in reported changes in survival rates over time. For example, the treatment guidelines concerning extremely preterm births (22 + 0/7 to 25 + 6/7 weeks) in the Netherlands were, until 2006, quite restrictive [6]. After modification of the national Dutch guideline toward more active management of pregnancies and newborns at 25–26 weeks' EGA, improved survival was noted to be concomitant with increased rates of those inborn at a hospital with a high-level NICU (24 weeks: 2000–5 = 61.1% versus 2007–11 = 94.9%; 25 weeks: 2000–5 = 70.5% versus 2007–11 = 90.2%) and was also accompanied by increased rates of live births. In comparison, in Victoria, Australia, an active management stance has been consistently taken since the late 1990s, with the majority of live-born infants of 23 and 24 weeks' gestation and virtually all those 25 and 26 weeks' gestation being offered intensive care intervention [14]. Contrary to concerns for increasingly adverse later outcomes particularly for extraordinarily preterm survivors, the VICS group not only reported increased survival rates but also increased quality-adjusted survival rates through the 1990s [14,17]. A more proactive approach to initial and early neonatal management was also suggested in the findings of the EPICure studies [12]. The improved survival seen in EPICure 2 compared with EPICure 1 can be entirely explained by improved survival in the first week after birth; the probability of survival among those who survived beyond the first 7 days was no different between the two EPICure epochs at 23, 24, or 25 weeks' gestation. Survival for infants in the EPICure 2 cohort was also noted to be greater when birth occurred at hospitals with level III neonatal services and further improved among those with higher-activity neonatal services [19]. Similarly reflective of differences in initial management, in the EXPRESS cohort there were large regional differences in the rate of death before 12 hours after birth in both the 22 and 24 weeks' EGA patients and for the 22–27 weeks' EGA group overall [10]. Importantly, there were no differences in 365-day mortality among regions for infants alive at 12 hours, and the rate of major neonatal morbidities among survivors at 1 year did not differ between the regions. In the Japanese Neonatal Research Network, 21% and 32% of those at 22 and 23 weeks' gestation, respectively, received antenatal steroids, only 8% of infants at 22 or 23 weeks' gestation were outborn, and 24% and 42% of infants at 22 or 23 weeks' gestation were delivered by cesarean section, consistent with a more active perinatal and intrapartum approach [18]. Similar findings related to perinatal interventions have been published by Ochiai, et al. [20]. Among 22–24 weeks' EGA infants live born at a single tertiary center in Japan, 32% received antenatal steroids, 54% were delivered by cesarean section, 86% were intubated at birth, and 71% received surfactant in 2005–9 compared with 6%, 38%, 78%, and 59% in 2000–4. Survival rates in this group increased from 52% to 79% between the two periods.

There is very little doubt that improved survival rates have been demonstrated even for extraordinarily preterm infants with a more proactive stance toward perinatal and neonatal management, but the

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question has consequently been posed whether the comprehensive costs associated with extremely preterm birth and its sequelae can be justified. Predicting outcomes such as survival with information known prenatally has been refined beyond the use of gestational age only, yet there remains substantial variability particularly for the most preterm infants [21,22], a finding likely influenced by center-based practice differences [23]. Among extremely preterm infants, prediction of specific postmenstrual age at NICU discharge is poor, although prediction of early or late hospital discharge is improved with knowledge of later occurring morbidities [24]. Similarly, prediction of death or early neurodevelopmental impairment is improved with dynamic models using information available later during the NICU course [25]. Attempts to estimate the economic consequences of hospitalizations and services are also challenging, and analyses may not be comparable with other regions, but financial resource utilization is not surprisingly estimated to be significantly greater for preterm than term children [26,27]. Nevertheless, in a regional economic analysis of quality-adjusted survival, Doyle demonstrated that the economic efficiency of neonatal intensive care among ELBW infants to 2 years of age has not declined significantly over two decades, with similar costs per quality-adjusted life-year gained over time [16]. Although important to consider in a societal sense, such academic economic considerations have little impact for medical providers as they counsel families or for families as they consider the circumstances of their infants. In these cases discussion around "comprehensive costs" often and appropriately focuses on the potential neurodevelopmental and functional sequelae of preterm birth. For families and other medical decision makers, knowledge of the range of outcomes beyond the neonatal period, as well as the often profound limitations of our ability to predict outcomes for an individual child, are critical components in approaching an understanding of the possible implications and consequences of extremely preterm birth. It is also important to recognize the impact of our own biases both in our approach to prenatal counseling and in our interpretation of the relative values of outcomes to families [28].

Many hundreds of neurodevelopmental and functional outcome studies of preterm infants have been published over the past five decades ranging from small or single-center cohorts to multisite observational analyses to follow-up after neonatal intervention. We do not attempt to present a comprehensive review of all published neurodevelopmental outcome studies in the following sections of this chapter, but rather we will concentrate on results from larger cohorts and regional population-based studies, presenting more recent data whenever possible. Furthermore, although the focus will be on early neurodevelopmental outcomes (18 months to 3 years), we fully recognize that evaluation at this point in time represents only a tiny and incomplete view into the future of a child. Very early neurodevelopmental outcomes certainly do not capture the myriad successes and challenges ahead for children at school age, adolescence, and beyond, nor do scores or categories of outcomes describe the joy a child can bring to a family or the impact of the difficulties they face together. Later childhood outcomes, including language and speech, academic skills, executive skills, and behavioral disorders, are reviewed in Chapter 46.

Early Neurodevelopmental Outcomes

Challenges and Limitations of Very Early Neurodevelopmental Outcome Evaluation

Neurodevelopmental outcome assessments in prospective studies of extremely preterm infants have often taken place during the toddler period or in very early childhood (18 months of age corrected for prematurity to 3 years). At this age, a battery of examinations and tests can be performed, including neurosensory and neurologic examinations to assess for blindness, deafness, and cerebral palsy (CP) and standardized cognitive and psychomotor assessments such as the Bayley Scales of Infant Development (BSID). Although these evaluations may be important and informative, interpretation and comparison of studies are difficult. Many studies report outcomes by categories and frequently combine any adverse finding from various aspects of the overall visit to attain an "impaired" or "not impaired" status. The definitions of *adverse* outcomes may not be consistent across studies; indeed, the definitions of the individual components of *impairment* such as CP, blindness, deafness, and developmental delay may also differ across studies. Furthermore, not all prospective studies have enrolled contemporaneous term, normal-birth-weight controls. Comparing test scores from a very or extremely preterm study group with standardized norms instead of scores from a peer, term-born control group has been demonstrated to substantively limit the relevance and veracity of the

findings and may have important public policy and resource implications [17,29–32].

Very early childhood developmental and neurologic outcome evaluations should only be considered as a first step to comprehensive follow-up; assessments into school age, adolescence, and adulthood are critically important to understand the functional and societal outcomes of former preterm infants [33–39]. Concerns regarding changes in cognitive abilities over time and an increasing recognition that physical and environmental effects as well as early intervention approaches may modify recovery underscore the need for later assessments [40–42]. Some neurocognitive, executive function, and behavioral challenges may only be detected at school age; even recognizing that such learning and attention problems may occur in preterm infants is a critical step to ensuring adequate support and services for families and teachers to help children achieve their best possible outcomes. Evaluation of neuromotor outcomes throughout childhood is also critical. Although most toddler age and very early childhood outcome studies focus narrowly on the diagnosis of CP, later neuromotor and coordination problems, such as developmental coordination disorder (DCD), are prevalent among school-age children born extremely preterm compared with term and can be associated with other functional challenges and academic difficulties [43,44]. Furthermore, parental perceptions of DCD are not reliable, yet interventions may be able to remediate the functional limitations of DCD, reiterating the importance of ongoing clinical assessments throughout childhood [44]. Similarly, there are substantial concerns regarding the ability of the newest version (third edition) of the BSID (BSID-III) [45] to detect developmental delay in children born preterm when using standardized test norms, as well as the validity of this very early childhood cognitive assessment tool to predict later childhood neuromotor and developmental impairments. In a group of extremely preterm and ELBW infants at 2 years of age corrected for prematurity, Anderson et al. found mean scores on Cognitive Composite of 96.9 and Motor Composite of 100.4 but also substantially higher than expected scores among a term-born control group [30]. If normative BSID-III cut-point criteria alone were applied to the scores of this extremely preterm cohort, it would severely underestimate moderate to severe cognitive and motor delay relative to the control group. Vohr et al. compared mean BSID-II versus BSID-III scores at 18–22 months corrected for prematurity among infants less than 27 weeks' EGA born in NICHD Neonatal Research Network hospitals over two adjacent periods and found mean Cognitive Composite scores on BSID-III to be 11 points higher than mean BSID-II MDI scores [46]. Even after adjusting for differences between groups, BSID-III was a significant factor in a perceived decrease in neurodevelopmental impairment in the more recent time period. Dilemmas also exist with regard to meaningful use of BSID-III Motor Composite and Fine Motor Scaled Score normative data and cut-points in the context of other gross motor assessments at 18–24 months' corrected age and the value of these early evaluations to predict later outcomes and intervene appropriately [47]. In a prospective longitudinal extremely preterm cohort from the VICS group, the BSID-III Motor Scale normative cut-points for impairment at 2 years seriously underestimated rates of motor impairment at 4 years [48]. In addition, although the BSID-III Cognitive and Language Scales at 2 years were associated with cognitive functioning at 4 years as assessed by the Differential Ability Scale, 2nd edition (DAS-II), developmental delay at 2 years as determined by BSID-III reference data and normative cut-points had low sensitivity in predicting future cognitive, verbal, and nonverbal reasoning impairments at 4 years [49]. As with previous findings from the VICS group at 2 years [30], the use of peer, term-born reference data improved the identification of children who went on to have later impairment. Following the findings from a study of 185 children born at 22–26 weeks' gestation in England who were administered both BSID-II MDI and BSID-III Cognitive and Language Scales, Johnson et al. suggested using BSID-III cut-points of less than 85 or combined Bayley-III score of less than 80 to identify developmental impairment similar to BSID-II for study primary outcomes [50]. Yet all these findings have important implications for resource availability and public policy. In countries, states, or regions without specific policies advocating for ongoing longitudinal assessments and services for children born extremely preterm, the 2- or 3-year evaluation may be the final opportunity to identify challenges before transitioning to the school system. If ongoing needs are determined only by scoring below a normative cut-point on the BSID-III, many children at significant risk for future impairments could be left behind.

Despite these many challenges and provisos, a substantial body of literature exists on early neurologic and cognitive outcomes. An understanding of the

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range of initial neurodevelopmental outcomes and the factors associated with adverse outcomes is crucial for both the family and the medical care team. In the following sections we will focus our attention on early neurodevelopmental outcomes from selected cohorts and recent data.

Early Neurodevelopmental Outcome Studies

The Victoria Infant Collaborative Study Group (VICS Group)

The VICS Group has reported on a series of birth cohorts of extremely preterm infants in Victoria, Australia. For the purposes of this chapter, we will focus on the early outcomes of the most recent published cohorts, born during 1997 and 2005, although we will also review data comparing outcomes back through the 1991–2 birth cohort (see Table 44.2) [16,17]. All live-born infants at 22–27 completed weeks of gestation born in Victoria in 2005 were included. Survivors received neurodevelopmental assessment at 2 years of age corrected for prematurity (1991–2: n =219, 97% of survivors; 1997: n = 149, 99% of survivors; 2005: n = 163, 95% of survivors). Importantly, and as noted previously in this chapter, contemporaneous normal birth weight (NBW) controls at greater than 36 weeks' gestation were enrolled and evaluated. Impairments evaluated included blindness, deafness (hearing loss requiring amplification or worse), and developmental delay. Development was assessed using the BSID, and cognitive and language composite scores were obtained relative to the mean and standard deviation (SD) for the NBW controls rather than the normative test scores and cut-points alone. Neurologic examination for CP was also performed using the Gross Motor Function Classification System [51] to delineate severity, describing "severe" CP as unlikely ever to walk and "moderate" CP as unable to walk at 2 years but likely to walk. Overall disability was considered "severe" for children with severe CP, blindness, or severe developmental delay; "moderate" with moderate CP, deafness, or moderate developmental delay; and "mild" with mild CP or mild developmental delay. To describe a *quality-adjusted survival rate*, survivors were also assigned "neurosensory utilities" according to the severity of the functional disability associated with impairments (0.4 for severe, 0.6 for moderate, 0.8 for mild, and 1 for no disability). Infants who died were assigned a utility of 0. [16,52).

Neurodevelopmental outcomes of the 2005 VICS cohort at 2 years of age corrected for prematurity are shown in Table 44.2. Comparing 1991–2, 1997, and 2005 cohorts, rates of CP, blindness, deafness requiring a hearing aid, developmental delay, and neurosensory disability were not significantly different across all eras, although those in 2005 were less likely to have most of these outcomes. Of note, for the 1991–2 and 1997 cohorts, rates of any CP were 11% and 12.1%, whereas for the 2005 cohort, the CP rate had decreased to 9.8%. Similarly, the 2005 cohort had significantly lower rates of severe developmental delay (3.7%) and severe neurologic disability (3.7%) than the 1997 cohort (14.8% and 15.4%), who, in turn, had significantly higher rates of these problems than the 1991–2 cohort (7.3% and 7.8%). Moderate or severe developmental delay and moderate or severe disability also were similar across all cohorts, with a decrease noted between 1997 and 2005 but an increase from 1991–2 to 1997 (moderate or severe developmental delay: 1991–2: 18.3%; 1997: 24.2%; 2005: 16%; moderate or severe disability: 1991–2: 21%; 1997: 28.2%; 2005: 20.3%). Given these findings, it is not surprising that the mean utility per survivor was higher (better) in 2005 than in either of the previous two cohorts at each gestational week from 22 to 26 weeks. Quality-adjusted survival increased with each gestational week, was greater for the 1997 cohort than for the 1991–2 cohort, and was stable between 2005 and 1997. Focusing on the 2005 cohort, the BSID-III cognitive and language composite mean scores were much higher than would be anticipated for the extremely preterm cohort (97.5 and 93.9) but also higher for the control cohort (108.9 and 108.2); developmental delay for the extremely preterm group would have been greatly underestimated had they not been evaluated relative to a term control group. Nevertheless, more than half the extremely preterm 2005 cohort had no developmental delay (52.1%) and no disability (50.9%) at 2 years. Thus these regional population-based studies reveal that although survival rates and quality-adjusted survival for 22–27 weeks' EGA infants increased through the 1990s and appears to have stabilized through the 2005 cohort, rates of severe delay and disability at 2 years appear to have improved from those of the late 1990s. This group of investigators has also contributed substantially to our understanding of longer-term outcomes of children

Table 44.2 Early Neurodevelopmental Outcomes of Selected Extremely Preterm Cohorts

	VICS 2005	EPICure 2	EXPRESS	Japan NRN	NICHD NRN	NICHD NRN
Study group description	22–27 + 6/7 weeks' EGA	22–26 + 6/7 weeks' EGA	<27 weeks' EGA	22–25 weeks' EGA	<25 weeks' EGA	22–26 weeks' EGA
Birth cohort	2005	2006	2004–7	2003–5	2002–4	2006–11
Age at follow-up corrected for prematurity	2 years	3 years	2.5 years	36–42 months (chronological)	18–22 months	18–22 months
Number (% follow-up of eligible survivors)	163 (95%)	576 (55%)[a]	415 (90%)	562 (72%)	405 (93%)	2,630 (92%)
Outcomes						
Blind	0	1%	0.9%	4.6%[b]	2.2%	0.4%
Deaf/require aids	2.5%	Not improved by aids: 0.2%; improved by aids: 5%	Not improved by aids: 0.2%; improved by aids: 0.7%	Requires aids: 1.7%	4.3%	1.4%
Developmental impairment	DQ[c] None/≤1 SD: 52% 1–2 SD: 32% 2–3 SD: 12% >3 SD: 4%	Predicted MDI[c] 70–84: 34% <70: 30%	Cognitive/language[c] None: 55% Mild: 25% Moderate: 11% Severe: 9%	KSPD DQ[c] <70: 35% <50: 11%	BSID-II MDI < 70: 51% MDI < 50: 19%	Bayley-III Cognitive 70–84: 16.5% <70: 9.3%
CP or motor delay	Any CP: 9.8%	Any CP: 14% Moderate motor: 3% Severe motor: 5%	Mild: 2.9% Moderate: 2.9% Severe: 1.3%	Any CP: 13.7% Profound CP: 8.2%	Moderate: 8.7% Severe: 6.2%	Moderate: 3.4% Severe: 2.5%
Overall disability or impairment	None: 51% Mild: 29% Moderate: 16% Severe: 4%	None/mild: 75% Moderate: 12% Severe: 13%	None: 42% Mild: 31% Moderate: 16% Severe: 11%	Any: 42.4%[d] Profound: 22.6%[d]	Any NDI: 58.5% Profound NDI: 17.5% None/minimal: 21.9%	Moderate NDI: 23.5% Severe NDI: 13.6%

[a] Face-to-face study examiner evaluations occurred in 55.3%. Multiple imputation from complete perinatal, neonatal, and sociodemographic information estimated outcomes for the entire cohort.

[b] Defined as no functional vision in one or both eyes.

[c] For VICS: DQ = developmental quotient compared with a contemporaneous NBW control group; for EPICure 2: predicted MDI (Mental Developmental Index) BSID-II from Bayley-III; for EXPRESS: aggregated Bayley-III cognitive and language score information, with mean and SD relative to a contemporaneous 37–41 weeks' GA control group; for Japan NRN: formal evaluation by the Kyoto Scale of Psychological Development (KSPD) was available for only 318.

[d] Includes 173 with informal assessments of developmental delay by pediatricians without formal developmental testing

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born extremely preterm through extended follow-up on these cohorts and have published extensively on school-age, adolescent, and young-adult outcomes [53–56].

EPICure 2

The EPICure 2 Study is a population-based mortality, morbidity, and neurodevelopmental outcome study [12,57]. All infants born at 22–26 + 6/7 weeks' gestation in England during 2006 were identified, and as noted previously, data were collected regarding death and morbidities from the delivery room through hospitalization [12]. Comparisons between EPICure 1 [11] (1995 birth cohort) and EPICure 2, both on short-term and neurodevelopmental outcomes, were limited to those 22–25 + 6/7 weeks' gestation and born in England. For EPICure 2, follow-up was hampered by changes in national research governance procedures in the United Kingdom and increased privacy restrictions by the National Health Service. Therefore, tracking success was substantially limited in comparison with the previous study, and multiple imputation was therefore used to estimate outcomes of patients lost to follow-up. Follow-up assessment for EPICure 2 occurred at a target age of 36 months rather than 30 months, as had been the case for EPICure 1. Evaluation of developmental outcome was by the BSID-III. In order to directly compare results from the EPICure 1 cohort (which used BSID-II) with the EPICure 2 cohort, combined BSID-III scores were converted to "predicted MDI" [58]. Evaluation of disability included a detailed neurologic examination for CP using the Gross Motor Function Classification System (GMFCS) to assign severity [51]. *Severe impairment* was defined as nonambulant CP (GMFCS 3–5), blindness, profound hearing loss, or a developmental quotient less than 3 SD below the mean for age. *Moderate impairment* was defined as ambulant CP (GMFCS 2), functionally impaired vision, hearing loss improved by aids, or a developmental score 2–3 SD below the mean. Of note, the definitions for impairment or disability differed slightly between the 1995 and 2006 cohorts.

EPICure 2 study outcomes are shown in Table 44.2. Of the 1,031 children in EPICure 2 who survived to follow-up age (1,041 survivors to discharge, 10 died after discharge), study examiners evaluated 576 (55.3%, median 34 months), and information from an additional 191 was available from local records (18.3%, median 25 months). The group evaluated face to face was similar to those without a formal study evaluation in terms of perinatal and neonatal factors, but socioeconomic factors differed; children from families with greater social disadvantage were less likely to have had formal study evaluation. Among the EPICure 2 group with formal study evaluations, 75% were free from overall impairment or had mild impairment only. Survival without disability for the entire EPICure 2 cohort, including imputed outcomes, among those admitted to the NICU demonstrated increases with each week in gestational age (22 weeks: 5%, 95% confidence interval [CI] 0–26%; 23 weeks: 15%, 95% CI 10–21%; 24 weeks: 30%, 95% CI 25–35%; 25 weeks: 49%, 95% CI 43–55%; 26 weeks: 62%, 95% CI 57–67%), and 66% had no hearing, vision or communication disability, but only 36% of children were reported to have no developmental disability (BSID-II score > 85). However, robust comparisons are difficult given that patient numbers were quite small, particularly for the 23 weeks' or less EGA group. This finding underscores the grave prognosis for survival among the most premature infants in this cohort; only 18% of 23 weeks' or less EGA infants admitted alive to a NICU survived to discharge compared with 48% of 25 weeks' EGA infants. Autism screening with the Modified Checklist for Autism in Toddlers (M-CHAT) was also performed in 523 of the EPICure 2 cohort, showing that 41% of this group had positive screens [59]. Although this prevalence rate is higher than that reported by others [60,61], those other groups included infants of more advanced gestational age.

EXPRESS (Sweden)

The EXPRESS cohort (birth year 2004–7, <27 weeks' gestation) was followed to a median of 30.5 months, at which point Bayley-III, clinical neurologic examinations and parental/ primary care provider questionnaires were administered [62]. Of 707 live-born infants, 491 survived to follow-up (69%), and 415 of 461 who were eligible for inclusion were formally assessed (90% follow-up rate), with 399 of those having any part of the Bayley-III. Chart review was available for 41 additional children. Not surprisingly, the composition of cohort of 456 extremely preterm children with either formal assessment or chart review was skewed to higher gestational age, with 33% of the group 25 weeks' gestation and 36% 26 weeks' gestation. Only 52 (11%) were 22 or 23 weeks' gestation. Of importance, a control group (37–41 weeks' gestation, 2:1 match with preterm group) was recruited by random selection from the

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Swedish Medical Birth Registry. Severe disability was defined as Bayley-lll composite cognitive, language, or motor score greater than 3 SD below the mean *relative to the control group*, severe CP, or bilateral blindness or deafness. Moderate disability was defined as scores between 2 and 3 SD from the mean of any of the Bayley-III scales, moderate CP, and moderate visual or hearing impairment. Mild disability was defined as scores between 1 and 2 SD from the mean of any of the Bayley-lll scales or mild CP.

Highlights of results are summarized in Table 44.2. Of children born extremely preterm, only 11.3% had moderate or severe disability by Bayley-III cognitive composite (relative to mean and SD of control scores) compared with 0.5% of control. When considering cognitive, language, or motor scores, 15% of extremely preterm and 3% of control had moderate disability, and 8.9% of extremely preterm and 0.3% of control had severe disability. The proportion of children with mild or no disabilities increased from 40% at 22 weeks to 83% at 26 weeks. There was a significant decrease in severe disabilities with each increase in gestational week, with an odd ratio (OR) of 0.58 (99% CI 0.39–0.86, $p < 0.001$). Overall, 42% of the extremely preterm children in this group had no disability as defined at 30 months compared with 78% of control children. The majority of the 58% of extremely preterm children had mild disability (31%). In a further analysis of these data, Serenius et al. explored whether intensity of perinatal care in regions across Sweden was associated with an increased risk of death or neurodevelopmental impairment (NDI) at 2.5 years [63]. The investigators found significant variation in obstetric and neonatal intervention activity scores. In regions with higher activity scores (i.e., more aggressive perinatal intervention practices), the risk of death or NDI at 2.5 years was reduced, but only for 22–24 weeks group. Furthermore, there was no increase in NDI among survivors associated with increased perinatal activity scores.

Japan Neonatal Research Network

The Neonatal Research Network of Japan reported outcomes for infants of 22 through 25 weeks' gestation live born during 2003–5 [18]. Neurodevelopmental assessments were performed at 36–42 months' chronological age and consisted of neurologic examination, functional assessment for vision and hearing, and cognitive evaluation by the Kyoto Scale of Psychological Development (KSPD). A developmental quotient (DQ) was derived, with a mean ± SD score of 100.6 ± 13.4. Neurodevelopmental impairment for this study was defined as any of CP with GMFCS 2–5, hearing impairment, visual impairment, or KSPD DQ score of less than 70. Profound impairment was defined as DQ less than 50 or CP with GMFCS 4 or 5.

Highlights of outcomes are shown in Table 44.2. Among 782 children surviving to 3 years, 562 (71.9%) were evaluated in any follow-up visit. Follow-up rate among survivors declined over gestational age weeks, from 85.2% (23/27) for those born at 22 weeks to 69.6% (240/345) for those born at 25 weeks' gestation. Among those examined, CP of any severity was diagnosed in 13.7%, profound CP was seen in 8.2%, with higher rates noted at lower gestational ages (22 weeks: 17.4%; 23 weeks: 10.2%). Only 318 children were formally assessed by the KSPD (56.6% of those followed), whereas 173 were evaluated as delayed or not delayed by judgment of a pediatrician. If judged as "delayed" by a pediatrician, the DQ was assumed to be less than 50 for the purposes of this study; therefore, rates of profound NDI or profound developmental delay may be overestimated when including these informal evaluations. Among those formally assessed, 34.6% had developmental delay of any severity (KSPD DQ < 70), and 11% were profoundly delayed (KSPD DQ < 50). For the children evaluated by pediatrician only, 37% were assessed as delayed. Overall, when including any assessment, NDI of any severity was reported for 208/491 (42.4%) of survivors. The composite outcome of death or any NDI was seen in 45.7% (483/1,057) and death or profound NDI in 36.5% (386/1,057).

Eunice Kennedy Shriver NICHD Neonatal Research Network Follow-Up Study

The NICHD Neonatal Research Network (NRN) was initiated in 1986 as a multicenter effort in the United States with the main objective of providing a registry of uniformly collected baseline and morbidity and mortality data information to provide the basis for planning and implementing clinical trials. The NICHD NRN Follow-up Study Group was later added to provide neurodevelopmental follow-up for trials and for those meeting NRN Follow-Up Study criteria, which now includes infants of less than 27 weeks' gestation. Numerous analyses have been published by this group, but for the purposes of this chapter we will focus on only a few recent studies evaluating extremely or extraordinarily preterm outcomes.

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The NICHD NRN reported 18–22 months' corrected-age outcomes of infants born at an NRN site at less than 25 weeks' gestation during two epochs, 1999–2001 (epoch 1) and 2002–4 (epoch 2) [64]. The follow-up visit during that period included administration of BSID-II MDI and PDI, as well as neurosensory and gross motor functional assessments (GMFCS). Examinations were performed by certified examiners, who were trained in annual 2-day workshops to ensure reliability. Moderate to severe CP included children who were nonambulatory or required assistive devices. Neurodevelopmental impairment (NDI) was defined as MDI or PDI of less than 70, moderate to severe CP, bilateral blindness (absence of functional vision in both eyes), or bilateral severe hearing loss requiring amplification. Profound NDI was defined as MDI of less than 50 or GMFCS level 4 or 5. Unimpaired or minimally impaired was defined as having none of the following: moderate to severe CP, bilateral severe hearing loss or blindness, and MDI or PDI of less than 85. Follow-up rates for both epochs were approximately 90%. Only about 25% of both epoch follow-up groups were composed of children born at 23 weeks' gestation or less. Although results showed an apparent absolute increase in NDI of 50.1–58.7% from epoch 1 to epoch 2, epoch was not found to be associated with NDI on multivariable analyses adjusting for baseline variable differences between the groups. Profound NDI was not increased between epoch 1 (16.8%) and epoch 2 (17.5%). Rates of adverse outcomes were higher for children of 23 weeks' gestation or less than for those of 24 weeks' gestation for both epochs, although patient numbers were small for rarer outcomes. Despite more aggressive perinatal management with increased cesarean section delivery (40.9–48.8%) and a dramatic reduction in postnatal steroid use (63.5–32.8%) from epoch 1 to epoch 2, no significant improvement in neurodevelopmental outcomes were observed. However, this study differed from others in that it narrowly focused on infants of less than 25 + 0/7 weeks, and they were evaluated at an earlier age. The difference of just a few months at time of evaluation for children born extraordinarily preterm may substantially alter findings. Of note, since this study, the NICHD NRN has changed the window for follow-up to 22–26 months' corrected age. Furthermore, these cohorts are not population based but rather representative of several academic centers. As with previous studies and analyses from this group [65], center differences in outcomes were also observed, suggesting that practice variability beyond what can be explained by perinatal risk factors and neonatal morbidities may play an important role.

Between-hospital variation in outcomes was further explored by Rysavy et al. among infants born at an NRN site at less than 27 weeks' gestation between 2006 and 2011, assessing survival and NDI at 18–22 months [23]. During this period, the Bayley-III was used. Impairment was defined as earlier, with the exception that Bayley-III cognitive scores of less than 70 were included in the severe NDI definition, and scores of 70–84 were included in the moderate NDI definition. Outcomes were evaluated in relation to hospital rates of "active treatment," defined as potentially lifesaving treatments initiated after delivery. For all infants, overall rates of survival without severe impairment were (mean) 3.4%, 17.9%, 44.7%, 61.1%, and 75.6% for 22, 23, 24, and 25 weeks' gestation. However, there were significant differences among hospital rates of active treatment for those born at 22, 23, and 24 weeks that accounted for a substantial proportion of variation in outcomes for children born at that gestational age range. The Bayley-III was used during this study period, which is of importance in evaluating absolute rates of impairment in this study and in comparing these results with those of previous NRN analyses. Furthermore, there was no control group. As noted previously, using the Bayley-III test cut-points alone has been reported to underestimate impairment in extremely preterm infants [30,46].

Swiss National Extremely Preterm Cohort

The Swiss National Extremely Preterm Cohort Study was a prospective, longitudinal study of infants live-born between 24 + 0/7 and 27 + 6/7 weeks' gestation in Switzerland between 2000 and December 31, 2008 [66]. Follow-up was at 18–24 months' corrected age, and outcomes were included only if follow-up was performed at sites using the BSID-II. Severe disability was defined as CP with GMFCS level 3–5, or MDI or PDI of less than 55, or absence of useful hearing even with aids, or bilateral blindness. Moderate disability was defined as CP with GMFCS level 2, or MDI or PDI of 55–69, or hearing loss corrected with aids, or moderately reduced vision but better than severe, or unilateral blindness with good vision in the contralateral eye. Of 1,266 live-born infants, 844 survived to 18–24 months, of whom 684 had follow-up (81%). For the cohort overall, 166 (24.3% of those with 18- to 24-

month follow-up) were reported to have moderate disability, and 78 (11.4%) had severe disability. In a previous report from this group that included infants in this cohort born to December 31, 2007 [67], data regarding CP were reported. Of the 541 children at 18–22 months' corrected age with follow-up in that group, 41 (7.6%) were reported to have CP of any severity.

Neuroimaging Findings Associated with Neurodevelopmental Sequelae

A number of perinatal, neonatal, and sociodemographic variables have been linked with early childhood neurologic and developmental disability in preterm infants. Outcomes may be influenced by an enormous array of biologic, environmental, and iatrogenic factors. Furthermore, the risk factors themselves may be associated with other variables, and one factor may modify or potentiate the effect of others; therefore, analyses can be complex and challenging to interpret despite the efforts of investigators to consider confounders. Furthermore, as touched on previously, there are substantial site and regional variations in early outcomes that have yet to be fully understood or elucidated. Nevertheless, several variables have been consistently recognized to be associated with adverse neuromotor outcomes and overall impairment in early childhood among ELBW and very preterm infants.

The objectives of neurodevelopmental outcome studies are not only to provide information to help better predict outcomes but, more important, to identify factors associated with adverse outcomes that may be modifiable. Recognition of such factors serves as a stimulus for further translational and clinical research, with the hope of uncovering the biologic basis of the connection and with the ultimate goal of changing care paradigms to improve long-term outcomes for preterm infants.

Brain Injury

Cranial Ultrasound

Cranial ultrasound (CUS) has been used to image preterm infant brain injury since the late 1970s [68,69]. Given the modality's portability, ease of repeatability, noninvasive technique, and the development of a standardized grading system for intracranial hemorrhage (ICH) [70], CUS quickly became and remains the neuroimaging standard of care for preterm infants [71] (see Chapter 24). Although many clinicians still seem to rely heavily on simply the presence of grade 3 ICH, intraparenchymal hemorrhage (IPH), or cystic periventricular leukomalacia (PVL) to counsel families about the neurodevelopmental outcomes of their preterm infants, the complexity of interpretation of CUS findings and limitations of prediction of outcomes with any single neuroimaging or other finding should give clinicians cause for prudence and careful consideration.

CUS Abnormalities and Neurodevelopmental Outcomes

Virtually every major study of early neurodevelopmental outcomes among preterm and ELBW infants has confirmed a strong association between major CUS abnormalities and adverse neurologic and developmental outcomes. Definitions of CUS abnormalities as well as specific outcomes differ among studies, however, most consider IPH, ventriculomegaly (VM), or cystic changes, regardless of laterality or extent of the findings, to be severe abnormalities. In some, persistence of periventricular echodensity or "flaring" is included [72–74]. The diagnosis reported in studies is frequently based on the results from a single CUS study, either the "worst" or the "final" imaging study, but some prospective cohorts [73–76] include serial imaging.

The focus of many studies has been on exploring the association of major CUS findings with CP. The Extremely Low Gestational Age Newborn (ELGAN) Study followed infants of less than 28 weeks' gestation from 14 institutions across 5 states in the United States during 2002–4 [75,76]. Three CUS studies were performed during hospitalization and by multiple radiologists. Standardized neurologic examinations for CP and BSID-II MDI and PDI were performed at 2 years. The investigators found strong independent associations of CUS findings with CP. About half the children with CUS echolucency or VM developed CP, and late occurrence of VM, bilateral echolucency, and IPH or PVL was strongly predictive of quadriparesis. However, almost half the children with CP at 2 years had completely normal CUS studies, and the positive predictive value (PPV) of VM or echolucency for moderate or severe CP was poor. Isolated IVH was not strongly predictive of CP. Furthermore, CUS findings alone appear to be poorly predictive of early developmental outcomes or later childhood cognitive and learning outcomes.

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Investigators have shown major CUS abnormalities to be associated with CP, but CUS findings alone are not significantly correlated with developmental scores [77–79]. The EPIPAGE group [72] and others [78,80] have demonstrated that 30–40% of those with normal CUS findings have neurodevelopmental challenges at 18–30 months. O'Shea et al. and the ELGAN study group showed that only when accompanied or followed by white matter lesions was IVH associated with increased risk for motor or developmental impairment at 2 years, highlighting the limited predictive value of both early CUS findings and IVH alone [81]. In longer-term follow-up studies of the EPIPAGE cohort born at 24–28 + 6/7 weeks' gestation, major CUS abnormalities remained strongly associated with CP [82]. However, approximately 40% of those with major neonatal CUS abnormalities had no significant cognitive or learning challenges identified at 8 years, whereas 30–40% of those with no neonatal CUS abnormalities had moderate to severe challenges [83]. This underscores the critical need for long-term surveillance through later childhood for all children born extremely preterm. Nevertheless, in skilled hands, with meticulous technical attention, and serial CUS imaging, much can be seen beyond ICH by CUS. In a single center, de Vries et al. found that the sensitivity and specificity of CUS abnormalities for CP at 2 years were an impressive 76% and 95% for patients les than 32 weeks' EGA [73]. Of importance, among those with major CUS abnormalities who developed CP, approximately 30% were only noted after 28 days. Major CUS abnormalities were also not strongly associated with cognitive delay at 2 years. More recent findings from this group using MRI at term-equivalent age to refine specific CUS findings has resulted in a PPV and negative predictive value (NPV) of 96% and 69%, respectively, for CP at 2 years among preterm infant [74].

CUS is an operator-dependent modality, imaging procedures and views differ among institutions and studies, and there is no uniform approach to serial imaging protocols. In an analysis of CUS central and local readings in the NICHD PiNO trial, although interrater reliability and accuracy were shown to be very good to excellent for severe ICH, agreement was fair or poor for more subtle findings and periventricular leukomalacia alone [84]. Cerebellar hemorrhage is increasingly recognized to be associated with neurodevelopmental disabilities in children born preterm [85,86], a finding that may be missed without appropriate CUS views, and transient lesions may be missed, including echodense periventricular lesions or collapsing small cystic lesions [73,87]. Isolated intraparenchymal hemorrhages and, of course, large IVHs can be seen by CUS; however, not all "severe" hemorrhages can be considered equivalent in terms of association with early neurodevelopmental outcomes. Characteristics of the hemorrhage including laterality, midline shift, and extent of hemorrhage [88,89], as well as the presence or absence of other adverse clinical factors [90], have been shown to affect predictions of neurodevelopmental outcomes.

Magnetic Resonance Imaging

Brain MRI has been used more extensively in recent years among preterm infants, both for research and for clinical indications. MRI allows for a more comprehensive and detailed picture of the brain and better delineation of deep structure and cortical injury. Potentially most important, MRI provides improved detection of white matter injury (WMI), which is common among preterm infants at term and critically important to understanding the structure-function relationship of the developing preterm brain, influences on later neuromotor and cognitive outcomes, and developing future neuroprotective strategies [91]. Advanced MR imaging in preterm infants at near term have shown that subtle WMI is associated with reduced total brain and gray matter volumes, reduced cerebellar volume, and reduced basal ganglia and thalamic volume [92–96], which, in turn, are associated with developmental impairment in childhood among preterm infants [97]. These findings and others have provided evidence that WMI in the preterm is associated with brain maturational disturbances, suggesting an overall link to impaired neural connectivity [98]. Thus clinical investigations have focused on whether MRI may provide enhanced prognostic information.

Conventional MRI findings and Early Neurodevelopmental Outcomes

Early studies attempting to compare term-equivalent MRI with CUS predictive capabilities were primarily small, single-center studies, and timing and approach to CUS differed [99–101]. Since that time, WMI scoring approaches have been developed, and larger cohort studies have been published, among the first of which was a multicenter effort in Australia and New Zealand comparing serial CUS with near-term MRI findings

and their association with 2-year outcome in 167 infants of less than 30 weeks' EGA [102]. This study demonstrated that moderate to severe white matter abnormalities on near-term MRI were significantly associated with neuromotor delay and CP, independent of CUS findings and other risk factors. Increasing WMI severity was also linearly related to worsening BSID-II MDI scores, but an independent association of moderate to severe WMI with severe cognitive delay was not reached. However, CUS was assessed only with regard to early findings, including grade of ICH and periventricular cystic changes, and a substantial proportion of infants with moderate to severe WMI by MRI did not have adverse 2-year outcomes. The NICHD Neuroimaging and Neurodevelopmental Outcomes (NEURO) Study was a prospective study of early and late CUS and near-term MRI including 480 infants of less than 28 weeks' gestation in NRN centers across the United States, with outcomes including Bayley-III assessed at 18–22 months [103]. In multivariable models, both late CUS findings reflective of WMI and MRI findings of significant cerebellar injury remained independently associated with adverse neurodevelopmental outcomes. In models that did not include late CUS, MRI findings of both moderate to severe WMI and significant cerebellar lesions were independently associated with adverse outcomes. Early CUS findings were not associated with adverse outcomes when any late neuroimaging was taken into account. These results demonstrate the need to understand the evolution of brain injury over time in outcome prediction rather than to rely on early findings. Similarly, in a prospective study of serial CUS and near-term MRI among infants of less than 27 weeks' gestation in Sweden, associations between MRI findings and 30-month outcomes were shown, but the investigators also determined that any substantial abnormalities on MRI were detected by the late CUS done on the same day [104]. Of note, diffuse excessive high signal intensity (DEHSI) on near-term MRI has been shown not to be associated with adverse early childhood outcomes in several studies [105,106].

Challenges and Future Directions

Despite what now appears to be extensive experience with CUS and conventional brain MRI in preterm infants, controversies and questions remain as to which studies to perform, when to perform them and under what circumstances, and relative values in prognosis. These are not simple questions because the "value" of additional information may be very different in varying clinical circumstances and for individual parents and physicians [107]. Guidelines published in 2002 do not recommend near-term MRI for routine preterm infant neuroimaging [32], and a recent publication has suggested avoidance of routine term-equivalent conventional brain MRI for screening purposes due to insufficient evidence that the practice improves long-term outcomes [108]. But recent studies in preterm infants continue to indicate that brain injury, including cerebellar hemorrhage, may be better delineated by MRI than by CUS and certainly underscore the point that early neuroimaging alone should not be relied on for prognostication of neurodevelopmental outcomes. Cerebellar injury seen by MRI but not by CUS may be associated with a higher risk for neurologic abnormalities [109], although the importance of punctate lesions remains unclear [110]. Others studies have shown that MRI may provide additive information to predict neuromotor outcomes [74] complementary to specific findings such as periventricular echodensities by CUS [111] or neurologic examination [112,113]. Neonatal sepsis and necrotizing enterocolitis (NEC) have been linked with progressive or higher rates of WMI on MRI, and adverse 2-year outcomes associated with these morbidities may be mediated by WMI [114,115]. Future studies should focus further on identifying specific high-risk groups of preterm infants for which MRI would definitively improve prediction of neurodevelopmental outcomes and, more important, allow for risk stratification for neuroprotective or interventional studies. Further investigation with advanced MRI techniques, including DTI, fcMRI, surface morphometry, and volumetric methods, hold enormous promise to help to explore these [116].

Conclusions

Despite advances in perinatal and neonatal management, early neurodevelopmental outcomes of extraordinarily preterm infants remain guarded. Factors associated with adverse neurodevelopmental outcomes include demographic and socioeconomic variables but also numerous neonatal morbidities that may be modifiable. A continued meticulous approach to follow-up to early childhood is needed for these extraordinarily vulnerable infants. But it is also clear that more routine longer-term follow-up to school age and beyond is required to understand successes and challenges that cannot be assessed at a very early age, appreciate the evolution of outcomes over time, and evaluate the

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impact of our interventions in the NICU. A better understanding of the mechanisms and pathways of brain injury and impaired development will inevitably lead us to potential opportunities for neuroprotective strategies for these extremely high-risk infants. Further study of advanced neuroimaging techniques will certainly assist in this endeavor. Certainly, given the extraordinary array of both antenatal and postnatal complex variables that influence outcomes, reliance solely on neuroimaging findings – or any single factor – to attempt "perfect prediction" of neurodevelopmental outcome is inappropriate. However, there are myriad opportunities yet to be fully explored and deployed to influence developmental outcomes beyond the NICU [42]. What is considered to be the "border of viability" has shifted substantially and continues to change. Much is invested in ensuring survival for the tiniest babies, and although the cost for follow-up research may be high, the time has come for us to invest at least as much in understanding and enhancing their truly long-term outcomes [117]. Just as the influences and outcomes of extremely preterm infants encompass a broad range, our approach to improving lifespan outcomes for these children and their families will need to be multipronged.

References

1. Blencowe H, Cousens S, Oestergaard M, et al. National, regional and worldwide estimates of preterm birth. *Lancet* 2012; **379**(9832): 2162–72.
2. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2013. *National Vital Statistics Reports* 2015; **64**(1); available at www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_01.pdf.
3. March of Dimes. Peristats, 2015. Available at www.marchofdimes.org/peristats/Peristats.aspx (acessed December 10, 2015).
4. Raju TNK, Mercer BM, Burchfield DJ, et al. Birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2014; **123**: 1083–96.
5. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity and mortality of extremely preterm neonates, 1993–2012. *JAMA* 2015; **314**(10): 1039–51.
6. Zegers MJ, Hukkelhoven CWPM, Uiterwaal CSPM, et al. Changing Dutch approach and trends in short-term outcome of periviable preterms. *Arch Dis Child Fetal Neonatal Ed* 2016; **101**: F391–6.
7. Anthony S, den Ouden L, Brand R, et al. Changes in perinatal care and survival in very preterm and extremely preterm infants in the Netherlands between 1983–1995. *Eur J Obstet Gyn Reprod Biol* 2004; **112**: 170–7.
8. Finnstrom O, Olausson PO, Sedin G, et al. The Swedish national prospective study on extremely low birth weight (ELBW) infants: incidence, mortality, morbidity, and survival in relation to level of care. *Acta Paediatr* 1997; **86**: 501–11.
9. Serenius F, Ewald U, Farooqui A, et al. Short-term outcome after active perinatal management at 23–25 weeks of gestation: a study from two Swedish tertiary care centres. 2. Infant survival. *Acta Paediatr* 2004; **93**: 1081–9.
10. The EXPRESS Group. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009; **301**(21): 2225–33.
11. Costeloe K, Hennessy E, Gibson AT, et al. The EPICure Study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 2000; **106**: 659–71.
12. Costeloe K, Henessy EM, Haider S, et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012; **345**: e7976.
13. Ancel P-Y, Goffinet F, EPIPAGE-2 Writing Group. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 Cohort Study. *JAMA Pediatr* 2015; **169**: 230–8.
14. Doyle LW, VICS Group. Neonatal intensive care at borderline viability: is it worth it? *Early Hum Dev* 2004; **80**: 103–13.
15. Doyle LW. Evaluation of neonatal intensive care for extremely-low-birth-weight infants. *Semin Fetal Neonatal Med* 2006; **11**: 139–45.
16. Doyle LW, VICS Group. Evaluation of neonatal intensive care for extremely low birth weight infants in Victoria over two decades. II. Efficiency. *Pediatrics* 2004; **113**: 511–14.
17. Doyle LW, Roberts G, Anderson PJ, VICS Group. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr* 2010; **156**: 49–53.
18. Ishii N, Kono Y, Yoneoto N, et al. Outcomes of infants born at 22 and 23 weeks' gestation. *Pediatrics* 2013; **132**: 62–71.
19. Marlow N, Bennett C, Draper ES, et al. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**: F181–8.

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.045

20. Ochiai M, Kinjo T, Takahata Y, et al. Survival and neurodevelopmental outcome of preterm infants born at 22–24 weeks of gestational age. *Neonatology* 2014; **105**: 79–84.
21. Tyson JE, Parikh NA, Langer J, et al. Intensive care for extreme prematurity: moving beyond gestational age. *N Engl J Med* 2008; **358**(16): 1672–81.
22. Lee HC, Green C, Hintz SR, et al. Prediction of death for extremely preterm infants in a population-based cohort. *Pediatrics* 2010; **126**: e644–50.
23. Rysavy MA, Li L, Bell EF, et al. Eunice Kennedy Shriver NICHD Neonatal Research Network: between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med* 2015; **372**: 1801–11.
24. Hintz SR, Bann CM, Ambalavanan N, et al. Predicting time to discharge for extremely preterm infants. *Pediatrics* 2010; **125**: e146–54.
25. Ambalavanan N, Carlo WA, Tyson JE, et al. Outcome trajectories in extremely preterm infants. *Pediatrics* 2012; **130**: e115–25.
26. Mangham LJ, Petrou S, Doyle LW, et al. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009; **123**(2):e312–27.
27. McCabe ERB, Carrino GE, Russell RB, Howse JL. Fighting for the next generation: US prematurity in 2030. *Pediatrics* 2014; **134**: 1193–9.
28. Janvier A, Lantos J, Deschenes M, et al. Caregivers attitudes for very premature infants: what if they knew? *Acta Pediatr* 2008; **97**(3): 276–9.
29. Aylward GP, Aylward BS. The changing yardstick in measurement of cognitive abilities in infancy. *J Dev Behav Pediatr* 2011; **32**: 465–8.
30. Anderson PJ, De Luca CR, Hutchinson E, et al. Underestimation of developmental delay by the new Bayley-III scales. *Arch Pediatr Adolesc Med* 2010; **164**(4): 352–6.
31. Msall ME. Measuring outcomes after extreme prematurity with the Bayley-III scales of infant and toddler development: a cautionary tale from Australia. *Arch Pediatr Adolesc Med* 2010; **164**: 391–3.
32. Marlow N, Wolke D, Bracewell M, et al. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005; **352**: 9–19.
33. Saigal S, Rosenbaum P. What matters in the long term: reflections on the context of adult outcomes versus detailed measures in childhood. *Semin Fetal Neonatal Med* 2007; **12**: 417–22.
34. Saigal S, Tyson J. Measurement of quality of life of survivors of neonatal intensive care: critique and implications. *Semin Perinatol* 2008; **32**: 59–66.
35. Saigal S. *Premie Voices:Young Men and Women Born Very Prematurely Describe Their Lives, Challenges, and Achievements*. 1st edn. Victoria, BC: Friesen Press, 2014.
36. Hack M, Flannery DJ, Schluchter M, et al. Outcomes in young adulthood for very low birth weight infants. *N Engl J Med* 2002; **346**: 149–57.
37. Hack M, Schluchter M, Forrest CB, et al. Self-reported adolescent health status of extremely low birth weight children born 1992–1995. *Pediatrics* 2012; **130**(1):46–53.
38. Litt JS, Gerry Taylor H, Margevicius S, et al. Academic achievement of adolescents born with extremely low birth weight. *Acta Paediatr* 2012; **101**(12): 1240–5.
39. Hack M. Adult outcomes of preterm children. *J Dev Behav Pediatr* 2009; **30**(5): 460–70.
40. Hack M, Taylor HG, Drotar D, et. al. Poor predictive validity of the Bayley scales of infant development for cognitive function of extremely low birth weight children at school age. *Pediatrics* 2005; **116**: 333–41.
41. Ment LR, Vohr B, Allan W, et. al. Change in cognitive function over time in very low-birth-weight infants. *JAMA* 2003; **289**: 705–11.
42. Spittle A, Orton J, Anderson PJ, et al. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev* 2015; **11**: CD005495.
43. Davis NM, Ford GW, Anderson PJ, Doyle LW. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. *Dev Med Child Neurol* 2007; **49**: 325–30.
44. Roberts G, Anderson PJ, Davis N, et al. Developmental coordination disorder in geographic cohorts of 8-year-old children born extremely preterm or extremely low birth weight in the 1990s. *Dev Med Child Neurol* 2011; **53**: 55–60.
45. Bayley N. *Bayley Scales of Infant and Toddler Development*, 3rd edn. San Antonio, TX: Harcourt Assessment, 2006.
46. Vohr BR, Stephens BE, Higgins RD, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr* 2012; **161**: 222–8.
47. Duncan AF, Bann C, Boatman C, et al. Do currently recommended Bayley-III cutoffs overestimate motor impairment in infants born < 27 weeks gestation? *J Perinatol* 2015; **35**: 516–21.
48. Spittle AJ, Spencer-Smith MM, Eeles AL, et al. Does the Bayley-III mkotor scale at 2 years predict motor outcome at 4 years on very preterm children? *Dev Med Child Neurol* 2013; **55**: 448–52.

49. Spencer-Smith MM, Spittle AJ, Lee KJ, et al. Bayley-III cognitive and language scales in preterm children. *Pediatrics* 2015; **135**: e1258–65.
50. Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res* 2014; **75**: 670–4.
51. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
52. Victorian Infant Collaborative Study Group. Economic outcome for intensive care of infants of birthweight 500–999 g born in Victoria in the post-surfactant era. *J Paediatr Child Health* 1997; **33**: 202–8.
53. Hutchinson EA, De Luca CR, Doyle LW, et al. School age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics* 2013; **131**(4): e1053–61.
54. Burnett AC, Scratch SE, Lee KJ, et al. Executive function in adolescents born < 1000 g or <28 weeks: a prospective cohort study. *Pediatrics*. 2015; **135**(4): e826–34
55. Burnett A, Davey CG, Wood SJ, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the late 1990s. *Psychol Med* 2014; **44**(7): 1533–44.
56. Roberts G, Burnett AC, Lee KJ, et al. Quality of life at age 18 years after extremely preterm birth in the post-surfactant era. *J Pediatr* 2013; **163**(4): 1008–13.
57. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ* 2012; **345**: e7961.
58. Moore T, Johnson S, Haider S, et al. Interpreting developmental test scores over time: using the scond and third editions of the Bayley scales of infant and toddler development. *J Pediatr* 2012; **160**: 553–8.
59. Moore T, Johnson S, Hennessy E, Marlow N. Screening for autism in extremely preterm infants: problems in interpretation. *Dev Med Child Neurol* 2012; **54**(6): 514–20.
60. Kuban KC, O'Shea TM, Allred EN, et al. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. *J Pediatr* 2009; **154**: 535–40.
61. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. *Pediatrics* 2008; **121**: 758–65.
62. Serenius F, Kallen K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; **309**: 1810–20.
63. Serenius F, Blennow M, Marsal K, et al. Intensity of perinatal care for extremely preterm infants: outcomes at 2.5 years. *Pediatrics* 2015; **135**: e1163–72.
64. Hintz SR, Kendrick DE, Wilson-Costello D, et al. Neurodevelopmental outcomes at 18–22 months are not improving for <25 week EGA infants. *Pediatrics* 2011; **127**: 62–70.
65. Vohr BR, Wright LL, Dusick AM, et al. Center differences and outcomes of extremely low birth weight infants. *Pediatrics* 2004; **113**: 781–9.
66. Schlapbach LJ, Adams M, Prioletti E, et al. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. *BMC Pediatr* 2012; **12**: 198.
67. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss national cohort of extremely premature infants. *Pediatrics* 2011; **128**: e348–57.
68. Pape KE, Blackwell RJ, Cusick G, et al. Ultrasound detection of brain damage in preterm infants. *Lancet* 1979; **1**(8129): 1261–4.
69. Slovis TL, Kuhn LR. Real-time sonography of the brain through the anterior fontanelle. *AJR* 1981; **136**: 277–86.
70. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weight less than 1500 gm. *J Pediatr* 1978; **92**: 529–34.
71. Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002; **58**: 1726–38.
72. Ancel P-Y, Livinec F, Larroque B, et al. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE Cohort Study. *Pediatrics* 2006; **117**: 828–35.
73. de Vries LS, Van Haastert IC, Rademaker KJ, et al. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. *J Pediatr* 2004; **144**: 815–20.
74. de Vries LS, van Haastert IC, Benders MJNL, Groenendaal F. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. *Semin Fetal Neonatal Med.* 2011; **16**(5): 279–87.
75. O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev* 2009; **85**: 719–25.
76. Kuban KCK, Allred EN, O'Shea TM, et al. Cranial ultrasound lesion in the NICU predict cerebral palsy at age 2 years in children born at extremely low gestational age. *J Child Neurol* 2009; **24**: 63–72.

77. Wood NS, Costeloe K, Gibson AT, et al. The EPICure Study: association and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F134–40.

78. Hack M, Wilson-Costello D, Friedman H, et al. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g, 1992–1995. *Arch Pediatr Adolesc Med* 2000; **154**: 725–31.

79. Broitman E, Ambalavanan N, Higgins R, et al. Clinical data predict neurodevelopmental outcome better than head ultrasound in extremely low birth weight infants. *J Pediatr* 2007; **151**: 500–5.

80. Laptook AR, O'Shea RM, Shankaran S, et al. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005; **115**: 673–80.

81. O'Shea TM, Allred EN, Kuban KCK, et al. Intraventricular hemorrhage and developmental outcomes at 24 months of age in extremely preterm infants. *J Child Neurol* 2012; **27**(1): 22–9.

82. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010; **52**: e119–25.

83. Marret S, Marchand-Martin L, Picaud J-C, et al. Brain injury in very preterm children and neurosensory and cognitive disabilities during childhood: the EPIPAGE Cohort Study. *PLoS One* 2013; **8**: e62683.

84. Hintz SR, Slovis T, Bulas D, et al. Interobserver reliability and accuracy of cranial ultrasound scanning in premature infants. *J Pediatr* 2007; **150**: 592–6.

85. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning and behavioral disability in survivors? *Pediatrics* 2007; **120**: 584–93.

86. Limperopoulos C, Chilingaryan G, Sullivan N, et al. Injury to the premature cerebellum: outcome is related to remote cortical development. *Cereb Cortex* 2014; **24**(3): 728–36.

87. Pierrat V, Duquennoy C, van Haastert IC, et al. Ultrasound diagnosis and neurodevelopmental outcome of localized and extensive cystic periventricular leucomalacia. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**: F151–6.

88. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics* 2007; **120**: 785–92.

89. Davis AS, Hintz SR, Bann CM, et al. Characteristics of severe intracranial hemorrhage and other factors in predicting early childhood outcomes of extremely preterm infants. *J Perinatol* 2014; **34**(3): 203–8.

90. Merhar SL, Tabangin ME, Meinzen-Derr J, Schibler KR. Fetal and postnatal brain MRI in premature infants with twin-twin transfusion syndrome. *J Perinatol* 2013; **33**: 112–18.

91. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. *Int J Dev Neurosci* 2011; **29**: 423–40.

92. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics* 2005; **118**: 536–48.

93. Inder TE, Warfield SK, Wang H, et al. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 2005; **115**: 286–94.

94. Inder TE, Huppi PS, Warfield S, et al. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol* 1999; **46**: 755–60.

95. Boardman JP, Counsell SJ, Rueckert D, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *NeuroImage* 2006; **32**: 70–8.

96. Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. *Brain* 2007; **130**: 667–77.

97. Peterson BS, Anderson AW, Ehrenkranz R, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics* 2003; **111**: 939–48.

98. Dean JM, Bennet L, Back SA, et al. What brakes the preterm brain? An arresting story. *Pediatric Res* 2014; **75**: 227–33.

99. Roelants-van Rijn AM, Groenendaal F, Beek FJA, et al. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. *Neuropediatrics* 2001; **32**: 80–9.

100. Mirmiran M, Barnes PD, Keller K, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. *Pediatrics* 2004; **114**: 992–8.

101. Sie LTL, Hart AAM, van Hof J, et al. Predictive value of neonatal MRI with respect to late MRI findings and clinical outcome: a study in infants with periventricular densities on neonatal ultrasound. *Neuropediatrics* 2005; **36**: 78–89.

102. Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental

.045

outcomes in preterm infants. *N Engl J Med* 2006; **355**: 685–94.

103. Hintz SR, Barnes PD, Bulas D, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics* 2015; **135**: e32–42.

104. Skiöld B, Eriksson C, Eliasson A-C, et al. General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. *Early Hum Dev* 2013; **89**(7): 467–72.

105. Jeon TY, Kim JH, Yoo SY, et al. Neurodevelopmental outcomes in preterm infants: comparison of infants with and without diffuse excessive high signal intensity on MR images at near-term-equivalent age. *Radiology* 2012; **263**(2): 518–26.

106. Skiöld B, Vollmer B, Böhm B, et al. Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. *J Pediatr* 2012; **160**(4): 559–66.

107. Janvier A, Barrington K. Trying to predict the future of ex-preterm infants: who benefits from a brain MRI at term? *Acta Paediatr* 2012; **101**(10): 1016–17.

108. Ho T, Dukhovny D, Zupancic JAF, et al. Choosing wisely in newborn medicine: five opportunities to increase value. *Pediatrics* 2015; **136**: e482–9.

109. Tam EW, Rosenbluth G, Rogers EE, et al. Cerebellar hemorrhage on magnetic resonance imaging in preterm newborns associated with abnormal neurologic outcome. *J Pediatr* 2011; **158**(2): 245–50.

110. Steggerda SJ, de Bruine FT, van den Berg-Huysmans AA, et al. Small cerebellar hemorrhage in preterm infants: perinatal and postnatal factors and outcome. *Cerebellum* 2013; **12**(6):794–801.

111. Sie LTL, Hart AAM, van Hof J, et al. Predictive value of neonatal MRI with respect to late MRI findings and clinical outcome: a study in infants with periventricular densities on neonatal ultrasound. *Neuropediatrics* 2005; **36**(2):78–89.

112. Spittle AJ, Boyd RN, Inder TE, Doyle LW. Predicting motor development in very preterm infants at 12 months' corrected age: the role of qualitative magnetic resonance imaging and general movements assessments. *Pediatrics* 2009; **123**(2): 512–17.

113. Skiöld B, Eriksson C, Eliasson A-C, et al. General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. *Early Hum Dev* 2013; **89**(7): 467–72.

114. Glass HC, Bonifacio SL, Chau V, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. *Pediatrics* 2008; **122**: 299–305.

115. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr* 2008; **153**: 170–5.

116. Mathur AM, Neil JJ, Inder TE. Understanding brain injury and neurodevelopmental disabilities in the preterm infant: the evolving role of advanced magnetic resonance imaging. *Semin Perinatol* 2010; **34**: 57–66.

117. Doyle LW, Clucas L, Roberts G, et al. The cost of long-term follow up of high-risk infants for research studies. *J Paediatr Child Health* 2015; **51**: 1012–16.

Chapter

45 Cerebral Palsy

Advances in Definition, Classification, Management, and Outcome

Christina A. Buysse and Heidi M. Feldman

Case: Ashley was born precipitously at 27 weeks' gestation when her mother developed a urinary tract infection. She required 3 weeks of mechanical ventilation and 4 subsequent weeks of oxygen supplementation. Ultrasound examination of the brain at age 7 days revealed grade 2 intraventricular hemorrhage bilaterally. Magnetic resonance imaging at term-equivalent age revealed mildly enlarged ventricles and reduced white matter volume. Physical examination at 4 months of age revealed diffuse hypotonia and delayed head control with normal cognitive developmental milestones. Examination at 9 months of age revealed increased tone in the lower extremities and delayed gross and fine motor milestones. Ashley was enrolled in physical therapy (PT) and occupational therapy (OT) at age 11 months. The diagnosis of diplegic cerebral palsy was confirmed at age 2 years. At that age, mild delays in cognitive abilities and communication led to referral for early intervention services and continued PT and OT. At age 44 months, she achieved independent mobility. By school age, she was classified as Gross Motor Function Classification System Level II and Manual Ability Classification System Level I. She developed learning disabilities and weak attention but participated in general education with limited support through high school.

Overview

Cerebral palsy (CP) is a group of long-term developmental motor disorders associated with muscle and movement impairment and mobility disability. It results from a nonprogressive injury in the brain that occurs early in life, often in the prenatal or neonatal period, though definitive diagnosis is often not made until children are age 1–3 years. Multiple etiologies are associated with CP, including prematurity, low birth weight, multiple-gestation pregnancy, infection, inflammation, neonatal encephalopathy, and genetic factors [1]. Motor abnormalities of CP are often accompanied by co-occurring disturbances in cognition, perception, and sensation. The disorders that are classified as CP represent a wide spectrum of severity; many individuals with CP, especially those who have supportive therapies, such as the child in the opening case, report a good quality of life.

Definitions

In 1843, orthopedic surgeon William John Little first described spastic rigidity after birth complications, and in 1889, Sir William Osler labeled the condition *cerebral palsy* (CP) [2]. In 1964, Martin Bax described CP as a disorder of "posture and movement due to a defect or lesion of the immature brain"[3]. In 2004, an international workshop on the definition and classification of CP at the US National Institutes of Health revised the definition and classification of CP as follows:

> Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems [4].

This revised definition carried two new emphases, aligning it with the International Classification of Functioning, Disability, and Health (ICF), the World Health Organization's framework for assessing health and disability [5,6]. First, functional and activity limitations must be present for a child to receive a diagnosis of CP. Second, the new definition recognized that associated conditions such as disturbances in communication and cognition might limit function, daily activity, and community participation to a greater degree than

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the motor impairment that defines the disorder. Together these criteria caused a shift in the conceptual framework in care of individuals with CP, emphasizing comprehensive assessment and wide-ranging treatment targets that could improve overall function rather than merely assessing neurologic status and motor skills or aiming in treatment for isolated changes in the movement of physical structures. Though CP results from a nonprogressive brain disturbance, functional manifestations may change over time and with therapy. For example, the child in the opening case had early hypotonia that developed into spasticity during her first year of life. Children with substantial early delays may learn to walk without assistance or with handheld mobility equipment. Conversely, spasticity may lead to increasing distal myofascial muscle stiffness, contractures, and orthopedic deformities that limit mobility [7,8].

Subclassifications Based on Presentation, Cause, and Severity

CP can be classified several different ways. Table 45.1 summarizes subclassification based on clinical symptoms, including definitions and prevalence of the subtypes [9]. The descriptive terms *spasticity, dyskinesia*, and *ataxia* are defined on the basis of clinical signs with further specification of the location of extremity involvement (hemiplegia, diplegia, or quadriplegia). Muscle tone (isotonic, hypotonic, hypertonic, or variable tone) is used when describing a child's physical examination. Spastic CP is the most common subtype within the spectrum of CP [10,11].

Classification of CP by subtype is helpful in linking symptoms to underlying etiology. The various causes of CP disrupt the development of neuronal networks in brain pathways that control movement. Selective vulnerability during critical periods of brain development leads to different injuries in different parts of the brain. Table 45.2 links the timing and causes of brain insults with the characteristic type of CP from that cause.

Encephalopathy at birth may be caused by a primary intrapartum event or be secondary to prenatal causes. International criteria, including documented metabolic acidosis at birth and early moderate to severe neonatal encephalopathy, have been established to help identify the cases of encephalopathy caused by intrapartum hypoxia [12]. Intrapartum asphyxia accounts for 10–20% of cases of CP, and the number is closer to 10% when CP and encephalopathy are carefully

Table 45.1 Subclassification of Cerebral Palsy by Type

Type	Clinical findings	Associated brain abnormalities and causes	Prevalence in CP (%) [9]
Spastic	Increased velocity-dependent muscle tone that leads to resistance to movement	Associated with cortical gray matter and/or subcortical white matter injury	79.2
Hemiplegia	Spasticity affecting left or right side of the body	Combined gray and white matter injury to one hemisphere	26.2
Diplegia	Spasticity affecting lower limbs	Injury to bilateral gray and periventricular white matter	34.4
Quadriplegia	Spasticity affecting all four limbs	Diffuse injury to multiple brain regions	18.6
Dyskinesia	Distortion or impairment of voluntary movement, including chorea and athetosis	Injury to basal ganglia	14.4
Ataxic	Poor coordination and unsteadiness due to unregulated body posture, strength, gait, and direction of limb movements.	Injury to cerebellum	3.9
Other	Mixture of the above	—	2.6

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Table 45.2 Variations in Timing and Nature of Brain Insult in Relation to Type of CP

Timing of insult	Etiologic cause of injury to motor pathways	Predominant type of CP
First trimester of pregnancy	Cerebral malformations, such as schizencephaly	Spastic quadriplegia
23–32 weeks of gestation	Injury to oligodendrocyte cell line from hypoxia, ischemia, and/or inflammation resulting in disturbances of white matter	Spastic diplegia
23–40 weeks of gestation	Injury to cerebellum from multiple causes	Ataxic
Third trimester of pregnancy through infancy	Vascular instability or hypoxic-ischemic injury to watershed regions resulting in stroke or focal injury	Hemiplegia
Term gestational age	Injury to basal ganglia and thalamus from hypoxia, ischemia, or inflammation	Dyskinesia or dystonia with or without spastic quadriplegia
Term gestational age	Injury to basal ganglia and auditory nerve from kernicterus	Dystonia
Postterm during infancy	Head trauma and meningitis	Variable presentations, depending on brain structures affected

defined. In order to attribute neurologic sequelae to neuronal injury sustained at the time of birth, a sentinel event such as uterine rupture, placental abruption, or cord prolapse must also be present [13].

Genetic factors are increasingly thought to contribute to the development of CP and likely are represented in all phases of neuronal vulnerability. No subclassification of genetic disorders has been proposed. Several single-gene disorders have been found to cause CP: for example, mutations in the *GPR56* gene cause severe bilateral frontoparietal polymicrogyria and CP. Copy-number variants are also associated with polymicrogyria and CP. Recent studies using whole-exome sequencing in cases of sporadic CP indicate that 14% of participants had likely-causative single-gene mutations and 31% had clinically relevant copy-number variants [12].

Another important subclassification is based on severity. Among children with CP, functional abilities range from mild hemiplegic gait differences and superior cognitive abilities to nonambulatory quadriparesis and intellectual disability. Approximately 60% of children with CP eventually walk independently, 10% walk with assistance, and 30% use a wheelchair for mobility [11]. The Gross Motor Function Classification System (GMFCS) is a classification system that describes the heterogeneity in gross motor skills. It was created in 1997 and revised in 2007 [14]. It uses five levels (I–V) to describe the gross motor function of children with CP from birth to age 18 years and has been shown to be valid, reliable, and stable [15,16]. Use of the system enables a clinician to establish a prognosis of an individual's later motor functioning because children rarely cross between levels as they age but continue to develop within their original GMFCS level. Table 45.3 shows the five levels of the GMFCS for children ages 2–4 years and the corresponding levels for children ages 6-12 years.[17] A similar classification system, the Manual Abilities Classification System (MACS), was designed to measure a child's ability to manipulate objects in everyday life [18]. This system also consists of levels I–V and has been found to be reliable, valid, and stable (Table 45.4) [19]. The five-level Communication Function Classification System (CFCS) has been developed recently to describe the level of communication function for people with CP. Test-retest reliability has been excellent, and validity and stability studies are underway [20].

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Table 45.3 Gross Motor Functional Classification System: Partial Description of Children at Levels I–V at Ages 2–4 years and at 6–12 Years [17]

Level	Ages 2–4 years	Ages 6–12 years
I	Children floor sit with both hands free to manipulate objects; walk as preferred method of mobility without assistive mobility device.	Children walk indoors and outdoors and climb stairs without limitations; speed, balance, and coordination in skills such as running and jumping are reduced.
II	Children floor sit but may have difficulty with balance if both hands manipulate objects, pull to stand on a stable surface, crawl on hands and knees with a reciprocal pattern, cruise holding onto furniture, and walk using an assistive mobility device.	Children walk indoors and outdoors and climb stairs holding onto a railing; limitations in walking on uneven surfaces and inclines, walking in crowds or confined spaces, and gross motor skills such as running and jumping.
III	Children maintain floor sitting by "W-sitting" (sitting between flexed and internally rotated hips and knees), creep on stomach, or crawl on hands and knees often without reciprocal leg movements, may pull to stand, cruise or walk short distances indoors using an assistive mobility device and adult assistance for turning.	Children walk indoors or outdoors on a level surface with an assistive mobility device, may climb stairs holding onto a railing, may propel a wheelchair manually or are transported when travelling for long distances or outdoors on uneven terrain.
IV	Children floor sit when placed, are unable to maintain alignment and balance without use of their hands, frequently require adaptive equipment for sitting and standing, achieve independent mobility by rolling, creeping on stomach, or crawling on hands and knees without reciprocal leg movement.	Children need adaptive seating for trunk control and to maximize hand function, move in and out of chair with adult assistance or a stable surface to push or pull up on with their arms, may walk short distances with a walker and adult, rely on wheeled mobility at home, school, and in the community, may achieve self-mobility using a power wheelchair.
V	Children are restricted in voluntary control of movement, inability to maintain antigravity head and trunk postures, functional limitations in sitting and standing not fully compensated for through adaptive equipment, no means of independent mobility.	Minimal developmental change from characteristics at ages 2–4 years.

Table 45.4 Manual Ability Classification System for Children with CP 4–18 Years of Age: Partial Descriptions of Children at Levels 1–V [18]

Level	Characteristic skills
I	Handles objects easily and successfully. At most, limitations in the ease of performing manual tasks requiring speed and accuracy.
II	Handles most objects but with somewhat reduced quality and/or speed of achievement. Certain activities may be avoided or be achieved with difficulty; alternative ways of performance may be used.
III	Handles objects with difficulty; needs help to prepare and/or modify activities. Limited success regarding quality and quantity of movement. Independent performance if activities have been set up or adapted.
IV	Handles a limited selection of easily managed objects in adapted situations. Performs parts of activities with effort and limited success. Requires continuous support and assistance and/or adaptive equipment to achieve even partial completion.
V	Does not handle objects and has severely limited ability to perform even simple actions. Requires total assistance.

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Epidemiology and Public Health Issues

CP has an overall prevalence of 2.1–3.6/1,000 people in developed countries [21,22]. Socioeconomic disadvantage is associated with increased rates of CP. Black non-Hispanic children have increased prevalence of CP compared with white non-Hispanic children above and beyond socioeconomic differences; this increased risk disappears after adjustment for gestational age and weight at birth [23]. Males have a slightly higher prevalence than females with a ratio of 1.4:1 [22]. The prevalence of CP in developing nations has not been well studied. It is estimated that 80% of children with CP live in low-resource countries. Though the incidence may be higher in these nations, high mortality may reduce differences in prevalence between low- and high-resource countries [24].

In developed countries, CP is highly associated with prematurity and low birth weight. A meta-analysis found the prevalence of CP to be 57/1,000 in children weighing less than 1,000 g at birth, 59/1,000 in those weighing 1,000–1,499 g, 10/1,000 in those weighing 1,500–2,499 g, and 1.3/1,000 in those weighing more than 2,500 g. Infants born before 28 weeks' gestation had a prevalence of CP of 112/1,000, whereas children born after 36 weeks had a prevalence of 1.35/1,000 [21]. Despite the lower incidence, infants born at term account for 50–65% of children with CP because 90% of children are born at term [25].

The prevalence of CP has remained relatively stable over the past 20 years despite many improvements in medical care, especially in the developed world [26]. Reduced prevalence would be expected based on several medical advances in treatment of newborns: (1) widespread rubella vaccination that eliminated chronic rubella syndrome as a cause of CP in the United States [27], (2) systematic treatment of neonatal jaundice that has dramatically reduced the incidence of kernicterus, (3) cooling for term infants with hypoxic-ischemic encephalopathy that reduces mortality and morbidity [28], and (4) the use of antenatal steroids and magnesium sulfate in women with preterm labor that has decreased the incidence of CP and the severity of complications [29,30]. Opposing forces, however, have maintained the prevalence rates: (1) improved survival rates of extremely low-birth-weight infants, who are more likely to develop CP than term infants, and (2) increased use of artificial reproductive technologies and multiple-gestation pregnancies with associated complications of low birth weight and preterm birth.

Clinical Presentation and Establishing the Diagnosis

Core Findings

CP is diagnosed clinically based on delays in motor development and abnormalities on physical and neurologic examination. In infancy, primitive reflexes, such as the Moro reflex, are integrated into voluntary movement patterns as the nervous system matures. Primitive reflexes persisting beyond the usual age alert clinicians to an increased risk for CP. As primitive reflexes disappear, postural reactions, such as head righting during tilting and protective arm extension to brace falling, develop. Absence of these postural reactions raises suspicion for CP. Upper motor neuron dysfunction is characterized by spasticity, hyperreflexia, and clonus. Over the first years of life, muscle hypotonia may progress to hypertonia in children with CP, as in the opening case. Asymmetries in tone, strength, reflexes, and coordination on neurologic examination also raise red flags for CP. CP is not diagnosed at birth because the classic diagnostic signs of motor delay and impairment do not reveal themselves until the child is older. Children with more severe CP are often diagnosed in the first year of life, and children with less severe CP are frequently diagnosed in the second year of life.

Clinical practice guidelines issued by the American Academy of Neurology and the Child Neurology Society in 2004 recommended neuroimaging of a child with CP if the etiology has not been established. They further recommended magnetic resonance imaging (MRI) as preferable to computed tomography (CT) scanning because of greater detail and no exposure to ionizing radiation [31]. More than 80% of children with CP demonstrate abnormalities on MRI, though the rest may have a normal MRI. Children with a normal MRI often have a milder form of CP; children with ataxic and dyskinetic CP compared with other subtypes are most likely to have a normal MRI [9]. MRI obtained at term equivalence has higher predictive sensitivity than cranial ultrasound [32]. In children with CP, white matter injury is found in 19–45% of cases and gray matter injury in 20%. Focal vascular insults and malformations are each seen 10% of the time [33]. Figures 45.1 and 45.2 show typical MRI scans of a child with CP.

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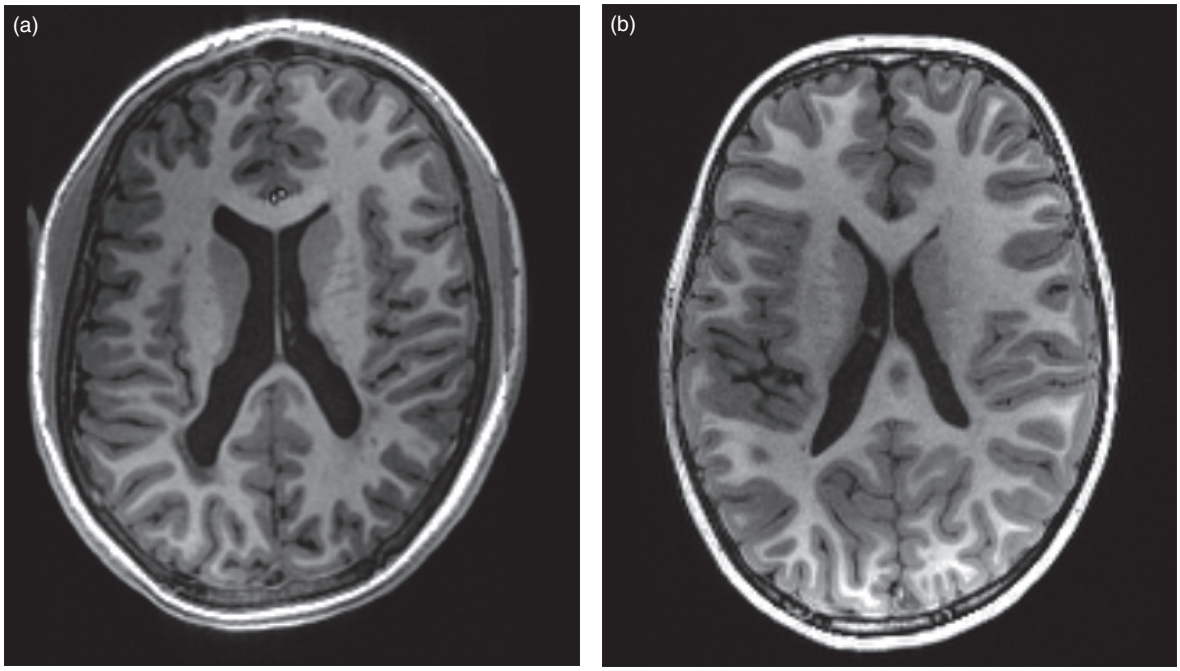


Figure 45.1 The classic appearance of periventricular leukomalacia in an infant with CP. Note the abnormal periventricular white matter signal, volume loss, and irregular ventricular margins.

Associated Impairments

Epilepsy and cognitive, behavioral, and sensory impairments may be associated with the motor impairments of CP because the underlying neuropathology puts the child at risk for disorders beyond the motor system. The child in the opening case had co-occurring cognitive and behavioral conditions. Rates of comorbidities in prevalence studies may be somewhat elevated because children with very mild CP may be underrepresented.

Cognitive and Intellectual Abilities. Studies report that almost 50% of children with CP have some degree of intellectual impairment [26,34,35], though they may not function in the range of intellectual disability (scores on intelligence tests greater than 2 standard deviations below the mean with comparable adaptive skills). Severity of cognitive impairment often correlates with severity of motor impairment. Children with spastic quadriplegia have the highest association with cognitive impairment [36]. The correlation between motor and cognitive impairment is low in dyskinetic CP. Children with epilepsy and an abnormal MRI are more likely to have intellectual impairment than those without these findings. To avoid underestimation of the intellectual abilities of children with CP, evaluation of intellectual functioning should use measures that do not require motor skills and that avoid the use of timed tests.

Behavioral Disorders. Behavioral and emotional disturbances are highly prevalent in children with CP, ranging from 25% to 40% across studies using different assessment measures and outcomes. Common behavioral problems include difficulties with peer interactions, attention problems, hyperactive behavior, and emotional dysregulation. The incidence of behavioral problems is increased among the 15–25% of children who also have epilepsy and among children with severe motor impairment, hearing loss, intellectual impairment, and pain [37,38]. Approximately 8% of children with CP receive the diagnosis of autism, frequently diagnosed later in life than in children without CP [26].

Hearing and Vision. Between 50% and 75% of children with CP have visual impairment, including refractive errors, strabismus, nystagmus, altered visual field, and optic atrophy, and 11% are severely visually impaired [35]. Cortical visual impairment plays a large role in the loss of visual acuity and is most commonly associated with quadriplegia [39,40].

Hearing loss is found in about 12% of children with CP and is associated with very low birth weight,

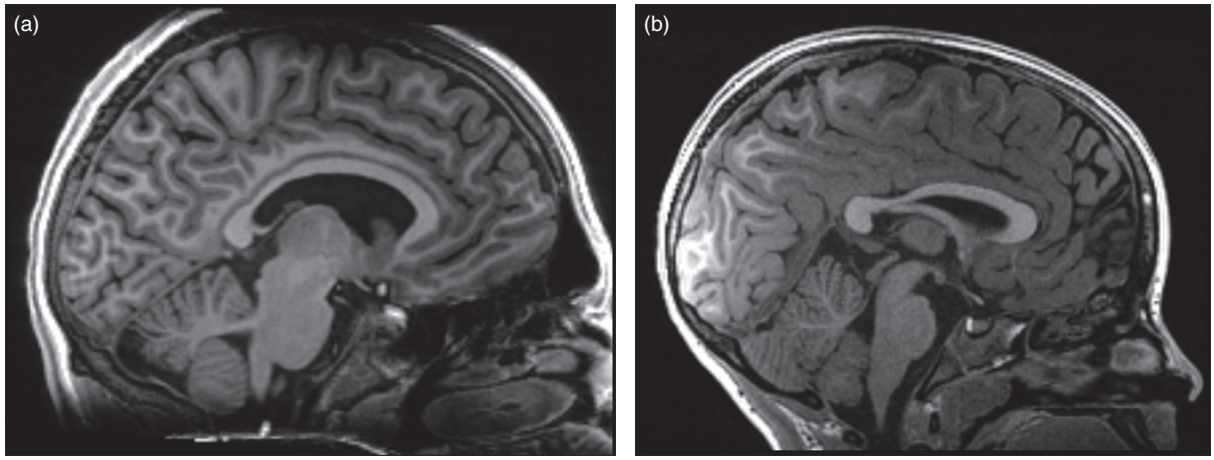


Figure 45.2 Sagittal scan of an infant with CP. Note the thin corpus callosum (arrow) and abnormal signal adjacent to the irregular ventricle.

kernicterus, neonatal meningitis, encephalopathy, and intellectual disability. Approximately 3% of children with CP have severe hearing loss [10,41].

Speech, Language, and Communication. Between 31% and 88% of children with CP have a communication disorder, and 25% of children are nonverbal [10,20]. Language development in children with CP correlates strongly with cognitive function. Speech impairment, such as dysarthria, is independent of cognition and strongly associated with the degree of motor impairment. Articulation disorders and limitations in speech intelligibility are seen in 40–88% of children with CP [42].

Feeding and Growth. Feeding difficulties occur in 30–40% of children with CP and are most common in children with severe motor impairment. Children may require help with feeding to allow adequate weight gain and to avoid choking and frequent vomiting [43]. Approximately 6% of children with CP require gavage feeding because they cannot safely or effectively obtain all their nutrition by mouth [10,35].

Pain and Sleep Disorders. Children and adults with CP experience pain that may decrease their quality of life and community participation. Pain has many causes, including spasms, contractures, hip dislocation, gastroesophageal reflux, skin breakdown and medical procedures. About 66% of school-aged children and 75% of teenagers with CP report having experienced pain in the previous week [44,45].

Up to 50% of children with CP have sleep difficulties, with 25% experiencing a moderate to severe sleep disorder [46]. Sleep-disordered breathing and difficulty initiating and maintaining sleep are the most common sleep disorders in this population. Sleep disorders are often associated with pain, poorly controlled epilepsy, and behavior disorders [47].

Quality of Life and Life Expectancy. Health-related quality of life is a multidimensional measure that integrates functional status with services needed, frequency of treatment, and activity restrictions. Health-related quality of life is lower in people with CP than in the general population. Adults with CP report employment disadvantages, fatigue, pain, and depressive symptoms [1]. Children with CP have an increased rate of behavioral and psychological difficulties compared with typically developing peers. Nonetheless, when describing quality of life, defined as perception of their position in life relative to their goals and expectations, children with CP reported quality of life similar to their typical peers, as the child in the opening case may have [48]. Adolescents with CP relate subjective well-being that is similar to that of their typical peers in all domains but social interaction with peers [1,48,49].

Approximately 5–10% of children with CP die during childhood, and life expectancy is otherwise near normal. Most often the children with early mortality had multiple areas of severe impairment, including epilepsy and intellectual disability [11]. As children with CP transition into adulthood, difficulties often arise in their ability to access healthcare and therapeutic services. Recent advocacy efforts have focused on ensuring that lifelong care provides rehabilitation that facilitates societal participation for adults as well as children with CP. Surveys of young adults with normal cognition and CP indicate that up to 33% have difficulty performing daily self-care activities and 66% have

unmet mobility needs [50]. About 50% of individuals with CP between the ages of 20 and 24 years are employed, but 33% of these individuals experience physical or situational barriers at work [51]. Approximately 75% of young adults with CP and normal cognition report having experienced dating; 25% are in a current romantic relationship, and the prevalence is unrelated to motor function, education, or gender [52].

Prevention

Current Approaches to Neuroprotection

A baby born at a gestational age below 28 weeks has 30–80 times the risk of CP as an infant born at term [53]. Because of this markedly increased risk of neurologic impairment in preterm infants, obstetricians and neonatologists continue to look for neuroprotective agents and strategies for high-risk pregnancies and neonates.

Many studies, including randomized trials, have found that CP rates are decreased in children prenatally exposed to magnesium sulfate [29,54]. The American College of Obstetricians and Gynecologists recommends the short-term use of magnesium sulfate for fetal neuroprotection for women in preterm labor under 32 weeks' gestation [55].

Antenatal corticosteroids also confer neuroprotection. Improved neonatal lung maturity leads to reduced rates of hypoxia and related problems. Besides improving lung maturity, antenatal steroids exert potent cerebral vasoconstrictive effects, minimizing fluctuations in cerebral blood flow. Infants born to women who received antenatal corticosteroids during preterm labor have a significantly decreased rate of CP [30].

Hypothermic cooling in term infants with neonatal encephalopathy has become a standard of care. A meta-analysis examining effectiveness demonstrated that hypothermia was associated with a reduction in the composite outcome of mortality or neurodevelopmental disability at 18–24 months of age. Seven at-risk infants must be treated with a hypothermia protocol to prevent one death or major disability [28].

Emerging Strategies for Neuroprotection

Human erythropoietin (Epo) is the primary regulator of erythropoiesis and is potentially neuroprotective. In vitro and in vivo experiments have demonstrated anti-inflammatory, antiexcitotoxic, antioxidant, and antiapopoptic effects of Epo on neurons and oligodendroglia. Recombinant human erythropoietin (rhEpo) promotes neurogenesis and angiogenesis. Retrospective reviews of infants treated with rhEpo for anemia of prematurity revealed improvements in neurodevelopmental outcomes over infants not receiving the medication. RhEpo is affordable, easy to administer, and has been found to be safe in phase II clinical trials [56]. It may potentiate other therapies, such as hypothermic cooling.

Inhaled nitric oxide (iNO) is a potent vasodilator used for the treatment of hypoxic respiratory failure and pulmonary hypertension. Early investigations suggest that iNO may decrease rates of severe intraventricular hemorrhage and periventricular leukomalacia and may ultimately reduce long-term disability rates [57].

Caffeine is a nonselective adenosine receptor antagonist used widely in the treatment of apnea in preterm infants. Despite promising early data, an ongoing randomized, controlled trial (RCT) of children receiving placebo or caffeine during the neonatal period demonstrated inconclusive benefit to neurodevelopmental outcomes at age 5 years. Data collection is ongoing [58].

Management of CP

Principles of Management

Care of children with CP requires a team of professionals working closely with individuals and their families. Current best practice finds that the primary care clinician in the medical home is an important anchor. The team may include members of many different professional fields: developmental pediatrics, neurology, orthopedic surgery, neurosurgery, physiatry, psychiatry, behavioral management, physical therapy, occupational therapy, speech and language pathology, orthotics, ophthalmology, and audiology. The spectrum of involvement for individual children determines their treatment needs and, therefore, their treatment team.

Treatment approaches are designed to capitalize on neuroplasticity. It is generally agreed that neuroplasticity is greatest in early childhood and gradually reduces as children age. Therefore, early intervention is recommended for children at risk for CP.

A tiered approach typically begins with rehabilitation services (PT, OT, treatment of sensory disorders,

communication therapy), educational interventions, and environmental adaptations. Adaptive equipment, including braces, walkers, and wheelchairs, may increase functional capacities. As needed, care progresses to medical treatments and surgical interventions. Outcome goals include improving functional skills and also preventing complications such as hip dislocation, deformities, and progressive rigidity. Overall goals should be broken down into measurable target objectives in order to inform treatment strategies and measure and evaluate outcomes. In line with the International Classification of Function framework, goals and objectives should emphasize increasing activity and community participation as well as addressing motor impairment. The goal is to educate and treat all children in the least restrictive environment while addressing their medical, rehabilitative, educational, social, and personal needs. Scientific evidence suggests that inclusive education rather than segregated education is associated with better outcomes, particularly in language, social, and emotional domains.

Rehabilitation

The mainstays of rehabilitative therapy of children with CP are PT and OT. A recent analysis of the literature suggests that child-active approaches, where the child practices real-life functional tasks for the purpose of gaining or consolidating skills, are more effective than passive approaches, such as stretching by a therapist [59]. Goal-directed child-active approaches and skills practice at high rates of repetition are thought to capitalize on neuroplasticity. Home programs are an important component of effective rehabilitation to increase opportunities to practice skills. Goals should be achievable for a child at each GMFCS level. For example, a child classified as GMFCS level IV who is unlikely to walk independently could learn self-mobility with a wheelchair. Fitness training has proven effective in increasing overall fitness in children with CP at all functional levels.

Constraint induced movement therapy (CI) is an intervention that targets upper extremity motor function in children with unilateral CP. Systematic reviews of trials using CI have demonstrated improved hand function on the affected side after CI [59,60]. The therapy consists of restraining the unaffected arm via casting or splinting while training the affected arm. The two theoretical mechanisms thought to make the treatment effective are overcoming *developmental disregard*, the preference to use the unaffected limb because of ease, and *cortical brain reorganization*, the changes in neural organization that occur when the limb is used.

Adaptive Devices/Facilitation

Rehabilitative therapists frequently recommend orthotic devices such as braces, splints, and seating and standing devices for children with CP. These devices are used to maintain range of motion, provide stability, prevent contractures, and improve function. The ankle-foot orthosis, one of the most commonly prescribed devices, stabilizes the position of the foot and stretches the Achilles tendon. Splints are used on the upper extremity to hold the wrist in a neutral position and abduct the thumb. Positioning devices promote skeletal alignment to facilitate independent function for activities such as eating.

Adaptive equipment, such as walkers, canes, and wheelchairs, is widely used to promote mobility. Motorized wheelchairs can be controlled by a switch that can be activated by the head, mouth, or hand. Prevention of pressure sores in people with CP with severe mobility restrictions is an essential element in the design of adaptive and positioning devices. Assistive technology is used to promote communication and improve quality of life for people with CP and severe dysarthria.

Medical Management

Medical management and secondary prevention interventions address the child's health and comorbidities, which may be more impairing than the motor deficits. They also strive to prevent worsening of physical disorders, such as contractures or hip dislocations.

Oral Medications. Diazepam has been found to be effective in reducing spasticity. The evidence regarding the effectiveness of dantrolene in reducing spasticity in children with CP is conflicting. At present, the evidence is insufficient to support the use of oral baclofen in the treatment of spasticity in children with CP. Biphosphonates are effective in maintaining bone density. Anticonvulsant therapy is an important part of the medical plan for children with seizure disorders [59,61].

Local Injections. Botulinum toxin A (BTX-A) is a neuromuscular blocking agent. When used in children with CP, BTX-A is injected into agonist muscles and causes transient muscle weakness for several months. Therapeutic goals include improving function, reducing

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pain from spasticity, and reducing joint deformity. BTX-A has been widely used for over two decades and has been found to be safe and effective for the treatment of localized spasticity in the upper and lower extremities of children with CP, generally leading to improvements in aspects of gait, such as ankle dorsiflexion and foot strike [59,61]. Intensive PT and OT after botulinum toxin injection have been shown to be effective in improving motor skills acquisition [59].

Orthopedic Management

Because of abnormal muscle tone, children with CP often develop joint deformities. Orthopedic surgery is performed to increase the range of motion of a joint and to treat secondary complications of spasticity. Serial ankle casting of an affected limb is effective in maintaining range of motion [59]. Hip dislocation in CP is potentially preventable if children are included from an early age in a surveillance program that includes repeat radiographic and clinical examinations and provided preventive treatment for hips that are displacing [62]. When necessary, orthopedic surgery can be effective by lengthening a tendon, cutting through a tendon or muscle (release), or moving the attachment point of tendon to bone. In children with spastic quadriplegia, surgery is frequently performed on hyperactive hip adductor muscles to improve the child's ability to sit and walk and to decrease the likelihood of hip dislocation. Hamstring release surgery may facilitate walking. Achilles tendons are frequently lengthened to improve walking. When complications such as hip dislocation or progressive scoliosis occur, orthopedic surgery is required for correction [7].

Neurosurgical Management

Intrathecal baclofen is often used in children over the age of 6 years with severe or generalized spasticity or dystonia. The medication is usually injected via a subcutaneous pump in the abdomen to a catheter in the intrathecal CSF compartment. Complications can include catheter difficulties, meningitis, and CSF leak. Intrathecal baclofen has been shown to significantly decrease spasticity in both upper and lower extremities in children with CP [61].

Selective dorsal rhizotomy interrupts the sensory component of the deep tendon reflex. It has been shown to be effective in reducing spasticity in the lower extremities of children with CP [59].

Future Treatment Options

Stem cells are multipotential cells that exist in both adult and developing tissue. True stem cells can differentiate into any tissue in the body and have unlimited proliferative and self-renewal capacity. Animal studies suggest that stem cells mediate neurologic repair by providing structural support to damaged tissue, remyelinating damaged axons, and expressing neurotrophic growth factors. Because true stem cells have the propensity to form teratomas, experimental treatment of CP has used partially differentiated stem cells injected either intravenously or intrathecally. Preliminary results from a phase I clinical trial using umbilical cord blood for the treatment of CP suggest improved cognition, motor function, and brain imaging findings in the stem cell treatment group over standard rehabilitation alone, but more adverse events were noted in the treatment group [63]. Further research must be done in this area before any conclusions about effectiveness or safety can be drawn. The recent development of "stem cell tourism" to unregulated clinics in different countries is an undesirable outcome of the early research in this field [64].

Clinical Considerations

The medical team in the neonatal intensive care unit (NICU) is frequently confronted with the difficult task of counseling families on possible adverse future neurodevelopmental outcomes for a child born preterm or with medical complications. Qualitative research has determined that parents want prognostic information early in a medical process [35]. This information can be particularly difficult to provide to family members when a child's medical condition is evolving and the ultimate diagnoses and prognoses remain uncertain. Up to 50% of parents of children with physical disability and 70% of parents of children with CP express dissatisfaction with the delivery of their child's diagnosis by physicians. These data indicate that clinicians must improve how they communicate potential bad news [65–67].

Qualitative research has found that the best approach for telling parents bad news is when a support person is present, the child is present, the clinician uses direct empathic language, and the clinician indicates a willingness and the time to answer family questions. Interpersonal physician behaviors such as empathy, availability for questions, accountability,

and acknowledging the child as a unique individual are helpful to parents. Leaving room for hope in the future has been identified as extremely important, particularly when outcomes remain uncertain [66]. In general, families are best served by an approach that balances honesty with hopefulness. An acknowledgment of the difficulty, such as, "How is it for you to sit with uncertainty?," can be therapeutic for a parent faced, for example, with evidence of white matter damage on their infant's MRI but without clinical evidence of neurologic injury. It is important to arrange referrals for early intervention, rehabilitative therapy, a pediatrician, and possibly a developmental follow-up clinic prior to the NICU discharge so that parents anticipate their child receiving care rather than simply waiting to learn the outcome. Identifying strategies for ongoing communication is also important because questions will inevitably arise after the child leaves the medical setting. Ideally, a clinician in the medical home coordinates care with the many specialists on the treatment team and guides the child and family as they make treatment decisions.

As a child ages, the primary care clinician on the medical home team assumes an important role in collecting, coordinating, and interpreting information from the various service providers. Even knowledgeable parents who have learned medical terminology may need help in understanding the issues before making difficult decisions. Over a child's lifespan, discussions with families should follow the principles of family-centered care, the practice of welcoming families and children as equal partners in the healthcare team. A key tenet of family-centered care is shared decision making, in which the family is encouraged to play an active role in helping to formulate the treatment plans for their child. In health conditions such as CP, where the scientific evidence does not necessarily dictate the one best treatment course, it is important to provide the family with unbiased information and support as they face critical treatment decision points.

Treatment goals should focus not only on improving a child's specific body functions but also on allowing a child to be active and to participate in society to his or her fullest ability. In the traditional medical model of care, the primary goal is to treat or cure a patient's symptoms, such as reducing spasticity or dystonia in a child with CP. In the social model of disability, the goal is to increase an individual's independence and participation in the larger community. Disadvantages experienced by individuals with CP may be caused by environmental and social factors as well as by the health condition. Consider, for example, the limitations for an individual who uses a motorized wheel chair for mobility and lives in a town without curb cuts to allow the wheel chair to go from sidewalk to street and back to sidewalk. Interventions in this situation may be required at the environmental, social, and even political level. Federal laws, such as the Americans with Disabilities Act and the Individuals with Disabilities Educational Act, that approach disability through the social model have significantly improved function and access for many individuals with CP [68].

With advancing medical knowledge and public awareness, improved functional outcomes are possible for all people with CP. Early identification and diagnosis leading to appropriate lifelong interventions and accommodations are all important to achieving good long-term outcomes for individuals with CP.

References

1. Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. *Lancet* 2014; **383**: 1240–9.
2. Pakula AT, Van Naarden Braun K, Yeargin-Allsopp M. Cerebral palsy: classification and epidemiology. *Phys Med Rehabil Clin North Am* 2009; **20**: 425–52.
3. Bax MC. Terminology and classification of cerebral palsy. *Dev Med Child Neurol* 1964; **6**:295.
4. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; **109**:9.
5. World Health Organization. International classification of functioning, disability, and health, 2001. Available at http://who.int/classifications/icf/icf_more/en/ (accessed May 23, 2015).
6. Rosenbaum P, Stewart D. World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. *Semin Pediatr Neurol* 2004; **11**:5–10.
7. Chan G, Miller F. Assessment and treatment of children with cerebral palsy. *Orthop Clin North Am* 2014; **45**: 313–25.
8. Foran JR, Steinman S, Barash I, et al. Structural and mechanical alterations in spastic skeletal muscle. *Dev Med Child Neurol* 2005; **47**: 713–7.
9. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. *JAMA* 2006; **296**: 1602–8.

10. Shevell MI, Dagenais L, Hall N. Comorbidities in cerebral palsy and their relationship to neurologic subtype and GMFCS level. *Neurology* 2009; **72**: 2090–6.
11. Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. *J Child Neurol* 2014; **29**: 1141–56.
12. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. *Am J Obstet Gynecol* 2015; **213**(6): 779–88.
13. Ellenberg JH, Nelson KB. The association of cerebral palsy with birth asphyxia: a definitional quagmire. *Dev Med Child Neurol* 2013; **55**: 210–6.
14. Rosenbaum PL, Palisano RJ, Bartlett DJ, et al. Development of the gross motor function classification system for cerebral palsy. *Dev Med Child Neurol* 2008; **50**: 249–53.
15. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
16. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. *Dev Med Child Neurol* 2008; **50**: 744–50.
17. Gross Motor Function Classification System, 2015. Available at https://canchild.ca/system/tenon/assets/attachments/000/000/058/original/GMFCS-ER_English.pdf (accessed May 27, 2015).
18. Manual Abilities Classification System, 2015. Available at www.macs.nu/files/Mini-MACS_English_2016.pdf (accessed May 27, 2015).
19. Ohrvall AM, Krumlinde-Sundholm L, Eliasson AC. The stability of the Manual Ability Classification System over time. *Dev Med Child Neurol* 2014; **56**: 185–9.
20. Hidecker MJ, Paneth N, Rosenbaum PL, et al. Developing and validating the Communication Function Classification System for individuals with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 704–10.
21. Oskoui M, Coutinho F, Dykeman J, et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2013; **55**: 509–19.
22. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, et al. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics* 2008; **121**: 547–54.
23. Durkin MS, Maenner MJ, Benedict RE, et al. The role of socio-economic status and perinatal factors in racial disparities in the risk of cerebral palsy. *Dev Med Child Neurol* 2015; **57**(9): 835–32.
24. Benfer KA, Jordan R, Bandaranayake S, et al. Motor severity in children with cerebral palsy studied in a high-resource and low-resource country. *Pediatrics* 2014; **134**:e1594–602.
25. McIntyre S, Taitz D, Keogh J, et al. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. *Dev Med Child Neurol* 2013; **55**:499–508.
26. Van Naarden Braun K, Christensen D, Doernberg N, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, metropolitan atlanta, 1991–2010. *PLoS One* 2015; **10**:e0124120.
27. Aisen ML, Kerkovich D, Mast J, et al. Cerebral palsy: clinical care and neurological rehabilitation. *Lancet Neurol* 2011; **10**: 844–52.
28. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013; **1**:CD003311.
29. Jacquemyn Y, Zecic A, Van Laere D, Roelens K. The use of intravenous magnesium in non-preeclamptic pregnant women: fetal/neonatal neuroprotection. *Arch Gynecol Obstet* 2015; **291**: 969–75.
30. Sotiriadis A, Tsiami A, Papatheodorou S, et al. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. *Obstet Gynecol* 2015; **125**: 1385–96.
31. Ashwal S, Russman BS, Blasco PA, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2004; **62**: 851–63.
32. Bosanquet M, Copeland L, Ware R, Boyd R. A systematic review of tests to predict cerebral palsy in young children. *Dev Med Child Neurol* 2013; **55**: 418–26.
33. Reid SM, Dagia CD, Ditchfield MR, et al. Population-based studies of brain imaging patterns in cerebral palsy. *Dev Med Child Neurol* 2014; **56**: 222–32.
34. Yin Foo R, Guppy M, Johnston LM. Intelligence assessments for children with cerebral palsy: a systematic review. *Dev Med Child Neurol* 2013; **55**: 911–8.
35. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics* 2012; **130**:e1285–312.
36. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil* 2006; **28**: 183–91.

37. Brossard-Racine M, Hall N, Majnemer A, et al. Behavioural problems in school age children with cerebral palsy. *Eur J Paediatr Neurol* 2012; **16**:35–41.
38. Parkes J, White-Koning M, Dickinson HO, et al. Psychological problems in children with cerebral palsy: a cross-sectional European study. *J Child Psychol Psychiatry* 2008; **49**: 405–13.
39. Fazzi E, Signorini SG, La Piana R, et al. Neuro-ophthalmological disorders in cerebral palsy: ophthalmological, oculomotor, and visual aspects. *Dev Med Child Neurol* 2012; **54**: 730–6.
40. Dufresne D, Dagenais L, Shevell MI. Spectrum of visual disorders in a population-based cerebral palsy cohort. *Pediatr Neurol* 2014; **50**: 324–8.
41. Dufresne D, Dagenais L, Shevell MI. Epidemiology of severe hearing impairment in a population-based cerebral palsy cohort. *Pediatr Neurol* 2014; **51**: 641–4.
42. Cockerill H, Elbourne D, Allen E, et al. Speech, communication and use of augmentative communication in young people with cerebral palsy: the SH&PE population study. *Child Care Health Dev* 2014; **40**: 149–57.
43. Andrew MJ, Parr JR, Sullivan PB. Feeding difficulties in children with cerebral palsy. *Arch Dis Child Educ Pract Ed* 2012; **97**: 222–9.
44. Parkinson KN, Dickinson HO, Arnaud C, et al. Pain in young people aged 13 to 17 years with cerebral palsy: cross-sectional, multicentre European study. *Arch Dis Child* 2013; **98**: 434–40.
45. Parkinson KN, Gibson L, Dickinson HO, Colver AF. Pain in children with cerebral palsy: a cross-sectional multicentre European study. *Acta Paediatr* 2010; **99**: 446–51.
46. Simard-Tremblay E, Constantin E, Gruber R, et al. Sleep in children with cerebral palsy: a review. *J Child Neurol* 2011; **26**: 1303–10.
47. Romeo DM, Brogna C, Musto E, et al. Sleep disturbances in preschool age children with cerebral palsy: a questionnaire study. *Sleep Med* 2014; **15**: 1089–93.
48. Bjornson KF, Belza B, Kartin D, et al. Self-reported health status and quality of life in youth with cerebral palsy and typically developing youth. *Arch Phys Med Rehabil* 2008; **89**: 121–7.
49. Colver A, Rapp M, Eisemann N, et al. Self-reported quality of life of adolescents with cerebral palsy: a cross-sectional and longitudinal analysis. *Lancet* 2015; **385**: 705–16.
50. Nieuwenhuijsen C, Donkervoort M, Nieuwstraten W, et al. Experienced problems of young adults with cerebral palsy: targets for rehabilitation care. *Arch Phys Med Rehabil* 2009; **90**: 1891–7.
51. Verhoef JA, Bramsen I, Miedema HS, et al. Development of work participation in young adults with cerebral palsy: a longitudinal study. *J Rehabil Med* 2014; **46**: 648–55.
52. Wiegerink DJ, Roebroeck ME, van der Slot WM, et al. Importance of peers and dating in the development of romantic relationships and sexual activity of young adults with cerebral palsy. *Dev Med Child Neurol* 2010; **52**: 576–82.
53. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008; **359**: 262–73.
54. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995; **95**: 263–9.
55. Magnesium sulfate use in obstetrics (Committee Opinion No. 573). *Obstet Gynecol* 2013; **122**: 727–8.
56. Fauchere JC, Koller BM, Tschopp A, et al. Safety of early high-dose recombinant erythropoietin for neuroprotection in very preterm infants. *J Pediatr* 2015; **167**(1): 52–7.e1–3.
57. Marks JD, Schreiber MD. Inhaled nitric oxide and neuroprotection in preterm infants. *Clin Perinatol* 2008; **35**:793–807.
58. Schmidt B, Anderson PJ, Doyle LW, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012; **307**: 275–82.
59. Novak I, McIntyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013; **55**:885–910.
60. Huang HH, Fetters L, Hale J, McBride A. Bound for success: a systematic review of constraint-induced movement therapy in children with cerebral palsy supports improved arm and hand use. *Phys Ther* 2009; **89**: 1126–41.
61. Delgado MR, Hirtz D, Aisen M, et al. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; **74**: 336–43.
62. Robb JE, Hagglund G. Hip surveillance and management of the displaced hip in cerebral palsy. *J Child Orthop* 2013; **7**: 407–13.
63. Min K, Song J, Kang JY, et al. Umbilical cord blood therapy potentiated with erythropoietin for children with cerebral palsy: a double-blind, randomized, placebo-controlled trial. *Stem Cells* 2013; **31**: 581–91.

64. Ruff CA, Faulkner SD, Fehlings MG. The potential for stem cell therapies to have an impact on cerebral palsy: opportunities and limitations. *Dev Med Child Neurol* 2013; **55**: 689–97.

65. Baird G, McConachie H, Scrutton D. Parents' perceptions of disclosure of the diagnosis of cerebral palsy. *Arch Dis Child* 2000; **83**: 475–80.

66. Orioles A, Miller VA, Kersun LS, et al. "To be a phenomenal doctor you have to be the whole package": physicians' interpersonal behaviors during difficult conversations in pediatrics. *J Palliat Med* 2013; **16**: 929–33.

67. Shevell AH, Shevell M. Doing the "talk": disclosure of a diagnosis of cerebral palsy. *J Child Neurol* 2013; **28**: 230–5.

68. Feldman HM. *Redesigning Health Care for Children with Disabilities: Strengthening Inclusion, Contribution, and Health*. Baltimore: Brookes Publishing, 2013.

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Chapter 46

Neurodevelopmental and Neurobehavioral Outcomes of Prematurity

Cognition, Language, Academic Skills, and Behavioral and Emotional Profiles

Irene M. Loe and Heidi M. Feldman

Introduction

Prematurity is an important public health issue not only because of the high prevalence of short-term major medical complications but also because of long-term adverse neurodevelopmental and neurobehavioral outcomes that require medical, educational, rehabilitative, and/or social services. *Neurodevelopmental outcomes* refer to the domains of cognition, language, and academic skills (Table 46.1). *Neurobehavioral outcomes* refer to behavioral and emotional profiles.

In the aftermath of preterm birth, neurodevelopmental and/or neurobehavioral deficits in the absence of major motor deficits have become the most prevalent adverse outcome [1]. Only 10–20% of survivors experience severe difficulties, including sensory and motor disorders [2], whereas 50% of children experience mild to moderate difficulties in neurodevelopment and/or neurobehavior. These challenges accumulate to put children born preterm at a distinct disadvantage compared with peers in educational, social, and ultimately occupational settings. Nonetheless, many young adults born preterm report a very good quality of life [3].

This chapter reviews the outcomes within neurodevelopment and neurobehavior. We emphasize outcomes of very low gestational age (<33 weeks) or birth weight (<1,500–1,800 g), and extremely low gestational age (<29 weeks) or birth weight (<1,000 g). Where possible, we discuss the results of systematic reviews and meta-analyses because the results of such studies, with large cumulative sample sizes, are likely to generalize to populations beyond those assessed. Children born preterm consistently score below matched controls born full term. We therefore report the absolute difference of mean scores or effect size without a negative sign for direction. After discussion of outcomes, we review medical complications of prematurity associated with the highest risk for adverse outcomes and environmental moderators of outcomes; knowledge of these factors increases our ability to identify the children at highest risk for adverse outcomes and may suggest intervention strategies to reduce morbidity. We also discuss neurologic factors that have been closely associated with adverse outcomes. Based on these findings, we conclude with recommendations for clinical practice and future research.

Cognition

Cognition can be defined as higher mental processes, including problem solving and abstract thinking. In clinical practice, cognition is often assessed using an intelligence test resulting in an intelligence quotient (IQ). IQ scores are presented as an age-adjusted standard score with a mean of 100 and a standard deviation of 15. An IQ of 100 indicates that the individual is functioning in the average range for chronological age. An IQ of less than 90 is considered low average, less than 80 is borderline range, and less than 70 with commensurate adaptive function and present before age 18 years is classified as intellectual disability. IQ represents a global measure that correlates with long-term academic achievement and occupational standing. However, intelligence tests are not designed to assess specific processing abilities. Neuropsychological processes, such as executive function skills, attention, and processing speed, contribute to performance on global cognitive measures and are assessed with specific neuropsychological measures.

Intelligence Quotient Scores

Children born preterm score, on average, in the average to low-average range on IQ tests. However, their mean IQ is consistently lower than that of well-matched peers born at term. A meta-analysis published in 2002 found that children born preterm scored 10.9 (95% confidence

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Table 46.1 Domains of function under the heading of neurodevelopment that are impacted by preterm birth

Domain	Definition	Measures
Cognition	Higher mental processes, including problem solving and abstract thinking	• Intelligence Quotient (IQ)
Executive Function	Constellation of skills that allow for purposeful goal-directed behavior, including cognitive flexibility, inhibitory control, and working memory	• Parent ratings • Laboratory measures • Computerized measures
Attention	Multi-faced construct that addresses mental focus, including selective attention, sustained attention, and executive attention	• Visual search tasks • Continuous performance task errors
Processing speed	Time required to register, manipulate, and respond to problem	• Encoding or response time • Cumulative time to complete complex tasks
Language	Distinctly human, structured and symbolic communication system	• Global measures • Specific measures of vocabulary, grammar, verbal memory
Speech	Verbal output of the language system	• Pronunciation of specific words or within conversation
Academic skills	Age-appropriate abilities to perform skills learned in school, including reading, spelling, writing, and mathematics	• Single word reading • Reading comprehension • Calculations • Applied mathematical problems

interval [CI] 9.2–12.5, $p < 0.001$) below full-term control children [4]. A larger meta-analysis covering 1980–2009 found a similar result; children born preterm had a mean IQ score that was 11.94 points lower (95% CI 10.47–13.42, $p < 0.001$) than full-term controls; the combined effect size of the difference was $d = 0.8$ [5]. While improvements in neonatal care have increased survival following preterm delivery, they have not changed morbidity in terms of IQ.

In both meta-analyses, differences between the preterm and full-term groups were stable across age at assessment, indicating that the children born preterm did not "catch up" to peers over time. Gestational age and birth weight have been positively associated with IQ [4,5]; lower gestational age, especially near the limits of viability, and lower birth weight are linked to unfavorable outcomes. Severe brain injury has been found to be the strongest predictor of low IQ and poor cognitive function, associated with a 20-point reduction in IQ [6].

Executive Function Skills

Executive function is an umbrella term referring to multiple complex and interrelated cognitive abilities that are used to direct purposeful, goal-oriented behavior [7]. They include component skills such as cognitive flexibility, inhibitory control, and working memory [7]. Expanded definitions include additional skills such as anticipation and deployment of attention, impulse control and self-regulation, initiation of activity, planning ability and organization, selection of efficient problem-solving strategies, and monitoring of performance [8]. In children born preterm, executive function skills are considered both a cognitive outcome and a mediator of other outcomes. In this population, executive function skills have been associated with multiple developmental and functional domains, including academic achievement, social competence, and adaptive function [9,10].

A systematic review of executive function in children born preterm included studies of preterm children at least 2 years of age published between 1990 and 2008 [11]. Separate meta-analyses were conducted for specific executive function skills, including inhibition, fluency, planning, and shifting. Group differences favoring controls were found for all skills (Table 46.2). Gestational age at birth less than 26 weeks was generally associated with worse outcomes. A second review included studies published between

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Table 46.2 Results of a meta-analysis of executive function skills demonstrate that children born preterm over age 2 years perform below controls born at term (10)

Subdomain	Definition or measure	Combined effect size (95% Confidence Interval [CI]
Response inhibition	Ability to withhold automatic or prepotent responses when a no-go signal is presented	0.25 SD (95% CI: .03-.47)***
Semantic verbal fluency	Ability to name words or items belonging to a specific category within specified time	0.43 SD (95% CI: .28-.59)
Phonemic verbal fluency	Ability to name words or items starting with a certain letter or sound within specified time	0.45 (95% CI: .0.3-0.6)*
Planning	Ability to develop strategies to reach a goal, usually a pre-specified tower in minimum moves	0.38 SD (95% CI: .008-.68)**
Shifting	Assessed as trail-making, in which participant connects numbers and letters in alphabetical or numerical order, shifting between the two	0.5 SD (95% CI: .36-.64)
Shifting	Assessed as observing if participant can shift rules after learning the first rule	0.1 SD (95% CI: -.06-.27)
Working memory	Ability to hold information in mind for future task, such as digit span	Inadequate number of studies

* $p < .05$, ** $p < .01$, *** $p < .001$

1998 and 2008 of very preterm/very low-birth-weight children who were at least age 5 years at the time of assessment. The results were similar: the preterm group performed below the full-term controls with small to medium combined effect sizes; children born preterm showed a decrement of 0.57 standard deviation (SD; 95% CI 0.82–0.32) for verbal fluency, 0.36 SD (95% CI 0.47–0.2) for working memory, and 0.49 SD (95% CI 0.66–0.33) for cognitive flexibility [12]. Mean age at assessment in this analysis was not correlated with the strength of the effect sizes.

Attention

Attention is a multifaced construct that refers to how we select among competing stimuli, thoughts, or actions what to focus on. Attention is often considered a core cognitive ability, necessary to acquire new skills and knowledge and to complete tasks, including executive function tasks [13]. Attention can be subdivided into different domains, including selective (the ability to focus on relevant stimuli or information and ignore distracting stimuli), sustained (the ability to maintain an alert state for an extended period), and executive attention (the higher-level control of attention related to planned, self-generated activity with objects) [11,13,14].

A review of attention development in children born preterm compared with full-term peers during the first 4 years of life found that the children born preterm had delays in all domains of attention studied, including less mature visual orienting of attention, less sustained attention, and more trouble with executive attention [14]. The studies of executive attention suggested particular problems with inhibition of potential distracters during executive attention tasks. The differences between preterm and full-term groups increased with increasing age.

The meta-analysis focusing on children 2 years of age or older described earlier found group differences favoring controls for both selective and sustained attention [11]. Selective attention was often assessed through visual search tasks that require participants to find targets among a large display of distracters. For selective attention, the combined mean effect size was 0.38 SD (95% CI 0.21–0.54); when restricted to children born at less than 26 weeks' gestation, the effect size increased to 0.58 SD (95% CI 0.43–0.74). The differences remained generally stable across different chronological ages with the exception of children born at 26 weeks or more, in whom a large effect size at preschool age gradually decreased with increasing age. For sustained attention, assessed through omission errors on continuous performance tests, a moderate

Table 46.3 Representative studies of neurodevelopmental and neurobehavioral outcomes in relation to white matter in children, adolescents and young adults born preterm

Domain	Age of participants	Findings	Reference
Cognition or Intelligence quotient	9–16 years	Associations of IQ and diffusion properties of multiple tracts within the preterm group only	81
	17–22 years	Association of cognitive performance and diffusion properties within white matter clusters	80
	18–22 years	Association of IQ and diffusion properties within the preterm group	79
	13–18 years	White matter volume and area of the corpus callosum associated with IQ in preterm group only	86
Executive function	15 years	Association of performance on Wisconsin Card Sort test diffusion properties within the left cingulum and bilateral fronto-occipital fascicles	87
Language	9–16 years	Association of multiple language measures and diffusion properties within a bilateral network	88
	16 years	In cases of language impairment, bilateral volume reduction in the uncinate and extreme capsule and in fibers of the splenium of the corpus callosum	89
Speech skills	16 years	Measures of speech associated with abnormalities in left hemisphere corticospinal and corticobulbar tracts	28
Reading skills	9–16 years	Association of single word reading and comprehension and diffusion properties of a distributed bilateral network	88
	16 years	Association of rapid naming with left and right arcuate fasciculus	90
Mathematics skills		Numerical distance estimation associated with properties of right anterior inferior parietal lobe and right inferior frontal gyrus	91
Behavior and emotion	6 years	Hyperactivity associated with differences in brain mean connectivity and bilateral intra-hemispheric mean connectivity	93
	9–16 years	Association of parent-ratings of attention and anxiety with diffusion properties of a distributed bilateral network	92

effect size of 0.45 SD (95% CI 0.23–0.66) reflected variability across studies. The effect size increased to 0.67 SD (95% CI 0.31–1.03) when restricted to those born at less than 26 weeks' gestation.

A large geographic cohort study of extremely preterm/extremely low-birth-weight 8-year-old children found significantly poorer performance in preterm compared with full-term children on several measures of attention, including selective, sustained, encoding, shifting, and divided attention; effect sizes ranged from 0.3 to 0.6 SD [15]. Adolescents with a history of extremely preterm/extremely low birth weight had deficits in selective, shifting, and divided attention but not sustained attention compared with matched full-term controls. [16].

Processing Speed

An increasing body of findings implicates slow processing speed as an unfavorable outcome of preterm

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birth and a mediator of other difficulties. *Processing speed* refers to the time required to detect, interpret, and respond to incoming stimuli. Speed of processing contributes to the efficiency with which information can be registered, manipulated, and integrated across multiple processes in the service of complex functions. Processing speed has been conceptualized as a fundamental component of the cognitive system [17].

Children born preterm show slow processing speed on a variety of tasks. For example, at age 11 years, processing speed and memory were associated with IQ in a combined sample of children born preterm and full term [18]. In another study, preterm-full term group differences in academic attainment scores could be accounted for in part by processing speed as measured on a neuropsychological battery [19]. In a study relating performance at age 7 years to neonatal neuroimaging, children born preterm performed significantly more poorly than term controls on attention and processing speed outcomes. The roots of these processing-speed differences appear in infancy and persist into adolescence [18].

Language and Speech

Language is a distinctly human form of communication that is highly structured and symbolic. Language skills are typically assessed in terms of *receptive language*, the ability to understand, and *expressive language*, the ability to produce. Further subdivisions such as vocabulary, syntax, and verbal memory can also be assessed. Speech is the verbal output of the language system. Speech can be assessed in a variety of ways, including performance on tests and analysis of language samples.

A few studies have found no delays in the earliest stages of language development in children born preterm in infancy [20,21], toddler years [22,23], and preschool [24]. However, a meta-analysis of language abilities in children ages 2–12 years found consistently poorer skills among children born preterm than control children. The combined effect size for expressive skills was 0.63 (95% CI −0.80 to 0.45) and for receptive skills was 0.77 (95% CI −0.94 to 0.60); preterm children performed below control subjects in expressive and receptive semantics and grammar [25]. A second meta-analysis of children born before 37 weeks' gestation and age 3–14 years at the time of assessment confirmed that the children born preterm scored significantly lower than the children born at term on assessments of simple language functions, primarily receptive vocabulary (combined effect size d = 0.45, 95% CI −0.59 to −0.30) and complex language (d = 0.62, 95% CI −0.82 to −0.43; $p < 0.001$), receptive language (d = 0.69, 95% CI −0.82 to −0.55, $p < 0.001$), and expressive language (d = 0.61, 95% CI −0.74 to −0.47, $p < 0.001$)[26]. These findings remained unchanged when the samples were restricted to children without major disabilities. The findings were independent of socioeconomic status. The group differences on complex language increased significantly from 3–12 years of age, indicating that the children born preterm fell further behind peers as they aged [26].

Language difficulties after prematurity can be explained in part on the basis of low IQ. However, even after controlling for nonverbal or verbal IQ and socioeconomic status, the degree of prematurity as measured by gestational age group was found to be a significant predictor of linguistic processing speed and verbal memory but not receptive vocabulary or syntactic comprehension [27].

Only a few follow-up studies have focused on speech outcomes in children born preterm. Articulation errors were rare in a British cohort of adolescents; however, approximately half of those assessed had difficulties on a measure of oral and verbal motor control, and 33% had received speech and language therapy at younger ages [28]. A prospective follow-up study of 8- year-old children found reduced articulation skills as well as poorer receptive language skills, performance IQ, and motor skills in a group of very low-birth-weight infants with bronchopulmonary dysplasia compared with children of very low birth weight without chronic lung disease and full-term control children. The groups also differed in enrollment in speech-language therapy; 48% of the group with bronchopulmonary dysplasia had been enrolled in speech-language therapy compared with 21% of the low-birth-weight group and 9% of the control group [29]. A large national cohort of children born at less than 25 weeks' gestation found speech as well as language problems in the preterm group. Differences in general cognitive scores explained language deficits but not ratings of speech in the preterm group [30].

One important factor likely to specifically influence the development of language and speech is the minimal amounts of maternal language that neonates are exposed to while in the neonatal intensive care unit (NICU) [31, 32]. Whereas under typical circumstances, the mother's voice would be the fetus's most salient source of acoustic stimulation, the sound environment of an infant within the NICU contains

many loud and nonhuman noises, only a tiny fraction of which is human speech [33].

Academic Outcomes

Academic skills refer to age-appropriate abilities to read, write, and do mathematical problem solving. Strong academic skills are critical to progressing through school and relate to general functioning in the community beyond school. Children with weak academic skills often receive assistance with learning at school in the form of additional instruction, individual tutoring, specialized instruction, separate classrooms, and separate schools.

Reading

Children born preterm have poorer reading skills than peers born at term. A meta-analysis that compared children born very preterm/very low birth weight with full-term peers found a combined effect size of 0.48 (95% CI −0.60 to −0.34, $p < 0.001$) for reading and of 0.76 (95% CI −1.13 to −0.40, $p < 0.001$) for spelling [12]. Reading has classically been divided into two fundamental component skills: *single-word reading*, also known as *decoding*, which refers to the ability to accurately identify written words, and *reading comprehension*, which refers to the ability to derive meanings from and form interpretations of written words and sentences. A second meta-analysis showed that children born preterm had significantly lower scores than those born at term for decoding ($d = 0.42$, 95% CI −0.57 to −0.27, $p < 0.001$) and reading comprehension ($d = 0.57$, 95% CI −0.68 to −0.46, $p < 0.001$). Lower gestational age was associated with larger differences between preterm and term groups in both decoding and reading comprehension. Differences between groups increased significantly with age for reading comprehension, the more demanding reading skill. A large Bavarian study found that approximately 50% of the variance in reading scores and 41% of the variance in spelling scores were explained by the combination of IQ, rhyming skills, and number knowledge. In these multifactor regression models, after accounting for the other factors, prematurity did not significantly contribute to the prediction [30]. These findings suggest that the same underlying factors are associated with reading skills in both preterm and full-term populations.

Mathematics

Compared with children born full term, children born preterm consistently show lower mathematics achievement scores, higher rates of learning difficulties in mathematics, and more mathematics difficulties based on teacher ratings [34]. A meta-analysis of children over age 5 years confirmed mathematics deficits on standardized tests [12]. The tests used assessed written math skills (i.e., addition, subtraction, multiplication, and division) and applied problems skills. The combined effect size was 0.6 SD (95% CI −0.074 to −0.46). Cohort studies confirm lower math scores compared with matched term controls [34], with effect sizes ranging from 0.5–0.6 SD in the extremely preterm/extremely low-birth-weight group at 8 years of age [35] to 1.7 SD for children born at 26 weeks' gestation or less at 11 years of age [36]. Among the latter group, the rate of mathematics impairment was nearly 70% compared with only 14% of classmates at age 11 years [36]. Many children born preterm qualify as having a learning disability in mathematics when the definition is lower scores in mathematics than predicted by IQ [37]. Using a low-achievement criteria for learning disability, children with a birth weight of less than 750 g were 6 times more likely to have a mathematics learning disability and 13 times more likely to have a combined reading/mathematics learning disability than peers born at term [38].

In typical development, individual differences in mathematical attainment implicate both domain-general and domain-specific skills [34,39]. *Domain-general skills* are skills including general intelligence; executive functions, in particular visuospatial skills, working memory, shifting, and inhibitory control; and language. *Domain-specific skills* refer to many skills linked specifically to mathematics: internal representations of number, referred to as *approximate number sense* or *symbolic distance effect*; the ability to carry out basic math procedures, such as counting sets of objects or reciting a number word list; the ability to assess, select, and apply computational strategies; and basic and complex conceptual understanding of mathematics. Overall, the data suggest that difficulties in mathematics attainment in children born preterm are more closely tied to domain-general than domain-specific skills. A study of 8-year-old children born preterm found no differences compared with full-term children on a measure of magnitude comparisons but found a trend for slower reaction times in the preterm group

when performing the task [40]. Similar results were found in a cross-sectional study of 6 and 8 year old children; the preterm group was as accurate, but significantly slower than the full term group on a measure of magnitude comparisons [41]. A study of extremely preterm 11 year old children found poorer performance compared to full term controls on all measures of a number estimation test [39]. However, using hierarchical linear regression models, the study found that number estimation scores accounted for only 2% of the variance whereas domain-general skills, including simultaneous and sequential processing, reading attainment, and visuospatial skills, accounted for 48% and 72% of the variance in mathematics attainment for both full term and preterm groups, respectively [39]. A rigorously designed and comprehensive study of very preterm 8 to 10 year old children included simultaneous assessment of mathematics achievement, working memory, visuospatial processing, inhibition, processing speed, numerical representations, and specific mathematics skills [34]. The preterm group compared with full-term group had significant difficulties in mathematics and several general and specific skills associated with mathematical achievement that were not attributed to differences in nonverbal IQ or socioeconomic status [34]. Furthermore, poor performance in specific mathematical tasks was entirely accounted for by domain-general deficits in working memory and visuospatial skills but not nonverbal IQ.[34]

Educational Resources and Services Utilization

Cognitive and academic difficulties in children born preterm are accompanied by increased utilization rates of educational resources and supports. Many studies across different countries corroborate this basic finding. A Dutch study found that children born preterm had a higher grade-repetition rate (25.5%) than full-term peers, although grade repetition did not improve their academic skills [24]. A population-based cohort study in southern Sweden of extremely preterm infants compared with full-term control infants at age 10 years found that 38% of the children performed below grade level and that 30% who attended mainstream schools received special education [42]. In the United States, compared with control children, children born preterm with and without brain injury required more school services (76% and 44% versus 16%) in all academic areas surveyed, including reading (44% and 28% versus 9%), writing (44% and 20% versus 4%), and mathematics (47% and 30% versus 6%). A study of four international population-based cohorts of children born weighing less than 1,000 g at birth found that school difficulties were a serious sequela in all four countries [43]. More than half of all cohorts required special education assistance and/or repeated a grade.

The cumulative impact of these cognitive and academic difficulties can be substantial. In the United States, a 10-point reduction in IQ score from the population mean of 100 to a group mean of 90 increases the risk of dropping out of high school from 6% to 35% and the risk of living in poverty from 6% to 16% [5]. In a longitudinal study of young adults, age 20 years, who had been born weighing less than 1,500 g, from 1977 to 1979, fewer participants born preterm had graduated from high school or obtained a general equivalency diploma, more had repeated a grade in school, and fewer were enrolled in postsecondary studies. The differences in educational attainment, grade repetition, and current educational program remained significant when excluding the participants with neurosensory impairment or subnormal IQ [44]. However, in a Canadian cohort aged 22 to 25 years, 82% of the young adults born preterm had graduated from high school compared with 87% of the control young adults, and a substantial proportion of both groups were pursuing higher education [3]. The Canadian sample was of higher socioeconomic status and had access to better healthcare and educational services than did the American counterpart, differences that may have contributed to differences in outcome.

Behavioral and Emotional Profiles

Behavior and emotional problems in children born preterm are reported frequently, starting as early as infancy and the toddler years [45,46] and continuing through childhood, adolescence, and young adulthood [47]. Studies often use standardized parent and/or teacher questionnaires and report scores above a cutoff for clinical significance; unfortunately, these methods are not as precise as diagnostic interviews for establishing a clinical diagnosis. A meta-analysis of nine studies of children born very preterm or very low birth weight using the Child Behavior Checklist and/or Teacher Report Form found significant effect sizes for parent and teacher ratings of

internalizing behavior problems, defined as withdrawal, depression, and anxiety (d = 0.20, 95% CI 0.48–0.08 and d = 0.28, 95% CI −0.45 to −0.12, respectively), and for ratings of attention problems (d = 0.59, 95% CI −0.74 to −0.44 and d = 0.43, 95% CI −0.61 to −0.25), but not for externalizing problems such as aggression [12]. However, another meta-analysis of school-aged children found that preterm children had increases in both externalizing and internalizing problems [4]. A review of studies on preterm birth and risk of childhood psychiatric disorders described a "preterm behavioral phenotype" as characterized by increased risk for disorders of inattention, anxiety, and social difficulties [48].

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD), the most common behavioral disorder in childhood, is characterized by high levels of inattention and/or hyperactivity-impulsivity. The symptoms go beyond that expected based on developmental level and impair function in at least two settings, usually home and school. A meta-analysis found that compared with children born at term, children born preterm had more than twice the relative risk (RR) for developing ADHD (pooled RR 2.64, 95% CI 1.85–3.78) [4]. Difficulties with behavior, including reduced attention, have been reported in infancy [45], preschool years [49,50], and school age [47,51] and adolescence [52]. ADHD in preterm groups is generally characterized by high rates of inattention without concomitant hyperactivity or impulsivity and with lower rates of comorbid conduct disorders than in full-term cohorts. These findings suggest different neurodevelopmental origins of ADHD in children born preterm compared with full-term children. In adolescents, a geographic cohort study using diagnostic interviews and symptom questionnaires found no other differences in lifetime mental health diagnoses or recent symptoms of depression or anxiety except ADHD [52].

Emotional Disorders

In children born preterm, emotional problems, including depression and anxiety, can be identified in infancy and persist through school age [46]. By school age, studies find a four- to sixfold increase in the odds for anxiety disorders without an increase in depression [53,54]. Children born at less than 26 weeks' gestation had a 9% prevalence of emotional disorders compared with 2% in term controls, for an odds ratio of 4.6; emotional disorders were primarily comprised of separation anxiety and generalized anxiety disorder [55]. A small prospective cohort study reported greater internalizing behaviors and increased rates of antidepressant prescriptions in young adults born very preterm/low birth weight [56]. A meta-analysis that used clinical psychiatric diagnostic criteria in individuals born preterm/low birth weight aged 10–25 years compared with full-term control individuals found an increased risk for the preterm/low-birth-weight group for any psychiatric diagnosis with an odds ratio of 3.66 (95% CI 2.57–5.21) and for anxiety or depressive disorder with an odds ratio of 2.86 (95% CI 1.73–4.73) [57]. Female sex and poor physical health have not been associated with emotional disorders in survivors of prematurity, in contrast with findings in the general population [55]. An association of cognitive impairment and emotional problems has been found in some [54] but not all studies [58].

Autism Spectrum Disorder

Definition: *Autism spectrum disorder* (ASD) is a developmental disorder characterized by core behavioral symptoms occurring in two major areas: (1) social communication and social interactions and (2) repetitive patterns of behavior, interests, or activities. The qualitative impairments in social communication and interactions include deficits in social and emotional reciprocity, nonverbal communicative behavior, and developing, maintaining, and understanding relationships. Repetitive and restrictive behaviors and interests include stereotyped or repetitive motor movements, insistence on sameness or inflexibility, restricted, fixated interests of abnormal intensity or focus, and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects in the environment.

Broadband behavioral rating scales frequently identify elevations in social problems in preterm compared with full-term children [48]. While these questionnaires are not specific for ASD, elevated rates of abnormal results have also been found in children born extremely preterm using parent screening questionnaires specific for autism [59–61]. The exclusion of children with motor, neurosensory, and cognitive impairments results in much lower rates of suspected autism, although rates are often still elevated

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compared with the general population [59–62]. There are few longitudinal studies on ASD to determine prevalence. One study of children born during the 1990s using a questionnaire found that 3.6% of extremely low-birth-weight (ELBW) children met criteria for ASD at 8 years of age [63]. In a geographic cohort study of children born at less than 26 weeks' gestation in the United Kingdom and Ireland, 8% of preterm children at age 11 years received a diagnosis of ASD [64]. Twice as many children had clinical symptoms but did not reach the level of clinical diagnosis or disorder, similar to other behavioral outcomes in preterm children.

Moderators and Mediators

Moderators

Many clinical conditions associated with prematurity are also associated with adverse outcomes, including chronic lung disease, recurrent apnea and bradycardia, transient hypothyroxemia of prematurity, hyperbilirubinemia, nutritional deficiencies, postnatal glucocorticoid exposure [65], and multiple surgeries before term-equivalent age [66]. These medical complications most likely influence outcomes by their impact on the developing brain, even in the absence of overt neurologic injury [65]. In addition, stressful environmental conditions in the NICU, such as decreased infant-caregiver interactions, reductions in environmental learning experiences, constant noise and bright light, and repeated painful procedures, may further compromise neurodevelopment [65,67]. These findings suggest that until medical therapies can prevent or minimize clinical complications of prematurity, it would be wise to fundamentally change the environment of NICUs to improve long-term morbidity [68].

Socioeconomic status moderates cognitive outcomes in children born preterm. Low birth weight and prematurity are more prevalent within low versus middle and upper socioeconomic groups [69,70]. Neurodevelopmental outcomes of children in low socioeconomic classes are also less favorable than outcomes for the middle and upper classes [71]. Specific social determinants of outcomes include maternal education, household structure (single-parent family), and minority race [6]. These findings highlight the cumulative risk for poor cognitive outcomes associated with poverty and socioeconomic disadvantage.

Mediators

Neuropsychological processes that characterize the preterm cognitive profile may contribute to or actually mediate the effects of preterm birth on specific skills in cognition, language, and academics and on behavioral and emotional profiles. Executive function skills have been found to mediate the effects of gestational age on adaptive function, academic skills, and behavioral symptoms [9]. Processing speed has also been found to mediate the significant effect of preterm birth on tests of executive function, including inhibition, working memory, shifting, and semantic fluency [72]. In a longitudinal study, structural equation modeling found that four cognitive domains identified at age 7 months, including processing speed, mediated the effects of prematurity on cognitive development, as measured by the Bayley Scales of Infant Development at age 2 years [73] and on later IQ [74]. Processing speed within the domain of language may be a mediator of later outcomes in the domain of language; linguistic processing speed at 18 months of age, as indexed by reaction time to look toward the picture corresponding to an auditory verbal stimulus, was highly correlated with scores on a receptive vocabulary test at age 3 years [75], even after consideration of the effects of socioeconomic status, developmental level, and parent-reported vocabulary size. Together these results suggest that how quickly and efficiently young children born preterm are able to detect, interpret, and respond in real time becomes critical for learning and for longer-term trajectories of development.

Neural Basis of Adverse Outcomes

Multiple factors act together to lead to adverse neurodevelopmental and neurobehavioral outcomes in the aftermath of prematurity. Figure 46.1 summarizes the cascade of events that can lead to neurologic consequences and adverse outcomes.

White Matter Injury

The most notable injury after preterm birth affects cerebral white matter [1,76]. In the past, necrosis in the deep periventricular white matter led to cystic lesions, readily apparent on cranial ultrasound or magnetic resonance imaging (MRI). These injuries were associated with motor and cognitive disabilities. Over the last two decades, changes in neonatal

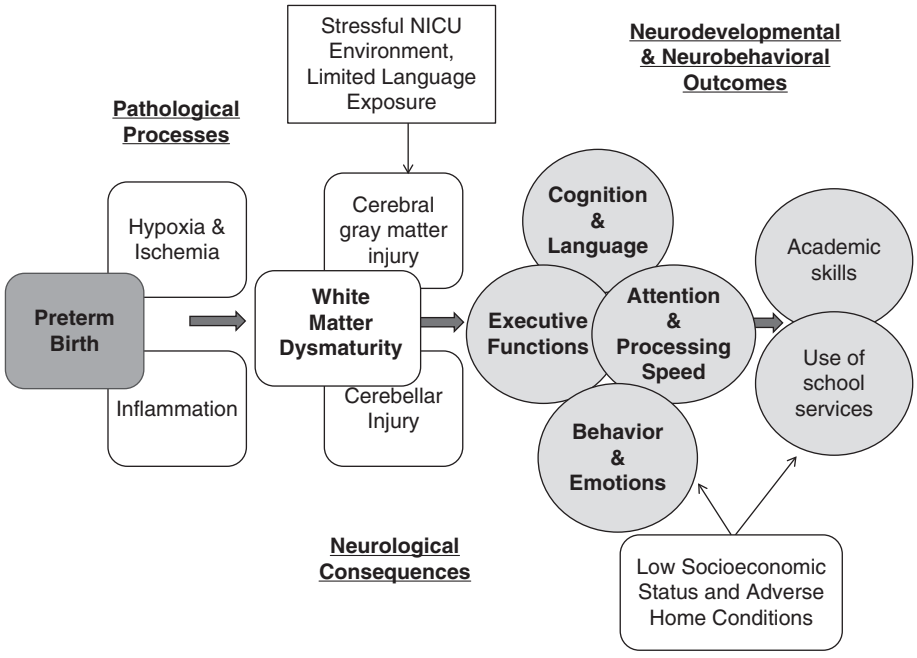


Figure 46.1 A schematic diagram of the consequences of preterm birth that lead to adverse outcomes. Sublethal hypoxia and ischemia and inflammation disrupt white matter in the brain as well as other injuries. The stressful NICU environment with deficient language exposure further contributes. These factors lead to the neurodevelopmental and neurobehavioral outcomes described in the text.

medical care have led to a decline in the prevalence of severe cystic injuries without a concomitant decline in the prevalence of noncystic white matter injuries [77]. These changes in neurologic outcomes of prematurity have been associated with increasing prevalence of neurodevelopmental and neurobehavioral deficits without accompanying motor disorders.

The pathogenesis of the noncystic injuries appears to relate to the fate of precursors of oligodendrocytes, the myelin-producing cells of the mature nervous system. These cells are particularly vulnerable to ischemia and hypoxia from approximately 24–32 weeks of postmenstrual age, prior to the onset of myelination. In animal models, hypoxia and ischemia result in significant losses of the oligodendrocyte precursors. New cells repopulate damaged regions, but these replacements fail to mature properly and, as a result, do not produce myelin [76]. Persistent noncystic injuries and white matter dysmaturity are difficult to detect and quantify on conventional neuroimaging, even MRI. However, white matter integrity and maturity can be assessed using quantitative MRI methods, especially diffusion MRI techniques. A systematic review of diffusion MRI tractographic studies at near-term gestational age confirms that diffusion properties are altered in children born preterm, with differences generally associated with postmenstrual age at scan [78]. Differences in white matter microstructure persist into adolescence and adulthood [79–81].

A growing body of research finds significant associations of white matter properties at term-equivalent age and later neurodevelopmental outcomes. Qualitative white matter abnormalities [82] and fiber tracking [83] both at term-equivalent age were found to predict cognitive delays at age 2 years and language skills at age 4 years [84]. The diffusion properties of white matter microstructure in children born preterm remain different from those in peers born at term into adolescence [81,85] and adulthood [79]. White matter findings at the older ages are associated with concomitant neurodevelopmental outcomes in children, adolescents, and adults who had been born preterm. Table 46.3 summarizes studies that find significant associations between neurodevelopmental and neurobehavioral outcomes of prematurity and various properties of the white matter of the brain. Associations have been found for IQ [79–81,86]; executive function [87]; language skills, including linguistic processing speed and verbal memory [88] and

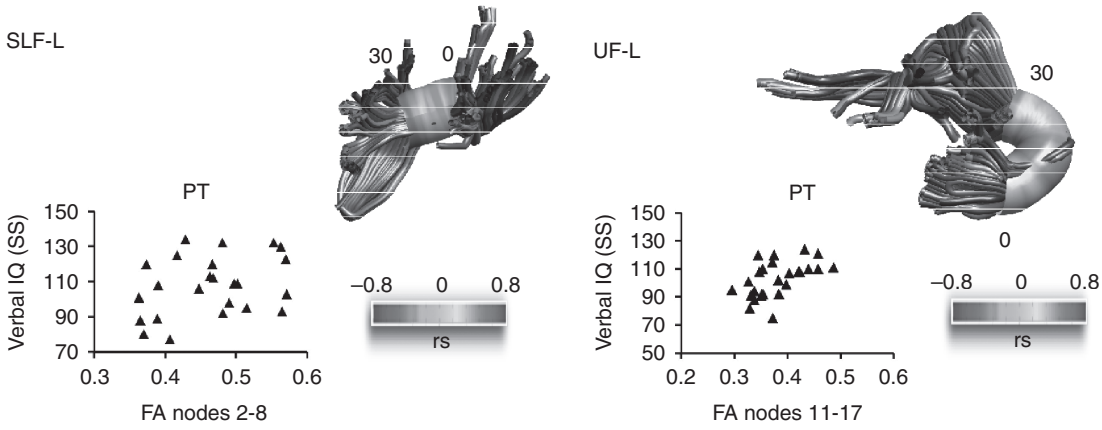


Figure 46.2 Associations between results of tractography analyses and verbal IQ standard score (SS). Shown are results from two tracts–the superior longitudinal fasciculs (SLF) in the left hemisphere (L) and the uncinate faciculus (UF) also in the left hemisphere. The main white matter diffusion measure is fractional anisotropy (FA); higher FA usually indicates more mature or healthy white matter. Each panel includes a rendering of the specific tract with the strength of the Spearman correlation between FA and IQ represented as a heat-map cylinder surrounding the tract. Each panel also includes a scatter plot representing the strength of the association between FA of the tract segment and IQ standard scores. FA is positively associated with IQ within the SLF-L and UF-L. Color bars represent Spearman correlation coefficients. (FA = fractional anisotropy; aSLF = anterior Superior Longitudinal Fasciculus; UF = uncinate fasciculus; CST = corticospinal tract; L= left; rs = Spearman correlation coefficient).

language impairment [89]; speech and oral motor function [28]; reading skills [88,90]; numerical skills and distance estimation [91]; attention and anxiety as rated by parents [92], and hyperactivity [93]. Figure 46.2 provides an example of a white matter tract in which the diffusion property called *fractional anisotropy* is highly associated with IQ.

Associated Brain Abnormalities

White matter injuries are typically accompanied by additional neuronal and axonal abnormalities [1]. Other structures that are associated with white matter injury include the thalamus, basal ganglia, hippocampus, cortex, and cerebellum. The degree of prematurity has been associated with volume reduction in the thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale. After controlling for the effects of prematurity, reduced thalamic volume predicted lower cortical volume; decreased volume in frontal and temporal lobes, including the hippocampus; decreased volume in parietal and occipital lobes; and altered diffusion properties in the corticospinal tracts and corpus callosum. These findings suggest that preterm delivery disrupts the thalamocortical system. Future research must evaluate the associations of these findings with neurocognitive outcomes. Caudate volume was weakly associated with IQ in 7-year-old children born preterm [94]. Hippocampal volumes were significantly reduced in children born preterm and especially among those with white matter injury [95]. At age 2 years, these hippocampal volumes were significantly correlated with the Mental and Psychomotor Development Indices of the Bayley Scales of Infant Development; after additionally adjusting for white matter injury and use of antenatal steroids, the only significant finding was the association on left hippocampal volume and Mental Developmental Index [95].

Brain Volume

Several studies find smaller head circumference in children born preterm than in children born at term [96], and small head circumference is associated with adverse developmental outcomes [97,98]. After controlling for gender and height, children born very preterm showed a 6.0% decrease in whole-brain volume, 11.8% decrease in cortical gray matter volume, 15.6% decrease in right hippocampal volume, and a 12.1% decrease in left hippocampal volume. They also had a 42.0% increase in the size of the lateral ventricles [99]. Small head circumference and reduced brain volume are likely caused by a loss of cellular elements from direct hypoxic-ischemic injury or axon degeneration after white matter injury. Though there is evidence of a global reduction of brain

volume among children born prematurely, regional reduction of volume particularly of the temporal lobes has been associated with a decrease in language functioning [100]. Increased gyrification of the temporal lobe, another indication of hypoxic-ischemic injury, has been associated with poor reading abilities in children born prematurely [101].

Cerebellar Injury

Cerebellar hemorrhagic injury may also be associated with developmental disorders in language, speech, and reading in children born prematurely [102]. Traditionally, the cerebellum was thought to be involved in motor activities and coordination. However, the cerebellum has now been implicated in cognitive, language, and reading tasks, though its precise function is not clear. Cerebellar damage may often be part of an extensive pattern of injuries after prematurity or found as an isolated lesion. Infants with isolated cerebellar hemorrhagic injury had lower expressive language, receptive language, and cognitive scores than full-term control infants [102]. Children with both parenchymal and cerebellar damage fared no worse than those with isolated cerebellar injury [102].

Clinical Implications

Neurodevelopmental skills are frequently delayed or disordered in the aftermath of prematurity. Neurobehavioral symptoms are also highly prevalent, though behavioral and emotional symptoms do not necessarily reach the level of clinical disorder. The severity of outcomes generally correlates with the degree of prematurity and medical complications. The white matter of the brain is particularly sensitive to recurrent sublethal hypoxia and ischemia and appears to be the most important neural factor associated with adverse neurodevelopmental and neurobehavioral outcomes. Other neural factors, such as small brain volume and cerebellar injury, may also contribute. However, using current clinical neural imaging at term-equivalent age does not necessarily detect the abnormalities of white matter that are associated with adverse outcomes.

Based on these findings, close clinical follow-up of children born preterm in terms of cognition, language, academic skills, behavior, and social-emotional functioning is clearly warranted. Because many of the issues of development and behavior can be detected during infancy, follow-up programs should begin early in life, before the child's first birthday. Follow-up programs must include at least children born at less than 33 weeks' gestation, regardless of medical complications or near-term neuroimaging results. Screening tools used in general pediatrics practice are not appropriate for this population. Screening tools that have been developed for general use among asymptomatic children are not appropriate for this population at high risk for abnormalities. Children born preterm should be evaluated with developmental measures and not screening tools. Behavior and social-emotional characteristics should be evaluated along with developmental standing. The best assessment protocol for children born preterm has not been established. Adjusting developmental scores for the degree of prematurity is still actively debated [103]. Adjusting too much or too long often renders children ineligible for special education and therapeutic services. As children age beyond 2 years, the adjustment makes less of a contribution to their scores, particularly in neurocognitive domains, and therefore may be counterproductive.

Most of the meta-analyses reported earlier do not find evidence of catch-up in developmental status as children get older. Therefore, early identification should lead to early intervention for the relevant issues. In the current era, all states within the United States offer early intervention services for children with developmental delays and disorders. Very few states find children eligible for early intervention strictly on the basis of extreme prematurity or low birth weight, even for children with multiple severe medical complications. Therefore, detection of developmental delay is essential for enrollment in early intervention services.

Problems in academic achievement are also highly prevalent in the aftermath of prematurity. While academic problems are associated with other neurodevelopmental and neurobehavioral problems, they may nonetheless not be detectable until school age. Given the enormous importance of academic achievement, follow-up of children born prematurely should continue until their literacy and mathematics skills can be accurately evaluated.

In summary, though clinicians and parents are relieved when a child born preterm is discharged from the neonatal hospitalization, it is important to emphasize follow-up care. Prematurity must be conceptualized as a chronic condition and not an acute event for most of the survivors. Systematic long-term follow-up with a strong emphasis on functional assessment may be required through adolescence to adulthood.

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Directions for Future Research

Learning more about the neural basis of developmental disorders after prematurity is essential to explain the adverse neurodevelopmental and neurobehavioral outcomes. Such information may also allow neonatologists and colleagues in other fields of medicine and science to improve clinical care in the newborn period to reduce these injuries. Studies on the effectiveness of neural protection require clinical trials with adequate long-term follow-up to evaluate improvements in neurodevelopmental and neurobehavioral outcomes at least until school age. The impact of change within the hospital environment should also be evaluated in terms of neurodevelopmental and neurobehavioral outcomes. Modest changes, such as reducing ambient noise and light and limiting the number of painful procedures, may lead to substantial improvements in long-term outcomes.

In the current era, children born preterm who experience delays or disorders receive similar interventions as their full-term peers with similar conditions. Infant specialists, speech/language therapists, and educators generally intervene with children who have delays on the basis of developmental levels, not on the basis of etiology or pathophysiology. However, research is desperately needed to investigate which educational and behavioral interventions truly improve outcomes in children born preterm. We need to consider whether specialized instructional methods for children born prematurely or children with specific neural injuries would allow more rapid gains than interventions based on generalized approaches. Furthermore, we must evaluate interventions for school age children with reading and attention problems in the aftermath of prematurity and associated neural injuries to determine whether children born prematurely benefit to the same degree as full-term children from pharmacologic and behavioral management treatments for ADHD or anxiety disorders.

Continued long-term follow-up of children born prematurely is important to document the outcomes of medical management in the newborn period and education and therapy throughout childhood. Such studies must consider functional outcomes in multiple domains, including learning, communication, socialization and interpersonal relationships, educational attainment, and success in major life areas, such as employment. Such follow-up should use a systematic and comprehensive approach, such as the International Classification of Functioning, Disability, and Health [104]. As research uncovers information about the long-term outcomes, treatments and management strategies from birth through hospitalization to intervention may all require adjustment.

References

1. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009; **8**(1): 110–24. PubMed PMID: 19081519.
2. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr* 2014; **35**(6): 394–407. PubMed PMID: 25007063.
3. Saigal S, Tyson J. Measurement of quality of life of survivors of neonatal intensive care: critique and implications. *Semin Perinatol* 2008; **32**(1): 59–66. PubMed PMID: 18249241.
4. Bhutta AT, Cleves MA, Casey PH, et al. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002; **288**(6): 728–37. PubMed PMID: 12169077.
5. Kerr-Wilson CO, Mackay DF, Smith GCS, Pell JP. Meta-analysis of the association between preterm delivery and intelligence. *J Public Health* 2012; **34**(2): 209–16.
6. Luu TM, Ment LR, Schneider KC, et al. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. *Pediatrics* 2009; **123**(3): 1037–44.
7. Miyake A, Friedman NP, Emerson MJ, et al. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cognitive Psychol* 2000; **41**(1): 49–100.
8. Anderson PJ, Reidy N. Assessing executive function in preschoolers. *Neuropsychol Rev* 2012; **22**(4): 345–60. PubMed PMID: 2012-32535-004.
9. Loe IM, Feldman HM, Huffman LC. Executive function mediates effects of gestational age on functional outcomes and behavior in preschoolers. *J Dev Behav Pediatr* 2014; **35**(5): 323–33. PubMed PMID: 24906034. Pubmed Central PMCID: NIHMS642002 (available on 06/01/15) and PMC4247205 (available on 06/01/15).
10. Loe IM, Lee ES, Luna B, Feldman HM. Executive function skills are associated with reading and parent-rated child function in children born prematurely. *Early Hum Dev* 2012; **88**(2): 111–8.
11. Mulder H, Pitchford NJ, Hagger MS, Marlow N. Development of executive function and attention in preterm children: a systematic review. *Dev Neuropsychol* 2009; **34**(4): 393–421.
12. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very

.047

low birth weight children. *Pediatrics* 2009; **124**(2): 717–28. PubMed PMID: 19651588.

13. Anderson PJ. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med* 2014; **19**(2): 90–6. PubMed PMID: 24361279.
14. van de Weijer-Bergsma E, Wijnroks L, Jongmans MJ. Attention development in infants and preschool children born preterm: a review. *Infant Behav Dev* 2008; **31**(3): 333–51. PubMed PMID: 18294695.
15. Anderson PJ, De Luca CR, Hutchinson E, et al. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. *Dev Neuropsychol* 2011; **36**(1): 57–73. PubMed PMID: 21253991.
16. Wilson-Ching M, Molloy CS, Anderson VA, et al. Attention difficulties in a contemporary geographic cohort of adolescents born extremely preterm/extremely low birth weight. *J Int Neuropsychol Soc* 2013; **19**(10): 1097–108. PubMed PMID: 24050646.
17. Kail R, Salthouse TA. Processing speed as a mental capacity. *Acta Psychol* 1994; **86**(2): 199–225.
18. Rose SA, Feldman JF. Memory and speed: their role in the relation of infant information processing to later IQ. *Child Dev* 1997; **68**(4): 630–41.
19. Mulder H, Pitchford NJ, Marlow N. Processing speed and working memory underlie academic attainment in very preterm children. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**(4): F267–72.
20. Eilers RE, Oller D, Levine S, Basinger D, et al. The role of prematurity and socioeconomic status in the onset of canonical babbling in infants. *Infant Behav Dev* 1993; **16**(3): 297–315. PubMed PMID: Peer Reviewed Journal: 1994–05051–001.
21. Reilly S, Eadie P, Bavin EL, et al. Growth of infant communication between 8 and 12 months: a population study. *J Paediatr Child Health* 2006; **42**(12): 764–70. PubMed PMID: 17096710.
22. Stolt S, Klippi A, Launonen K, et al. Size and composition of the lexicon in prematurely born very-low-birth-weight and full-term Finnish children at two years of age. *J Child Language* 2007; **34**(2): 283–310.
23. Menyuk P, Liebergott J, Schultz M. *Early Language Development in Full-Term and Premature Infants*. Hillsdale, NJ: Erlbaum Associates, 1995.
24. Aarnoudse-Moens CS, Oosterlaan J, Duivenvoorden HJ, et al. Development of preschool and academic skills in children born very preterm. *J Pediatr* 2011; **158**(1): 51–6. PubMed PMID: 20708749.
25. Barre N, Morgan A, Doyle LW, Anderson PJ. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. *J Pediatr* 2011; **158**(5): 766–74.
26. van Noort-van der Spek IL, Franken M-CJP, Weisglas-Kuperus N. Language functions in preterm-born children: a systematic review and meta-analysis. *Pediatrics* 2012; **129**(4): 745–54.
27. Lee ES, Yeatman JD, Luna B, Feldman HM. Specific language and reading skills in school-aged children and adolescents are associated with prematurity after controlling for IQ. *Neuropsychologia* 2011; **49**(5): 906–13.
28. Northam GB, Liegeois F, Chong WK, et al. Speech and oromotor outcome in adolescents born preterm: relationship to motor tract integrity. *J Pediatr* 2012; **160**(3): 402–8. PubMed PMID: 22000302. Pubmed Central PMCID: PMC3657185.
29. Lewis BA, Singer LT, Fulton S, et al. Speech and language outcomes of children with bronchopulmonary dysplasia. *J Commun Disord* 2002; **35**(5): 393–406.
30. Wolke D, Meyer R. Cognitive status, language attainment, and prereading skills of 6-year-old very preterm children and their peers: the Bavarian Longitudinal Study. *Dev Med Child Neurol* 1999; **41**(02): 94–109.
31. McMahon E, Wintermark P, Lahav A. Auditory brain development in premature infants: the importance of early experience. *Ann NY Acad Sci* 2012; **1252**(1): 17–24.
32. Rand K, Lahav A. Impact of the NICU environment on language deprivation in preterm infants. *Acta Paediatr* 2014; **103**(3): 243–8.
33. Caskey M, Stephens B, Tucker R, Vohr B. Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics* 2011; **128**(5): 910–6.
34. Simms V, Gilmore C, Cragg L, et al. Nature and origin of mathematics difficulties in very preterm children: a different etiology than developmental dyscalculia. *Pediatr Res* 2015; **77**(2): 389–95.
35. Anderson P, Doyle LW, Callanan C, et al. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *JAMA* 2003; **289**(24): 3264–72. PubMed PMID: Peer Reviewed Journal: 2003–06381–001.
36. Johnson S, Hennessy E, Smith R, et al. Academic attainment and special educational needs in extremely preterm children at 11 years of age: the EPICure study. Arch *Dis Child Fetal Neonatal Ed* 2009; **94**(4): F283–9. PubMed PMID: 19282336.
37. Taylor HG, Espy KA, Anderson PJ. Mathematics deficiencies in children with very low birth weight or very preterm birth. *Dev Disabil Res Rev* 2009; **15**(1): 52–9. PubMed PMID: 19213016.
38. Litt J, Taylor HG, Klein N, Hack M. Learning disabilities in children with very low birthweight:

prevalence, neuropsychological correlates, and educational interventions. *J Learning Disabil* 2005; **38**(2): 130–41. PubMed PMID: 15813595.

39. Simms V, Cragg L, Gilmore C, et al. Mathematics difficulties in children born very preterm: current research and future directions. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**(5): F457–63. PubMed PMID: 23759519.
40. Guarini A, Sansavini A, Giovanelli G, et al. Basic numberical processes in preterms. *World J Pediatr* 2006; **2**(2): 102–8.
41. Guarini A, Sansavini A, Fabbri M, et al. Basic numerical processes in very preterm children: a critical transition from preschool to school age. *Early Hum Dev* 2014; **90**(3): 103–11. PubMed PMID: 24331582.
42. Stjernqvist K, Svenningsen N. Ten-year follow-up of children born before 29 gestational weeks: health, cognitive development, behaviour and school achievement. *Acta Paediatr* 1999; **88**(5): 557–62.
43. Saigal S, Ouden Ld, Wolke D, et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. *Pediatrics* 2003; **112**(4): 943–50.
44. Hack M, Flannery DJ, Schluchter M, et al. Outcomes in young adulthood for very-low-birth-weight infants [see comment]. *N Engl J Med* 2002; **346**(3): 149–57. PubMed PMID: 11796848.
45. Spittle AJ, Treyvaud K, Doyle LW, et al. Early emergence of behavior and social-emotional problems in very preterm infants. *J Am Acad Child Adolesc Psychiatry* 2009; **48**(9): 909–18. PubMed PMID: 19633579.
46. Arpi E, Ferrari F. Preterm birth and behaviour problems in infants and preschool-age children: a review of the recent literature. *Dev Med Child Neurol* 2013; **55**(9): 788–96. PubMed PMID: 23521214.
47. Johnson S, Marlow N. Growing up after extremely preterm birth: lifespan mental health outcomes. *Semin Fetal Neonatal Med* 2014; **19**(2): 97–104.
48. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. *Pediatr Res* 2011; **69**(5 Part 2): 11R–8R.
49. Woodward LJ, Moor S, Hood KM, et al. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**(5): F339–44. PubMed PMID: 19307223.
50. Elgen SK, Leversen KT, Grundt JH, et al. Mental health at 5 years among children born extremely preterm: a national population-based study. *Eur Child Adolesc Psychiatry* 2012; **21**(10): 583–9. PubMed PMID: 22752364.
51. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. *J Dev Behav Pediatr* 2012; **33**(3): 202–13.
52. Burnett A, Davey CG, Wood SJ, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. *Psychol Med* 2014; **44**(7): 1533–44. PubMed PMID: 23981686.
53. Botting N, Powls A, Cooke RW, et al. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *J Child Psychol Psychiatry* 1997; **38**(8): 931–41. PubMed PMID: 9413793.
54. Indredavik MS, Vik T, Heyerdahl S, et al. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonat Ed*. 2004; **89**(5): F445–50. PubMed PMID: 15321968.
55. Johnson S, Hollis C, Kochhar P, et al. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Child Adolesc Psychiatry* 2010; **49**(5): 453–63. PubMed PMID: 2010–09510–007.
56. Saigal S, Stoskopf B, Streiner D, et al. Transition of extremely low-birth-weight infants from adolescence to young adulthood: comparison with normal birth-weight controls [see comment]. *JAMA* 2006; **295**(6): 667–75. PubMed PMID: 16467235.
57. Burnett A, Anderson P, Cheong J, et al. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. *Psychol Med* 2011; **41**(12): 2463–74.
58. Loe I, Lee E, Luna B, Feldman H. Behavior problems of 9–16 year old preterm children: biological, sociodemograhic, and intellectual contributions. *Early Hum Dev* 2011; **87**(4): 247–52.
59. Kuban KC, O'Shea TM, Allred EN, et al. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. *J Pediatr* 2009; **154**(4): 535–40. PubMed PMID: 19185317. PubMed Central PMCID: NIHMS106672 PMC2693887.
60. Luyster RJ, Kuban KC, O'Shea TM, et al. The Modified Checklist for Autism in Toddlers in extremely low gestational age newborns: individual items associated with motor, cognitive, vision and hearing limitations. *Paediatr Perinat Epidemiol* 2011; **25**(4): 366–76. PubMed PMID: 21649679.
61. Moore T, Johnson S, Hennessy E, Marlow N. Screening for autism in extremely preterm infants: problems in interpretation. *Dev Med Child Neurol* 2012; **54**(6): 514–20. PubMed PMID: 22458327.

62. Guy A, Seaton SE, Boyle EM, Draper ES, Field DJ, Manktelow BN, et al. Infants born late/moderately preterm are at increased risk for a positive autism screen at 2 years of age. *Journal of Pediatrics*. 2015 Feb; **166**(2): 269–75.e3. PubMed PMID: 25477165. English.

63. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. *Journal of Developmental & Behavioral Pediatrics*. 2009 Apr; **30**(2): 122–30. PubMed PMID: 19322106. Pubmed Central PMCID: NIHMS273114 PMC3074440. English.

64. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *The Journal of Pediatrics*. 2010 Apr; **156**(4): 525–31. PubMed PMID: Peer-Reviewed Status-Unknown: 2010–07245-017. English.

65. Perlman JM. Neurobehavioral deficits in premature graduates of intensive care: potential medical and neonatal environmental risk factors. *Pediatrics* 2001; **108**(6): 1339–48.

66. Gano D, Andersen SK, Glass HC, et al. Impaired cognitive performance in premature newborns with two or more surgeries prior to term-equivalent age. *Pediatr Res* 2015; **78**(3): 323–9.

67. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. *Ann Neurol* 2012; **71**(3): 385–96.

68. Goldstein RF. Developmental care for premature infants: a state of mind. *Pediatrics* 2012; **129**(5): e1322–3.

69. Parker JD, Schoendorf KC, Kiely JL. Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. *Ann Epidemiol* 1994; **4**(4): 271–8.

70. Joseph K, Liston RM, Dodds L, et al. Socioeconomic status and perinatal outcomes in a setting with universal access to essential health care services. *Can Med Assoc J* 2007; **177**(6): 583–90.

71. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behavl Pediatr* 2005; **26**(6): 427–40.

72. Mulder H, Pitchford NJ, Marlow N. Processing speed mediates executive function difficulties in very preterm children in middle childhood. *J Int Neuropsychol Soc* 2011; **17**(03): 445–54.

73. Rose SA, Feldman JF, Jankowski JJ, Van Rossem R. Pathways from prematurity and infant abilities to later cognition. *Child Dev* 2005; **76**(6): 1172–84. PubMed PMID: 16274433.

74. Rose SA, Feldman JF, Jankowski JJ. Processing speed in the 1st year of life: a longitudinal study of preterm and full-term infants. *Dev Psychol* 2002; **38**(6): 895–902. PubMed PMID: 12428702.

75. Marchman V, Adams K, Loi E, et al. Early language processing efficiency predicts later receptive vocabulary outcomes in children born preterm. *Child Neuropsychol* 2015; **22**(6): 649–65.

76. Back SA, Miller SP. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol* 2014; **75**(4): 469–86. PubMed PMID: 24615937.

77. Back SA. Perinatal white matter injury: the changing spectrum of pathology and emerging insights into pathogenetic mechanisms. *Ment Retard Dev Disabil Res Rev* 2006; **12**(2): 129–40. PubMed PMID: 16807910.

78. Pannek K, Scheck SM, Colditz PB, et al. Magnetic resonance diffusion tractography of the preterm infant brain: a systematic review. *Dev Med Child Neurol* 2014; **56**(2): 113–24. PubMed PMID: 24102176.

79. Eikenes L, Lohaugen GC, Brubakk AM, et al. Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. *Neuroimag*ing 2011; **54**(3): 1774–85. PubMed PMID: 20965255.

80. Allin MPG, Kontis D, Walshe M, et al. White matter and cognition in adults who were born preterm. *PLoS One* 2011; **6**(10): e24525.

81. Feldman HM, Lee ES, Loe IM, et al. White matter microstructure on diffusion tensor imaging is associated with conventional MRI findings and cognitive function in adolescents born preterm. *Dev Med Child Neurol* 2012; **54**(9): 775–868.

82. Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006; **355**(7): 685–94. PubMed PMID: 16914704.

83. van Kooij BJ, van Pul C, Benders MJ, et al. Fiber tracking at term displays gender differences regarding cognitive and motor outcome at 2 years of age in preterm infants. *Pediatr Res* 2011; **70**(6): 626–32. PubMed PMID: 21857376.

84. Foster-Cohen SH, Friesen MD, Champion PR, Woodward LJ. High prevalence/low severity language delay in preschool children born very preterm. *J Dev BehavPediatr* 2010; **31**(8): 658–67. PubMed PMID: 20613625.

85. Groeschel S, Tournier J-D, Northam GB, et al. Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. *NeuroImage* 2014; **87**: 209–19.

86. Northam GB, Liégeois F, Chong WK, et al. Total brain white matter is a major determinant of IQ in adolescents born preterm. *Ann Neurol* 2011; **69**(4): 702–11.

87. Skranes J, Lohaugen GC, Martinussen M, et al. White matter abnormalities and executive function in children with very low birth weight. *NeuroReport* 2009; **20**(3): 263–6. PubMed PMID: 19444947.

88. Feldman HM, Lee ES, Yeatman JD, Yeom KW. Language and reading skills in school-aged children and adolescents born preterm are associated with white matter properties on diffusion tensor imaging. *Neuropsychologia* 2012; **50**(14): 3348–62. PubMed PMID: 23088817. Pubmed Central PMCID: NIHMS419970 PMC3631607.

89. Northam GB, Liegeois F, Tournier JD, et al. Interhemispheric temporal lobe connectivity predicts language impairment in adolescents born preterm. *Brain* 2012; **135**(Pt 12): 3781–98. PubMed PMID: 23144265. Pubmed Central PMCID: PMC4031625.

90. Mullen KM, Vohr BR, Katz KH, et al. Preterm birth results in alterations in neural connectivity at age 16 years. *Neuroimage* 2011; **54**(4): 2563–70. PubMed PMID: 21073965.

91. Starke M, Kiechl-Kohlendorfer U, Kucian K, et al. Brain structure, number magnitude processing, and math proficiency in 6- to 7-year-old children born prematurely: a voxel-based morphometry study. *NeuroReport*. 2013; **24**(8): 419–24. PubMed PMID: 23587788.

92. Loe IM, Lee ES, Feldman HM. Attention and internalizing behaviors in relation to white matter in children born preterm. *J Dev Behav Pediatr* 2013; **34**(3): 156.

93. Fischi-Gómez E, Vasung L, Meskaldji D-E, et al. Structural brain connectivity in school-age preterm infants provides evidence for impaired networks relevant for higher order cognitive skills and social cognition. *Cerebral Cortex* 2015; **25**(9): 2793–805.

94. Abernethy LJ, Cooke RW, Foulder-Hughes L. Caudate and hippocampal volumes, intelligence, and motor impairment in 7-year-old children who were born preterm. *Pediatr Res* 2004; **55**(5): 884–93.

95. Thompson DK, Wood SJ, Doyle LW, et al. Neonate hippocampal volumes: Prematurity, perinatal predictors, and 2-year outcome. *Ann Neurol* 2008; **63**(5): 642–51.

96. Kilbride HW, Thorstad K, Daily DK. Preschool outcome of less than 801-gram preterm infants compared with full-term siblings. *Pediatrics* 2004; **113**(4): 742–7.

97. Peterson J, Taylor HG, Minich N, et al. Subnormal head circumference in very low birth weight children: neonatal correlates and school-age consequences. *Early Hum Dev* 2006; **82**(5): 325–34. PubMed PMID: 16360293.

98. Allen MC. Neurodevelopmental outcomes of preterm infants. *Curr Opin Neurol* 2008; **21**(2): 123–8.

99. Nosarti C, Al-Asady MHS, Frangou S, et al. Adolescents who were born very preterm have decreased brain volumes. *Brain* 2002; **125**(7): 1616–23.

100. Kesler SR, Ment LR, Vohr B, et al. Volumetric analysis of regional cerebral development in preterm children. *Pediatr Neurol* 2004; **31**(5): 318–25. PubMed PMID: 15519112.

101. Kesler SR, Vohr B, Schneider KC, et al. Increased temporal lobe gyrification in preterm children. *Neuropsychologia* 2006; **44**(3): 445–53. PubMed PMID: 15985272.

102. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? *Pediatrics* 2007; **120**(3): 584–93.

103. Wilson SL, Cradock MM. Review: accounting for prematurity in developmental assessment and the use of age-adjusted scores. *J Pediatr Psychol* 2004; **29**(8): 641–9.

104. World Health Organization. *International Classification of Functioning, Disability and Health*. Geneva: WHO, 2001.

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Chapter

47

Neurocognitive Outcomes in Term Infants with Neonatal Encephalopathy

Beatrice Latal, Rabia Liamlahi, and Steven P. Miller

Introduction

Neonatal brain injuries represent a group of common yet heterogeneous disorders that result in long-term neurodevelopmental deficits. A significant proportion is related to hypoxic-ischemic brain injury, either diffuse or focal (e.g., stroke). Neonatal brain injury is recognized clinically by a characteristic encephalopathy that evolves over days in the newborn period [1]. This clinical syndrome includes a lack of alertness, poor tone, abnormal reflex function, poor feeding, compromised respiratory status, and seizures [2]. Neonatal encephalopathy occurs in 1–6/1,000 live term births and is a major cause of neurodevelopmental disability [1]. The prevalence of neonatal encephalopathy has not decreased despite continuing basic and clinical research [3]. Therefore, the focus has shifted to the improvement of neurodevelopmental impairments associated with neonatal encephalopathy. Prior to the area of therapeutic intervention, up to 20% of affected infants died during the newborn period, and another 25% sustained permanent deficits of motor and also cognitive function [4,5]. Functional motor deficits are often described as cerebral palsy (CP), a nonprogressive disorder of motor function or posture originating in early life. Cognitive deficits include mental retardation or learning disabilities, impaired executive functions, impaired language skills, or impaired social ability. Other forms of neonatal brain injury, particularly in the term newborn, such as stroke, have an incidence as high as 1/4,000 live births [6]. More than 95% of infants with neonatal stroke survive to adulthood, and many have some form of motor or cognitive disability across their life course.

Thus neurocognitive deficits that follow neonatal encephalopathy are serious problems that frequently result in lifelong disability with a significant impact for the child, family, and society. In addition, even if neurocognitive deficits are mild, they often co-occur and may affect academic achievement and quality of life. Predicting the long-term outcome of newborns with encephalopathy in the earliest days of life has improved, with newborn brain imaging studies yielding important insights into expected patterns of neurocognitive outcomes. These patterns of injury reflect the etiology and timing of this injury, as well as the selective vulnerability of the neonatal brain to injury.

Understanding the full spectrum and evolution of neurocognitive outcome following neonatal encephalopathy is critical to applying and evaluating strategies to protect the neonatal brain from injury, such as therapeutic hypothermia (TH) [7–9] and other emerging therapies such as erythropoietin [10]. TH has been shown to significantly reduce cerebral injury and improve neurodevelopmental outcome until school age (Tables 47.1 and 47.2). As a consequence, the National Institute for Health and Clinical Excellence and the National Institute of Child Health and Human Development recommend that neonates with moderate or severe hypoxic-ischemic encephalopathy (HIE) should be treated with TH. Because outcome has improved with TH, the prevalence, spectrum, and severity of outcomes described for infants born prior to this era may differ significantly. However, children treated with TH have only now reached school age, and outcome is not yet available for older children and youth. In contrast to other at-risk populations such as preterm-born children and patients with congenital heart defects, little is known on the life-course effects of neonatal encephalopathy, which includes the assessment of quality of life, psychological well-being, and academic achievement in adulthood. In addition, no information on these important outcome parameters is available for those treated with TH. Better delineating the long-term impact and the personal and societal burden across the life course remains an important goal for future research.

Further, with the introduction of TH, previously established clinical and neuroradiologic predictors of outcome after HIE may alter their predictive power

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Table 47.1 Two-year outcome after therapeutic hypothermia for hypoxic ischemic encephalopathy

Author	Trial	Number of surviving participants with follow up data (%)	Primary outcome parameter	Age (mo) at follow up	Assessment battery	Mortality (%)		Cerebral palsy (%)		IQ	
						Cooled	Non cooled	Cooled	Non cooled	Cooled	Non cooled
Shankaran S. et al (2005)	NICHD	143 (69%)	death or IQ<70 at 6 to 7 years of age	18 to 22	BSID II	24	37	19	30	MDI (mean) 82	77
										<70 (%) 25	39
Azzopardi D.V. et al (2009)	TOBY	237 (73%)	death or severe disability at 18 month of age	18	BSID II	26	27	28	41	MDI (median) 96	93
										<70 (%) 24	35
Jacobs S.E. et al (2011)	ICE	152 (63%)	death or major disability	24	BSID II and BSID III	25	39	27	29	MDI <70 (%) 23	28
Gluckman P.D. et al (2005)	Cool Cap	140 (60%)	death or severe disability at 18 month of age	18	BSID II	33	38	19*	31*	MDI (median) 85	77
										MDI <70 (%) 30	39
Simbruner G. et al (2010)	neo. nEURO. network	70 (57%)	death or severe disability	18 to 21	Griffith, Brune-Lezine	38	57	13^{+}	48^{+}	Developmental quotient of <2 SD (%) 21	57

* severe neuromotor disability, + disabling cerebral palsy

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Table 47.2 School-age outcome after therapeutic hypothermia for hypoxic ischemic encephalopathy

Author	Trial	Number of surviving participants with follow up data (%)	Age (y) at follow up	Assessment battery	Mortality (%)		Cerebral palsy (%)		IQ	
					Cooled	Non cooled	Cooled	Non cooled	Cooled	Non cooled
Shankaran S. et al (2012)	NICHD	110 (53%)	6 to 7	WPPSI III,	28	44	17	29	IQ (median)	
				WISC IV,					83	81
Pappas A. et al (2015)				NEPSY,					IQ 70–84 (%)	
				Child Health Questionnaire					27	21
									IQ < 70 (%)	
									25	32
Azzopardi D. et al (2014)	TOBY	181 (56%)	6 to 7	WPPSI III,	29	30	21	36	IQ (mean)	
				WISC IV,					103.6	98.5
				NEPSY II,					IQ <85 (%)	
				Working Memory Test Battery for Children,					23	37
				SDQ Questionnaire,						
				ADHD Rating Scale IV			p = 0.03		p = 0.05	
Guillet R. et al (2011)	Cool Cap	62 (44%)	7 to 8	WeeFIM (assessed via telephone interview)	35	41	detailed scores not provided (see text)			

NICHD, National Institutes of Health; TOBY, Total Body Hypothermia for Neonatal Encephalopathy Trial; ICE, Infant Cooling Evaluation Collaboration; BSID, Bayley Scales of Infant Development; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WISC, Wechsler Intelligence Scale for Children; NEPSY, Neuropsychological Assessment Scale; SDQ, Strength and Difficulties Questionnaire; ADHD, Attention Deficit Hyperactivity Disorder; WeeFIM, Pediatric Functional Independence Measure

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and need to be reevaluated. In addition, modifications in the treatment of TH, such as the inclusion of preterm-born newborns, deeper and longer TH, or, as suggested, milder hypothermia may modify the effect of "classic" TH on outcome of children with HIE. Therefore, these changes in the TH protocol need to be performed through randomized, controlled trials (RTCs), and detailed long-term outcome needs to be carefully assessed [11]. This chapter focuses on describing the brain injuries leading to neurocognitive deficits following neonatal encephalopathy, including the etiology and timing of brain injury in this condition and the most commonly observed patterns of brain injury. The prevalence, spectrum, and severity of neurocognitive abnormalities following neonatal encephalopathy will be discussed, and outcome for children treated with TH will be presented in detail. Predictors of outcome, particularly patterns of brain injury, will be described. Open research questions and the consequences for healthcare providers are discussed.

Brain Injuries Leading to Neurocognitive Deficits Following Neonatal Encephalopathy

Etiology of Neonatal Encephalopathy

Neonatal encephalopathy is a heterogeneous condition with multiple etiologies. It is increasingly clear that most neonatal brain injury is metabolic, whether from transient ischemia-reperfusion or inherited defects in metabolic pathways resulting in energy failure. HIE accounts for a substantial fraction of neonatal brain injury, yet many cases of neonatal encephalopathy have no documented hypoxic-ischemic insult [3,12,13]. Other causes of neonatal encephalopathy include metabolic abnormalities such as acute bilirubin encephalopathy, hypoglycemia, and inborn errors of metabolism, infections, trauma, and malformations of cerebral development. Because many etiologies of neonatal encephalopathy have specific therapies and the underlying cause of the encephalopathy is an important determinant of neurocognitive outcome, a critical part of clinical management is to determine the underlying *etiology*. Because the etiology of a newborn's encephalopathy and its treatment are key determinants of the expected neurodevelopmental outcome, this chapter focuses on neonatal encephalopathy presumed to be secondary to hypoxia-ischemia.

Timing of Brain Injury in Neonatal Encephalopathy

Studies have determined the antenatal, perinatal, and postnatal factors that underlie the vulnerability of the newborn brain, as well as the mechanisms that contribute to resilience and recovery. There is continuing controversy as to whether neonatal encephalopathy from hypoxia-ischemia is related primarily to insults sustained in the antepartum or intrapartum period.

In a study of *risk factors* for neonatal encephalopathy, 69% of cases had antepartum risk factors such as maternal hypothyroidism, preeclampsia, or chorioamnionitis; 5% only had intrapartum risks such as cord prolapse or abruptio placentae; and 24% had both antepartum and intrapartum risks [14]. In prospective studies using MRI in the first days of life, it is increasingly apparent that most term newborns with encephalopathy presumed to be secondary to hypoxia-ischemia have an acquired brain injury at or near the time of birth that progresses over several *days* [15,16]. In one prospective cohort of neonatal encephalopathy, more than 90% of affected newborns had evidence of perinatally acquired insults on MRI, with a very low rate of long-standing antenatal brain injury [15]. The imaging findings of acquired brain injury in these studies include brain swelling, loss of gray-white matter differentiation, abnormal signal intensities in the deep gray nuclei or posterior limb of the internal capsule, or an acutely developing region of infarction. The use of diffusion-weighted MRI has also greatly improved our ability to assess the onset of brain lesions in term newborns with encephalopathy. The reduction in free water diffusion in areas of brain injury, reflected in decreased average diffusivity or decreased apparent diffusion coefficients on diffusion-weighted imaging, evolves over the first days of life and normalizes over the second week following acute brain injury in the term newborn [17,18].

Taken together, these data support the appropriateness of the term *hypoxic-ischemic encephalopathy* (HIE) when supported by the clinical scenario and imaging findings [13]. The revised American College of Obstetricians and Gynecologists' (ACOG's) statement on neonatal encephalopathy recognizes multiple pathways to neonatal encephalopathy, including

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proximate and distal risk factors that may occur pre-, intra-, and postpartum [19]. In some neonates it is possible that antenatal factors may lead to greater susceptibility to perinatal problems, whereas in others an acute sentinel is documented as a single perinatal event. These data suggest that because the brain injury is recent, it may be amenable to postnatal interventions such as hypothermia in the first days of life. With the increasing application of TH in newborns with moderate to severe encephalopathy, it is expected that the neurocognitive sequelae outlined below will change over the next 5–10 years. Recent brain imaging data also indicate the urgent need to discover the mechanistic link between antenatal risk factors and brain injury that occurs near the time of birth so that new prevention strategies for encephalopathy can be implemented to further improve neurocognitive outcomes.

Selective Vulnerability in the Neonatal Brain

Neonatal brain injury involves a complex set of interrelated biochemical and molecular pathways including oxidative stress and excitotoxicity, inflammation, and genetic effects, as addressed elsewhere in this book (see Chapter 3). Underlying these mechanisms is a selective vulnerability of specific cell types at specific developmental stages. Together these factors underlie the regional vulnerability of the developing brain in the human newborn, including the characteristic patterns of injury and resulting neurodevelopmental outcomes.

Patterns of Brain Injury in Neonatal Encephalopathy

Advanced neuroimaging techniques such as MRI can now be applied in the human newborn to better understand the heterogeneity of brain injury associated with neonatal encephalopathy. The typical patterns of brain injury in neonatal encephalopathy are each associated with different patterns of neurodevelopmental outcomes. In a primate model of term neonatal brain injury, the specific regional distribution of injury was associated with different durations and severities of ischemia: partial asphyxia caused cerebral white matter injury, and acute and profound asphyxia produced selective injury to the basal ganglia and thalamus [20,21]. Because changes on MRI correspond closely with histopathologic changes found on postmortem examination [22-25], MRI can be applied in vivo to better understand the heterogeneity of brain injury associated with neonatal encephalopathy. A comparable regional vulnerability is observed in the brain of term newborns following hypoxia-ischemia, resulting in two major patterns of injury detectable by MRI: (1) a *watershed predominant pattern* involving the white matter, particularly in the vascular watershed, extending to cortical gray matter when severe, and (2) a *basal nuclei predominant pattern* involving the deep gray nuclei, perirolandic cortex, and hippocampus and extending to the total cortex when severe [1,26–29]. These patterns reflect the predominant regions of injury with frequent overlap in affected newborns. Involvement of the hippocampus has been linked to specific neurocognitive deficits later in childhood [30]. As expected from the primate models, newborns with basal nuclei patterns of injury have the most intensive need for resuscitation and the most severe clinical encephalopathy. Focal infarctions, either arterial or venous, of the brain are an additional but underrecognized pattern of injury in the term newborn, occasionally occurring in the setting of neonatal encephalopathy [15,31]. Consistent with observations of childhood stroke, many newborns with stroke have *multiple* risk factors for brain injury, including intrapartum complications [32].

Therapeutic Hypothermia

After extensive animal research, the first clinical trials emerged, demonstrating a clear beneficial effect of TH. TH was administered in these trials either by active whole-body cooling or by selective head cooling. Recent systematic reviews summarized previous studies and could show that TH consistently improves early childhood neurodevelopmental outcome by reducing the rate of mortality and major neurodevelopmental disabilities [7-9]. Importantly, this effect was true for neonates with moderate but also severe HIE and did not increase the rate of children with severe neurodevelopmental disabilities at the cost of reducing mortality in severe HIE. Recently, long-term outcome to school age has also been reported. Based on these data, TH has become the standard of care for term-born infants with moderate and severe HIE.

In the following section, the severity and spectrum of short- and long-term neurocognitive sequelae after HIE will be discussed in detail for children born prior to TH treatment because there is significantly more

detailed information available. Thereafter, the literature available so far for children treated with TH is presented and discussed. It is noteworthy that currently this literature is sparse and that more studies will need to follow presenting long-term outcome and potential developmental impairments in the absence of overt disability.

Spectrum of Neurocognitive Abnormalities Following Neonatal Encephalopathy

The neurocognitive outcome following neonatal encephalopathy is variable and may include deficits of neuromotor, neurosensory, and cognitive functions. Cognitive deficits may result from the cerebral cortical injury that frequently accompanies basal nuclei injury. In contrast, the watershed pattern of injury is most commonly associated with cognitive impairments, particularly in language, that are not accompanied by major motor deficits [2,33,34]. The clinical correlate of the basal nuclei pattern of injury in the neonatal period is a severe encephalopathy, whereas the watershed pattern more frequently manifests as a more moderate encephalopathy. While both patterns may be accompanied by neonatal seizures, these are seen in almost 90% of those with the basal nuclei pattern and closer to half of those in whom watershed injury predominates [29]. The cognitive deficits associated with watershed injury may not be apparent in early infancy and often need more prolonged follow-up for detection. It should be stressed that abnormal outcome following neonatal encephalopathy is not limited to cerebral palsy *and* often requires follow-up beyond 1 year of age to be detected. Postnatal factors such as socioeconomic status have important effects on neurodevelopmental outcome following brain injury in the term newborn [33,35]. The impact of postnatal factors, particularly socioeconomic factors, on modifying outcomes following TH warrants further investigation.

Our clinical experience and recently reviewed data [36] suggest that the outcome of neonatal encephalopathy includes cognitive deficits as a prominent feature, even in the absence of CP, and is associated with the watershed pattern of injury and white matter damage [29,35]. A number of studies examining the long-term outcomes of children with neonatal encephalopathy or children with risk factors for hypoxia-ischemia have described isolated cognitive deficits in the absence of functional motor deficits [30,35,37–41]. The ACOG task force on neonatal encephalopathy now concludes that the outcomes following an acute intrapartum event may include CP of the spastic quadriplegic or dyskinetic type, and other subtypes of CP are less likely [19]. The new guidelines also note that other developmental abnormalities may be seen but are not specific to intrapartum asphyxia. In this era of increasing medical litigation, it is critical to stress that the referenced studies address the outcomes of critically ill newborns with overt encephalopathy rather than children identified later in life on the basis of isolated cognitive impairments. In addition to these clinical reports, experimental studies using a variety of large and small animal models demonstrate the selective vulnerability of the developing brain to hypoxia-ischemia. In the immature brain exposed to hypoxia-ischemia, injury predominates in the hippocampus, striatum, and parasagittal cortex [27]. The resulting hypoxic-ischemic injury often causes impairments in memory, learning, and spatial orientation, frequently in the absence of gross motor deficits (reviewed in Gonzalez & Miller [36]). The learning and behavior abnormalities may not be evident early in life but may only become apparent in adulthood. These studies highlight the need for a better understanding of the early brain lesions that underlie long-term neurodevelopmental impairments in this population. In addition, it is mandatory to assess the full spectrum of specific neurocognitive outcomes following neonatal encephalopathy, which include the following domains: neuromotor (CP and other motor abnormalities), neurosensory (vision and hearing), epilepsy, cognitive abilities (general, memory, executive function, language), behavior, and quality of life.

Specific Neurocognitive Outcomes Following Neonatal Encephalopathy

Compared with the extensive literature on outcomes of other populations at risk for neurodevelopmental impairment such as preterm-born children, the body of literature is remarkably small for survivors of neonatal encephalopathy. Previous publications on long-term outcome described children who suffered from "asphyxia" defined by abnormal biochemical or clinical markers (e.g., pH, base excess, Apgar score, intrauterine distress with bradycardia, abnormal cardiotocogram) but in whom the neurologic impairment after birth was not a defining criterion [42,43]. It is thus difficult to compare outcome of these studies with those using

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the severity of neonatal encephalopathy [44] as a defining criterion [39,45], particularly in the era of TH [46]. The current definition of hypoxic-ischemic encephalopathy mandates clinical signs of neonatal encephalopathy in the absence of other etiologies. While recent *imaging studies* support the assumption that once other causes of neonatal encephalopathy are excluded, such as genetic syndromes and congenital infections, the remaining cases are primarily related to hypoxia-ischemia, few of the *outcome studies* rigorously document intrapartum asphyxia in all subjects. Overall, studies of outcome following neonatal encephalopathy presumed to be secondary to hypoxic-ischemic injury have focused on mortality, neurologic disability, and, to a much lesser extent, cognition.

In addition to the major motor and cognitive disabilities that can be diagnosed in early childhood, a complete assessment of neurocognitive outcomes needs to consider domains that are more readily assessed as children develop to school age: learning (including writing, reading, and math), executive functions, behavior, and social competence. Impairments in these domains are often only detected with the increased demands of school and peer groups. Neurocognitive or intellectual abnormalities are recognized as important long-term sequelae, even in the absence of major motor impairments (reviewed in Gonzalez & Miller [36] and de Vries & Jongmans [47]). Intellectual abilities and, in particular, executive functions such as planning, organization, flexibility, and attention play an increasingly important role in today's society [48]. In addition, specific dysfunctions such as attention deficit hyperactivity disorder, developmental coordination disorder, autism spectrum disorder, and specific language impairment may follow neonatal brain injury either in isolation or more often in conjunction with each other (reviewed in de Vries & Jongmans [47] and van Handel et al. [49]).

Quality of life, an individual's subjective perception of physical and psychological health, is an important aspect of outcome that is only beginning to be probed following neonatal brain injury. Thus the assessment of long-term neurocognitive outcomes needs to consider the child's function in a variety of environments – family, school, employment, and society.

Many studies on neurocognitive sequelae after neonatal encephalopathy report outcomes at an early age. Early cognitive testing has limited predictive value for later functioning in part because early developmental testing relies on cognitive concepts that differ from later intellectual assessments where memory, executive function, language, and visuomotor functions are specifically tested. Thus early prognosis of later cognitive functioning is difficult and may be affected by a host of other factors such as genetics and environment, in particular, socioeconomic factors [35,45]. Very few studies report long-term outcome into adolescence or young adulthood [45,50–52]. These studies, however, do not uniformly use neonatal encephalopathy or HIE as an inclusion criterion and usually did not perform detailed neonatal brain imaging, limiting our ability to link long-term outcomes with patterns of injury in the newborn. Only two recent studies using current definitions of HIE showed that children at 9–10 years had lowered full-scale and performance IQ scores, also in the absence of CP [33,53].

In children treated with TH, cognitive impairment remains an important concern [54]. In school age survivors in the NICHD TH trial, subnormal IQ scores (IQ 70–84) were seen in almost one-third of those without CP. Importantly, more than one in five of children with IQ scores between 70 and 84 received special educational services or were held back at least one grade [54]. Knowledge on long-term outcomes of these children is crucial not only for parental counseling but also for tailoring follow-up services, appropriate therapies, and advising teachers and therapists caring for these children.

Neuromotor Outcome

Cerebral Palsy

In survivors of HIE, CP or severe disability ranges from 13% [38,55] to about 36% [29,37,39,41,51,56] but strongly depends on the severity of encephalopathy. Survivors of a severe neonatal encephalopathy face a high risk of CP. In one study, all surviving children after severe encephalopathy had a severe disability [41]. A more recent study reported that 42% of children with severe encephalopathy were diagnosed with CP at age 7 years [39]. At school age, spastic quadriparesis is the most common severe neurologic disability, although athetoid or spastic hemiparesis may also occur. Other disabilities often co-occur with CP and include sensorineural hearing loss, cortical blindness, and learning difficulties [39].

Motor Function in the Absence of CP

Few studies have examined motor functioning in the absence of CP in children with neonatal encephalopathy.

Their results indicate that motor problems in the absence of CP may occur and may also occur in children after mild neonatal encephalopathy. Parents reported an increased rate of minor motor impairments and fine motor problems for school age children with low Apgar scores and signs of neonatal encephalopathy (e.g., seizures, feeding difficulties, and/or ventilator treatment) [40]. The presence of a neonatal encephalopathy seems to be a critical risk factor for impaired motor skills. In a cohort with mild intrapartum fetal asphyxia but without neonatal neurologic signs in the majority, no difference in gross and fine motor performance was seen at 7 years of age (assessed by the Bruinicks-Oseretsky Test of Motor Proficiency and the Motor Accuracy Test) [57]. Motor performance using a standardized motor test (Movement Assessment Battery for Children) in sixty-one 9- to 10-year-old children with neonatal encephalopathy but without CP related motor performance to corpus callosum size on MRI. Definitely abnormal motor performance (≤5th percentile) was more frequently diagnosed in children with moderate encephalopathy but importantly also in children with mild encephalopathy (37.5% and 29%, respectively) [58]. Similar findings were reported for 5- to 6-year-old children: 23.5% of children with neonatal encephalopathy without CP were diagnosed with minor neurologic dysfunction and/or perceptual motor difficulties [37]. This was confirmed in a recent small study in which more than half of all children without CP had poor motor performance at school age (Movement Assessment Battery for Children, second version) [59]. Very little information is available on long-term outcome of neuromotor functions. Perez et al. demonstrated that at 10 years of age, all motor domains (pure motor, fine motor, dynamic balance) persisted to be impaired [33]. Around one-third to one-half of all children showed motor problems in these domains, and movement quality was also poorer. This shows that problems most likely persist and even may become more apparent, leading to difficulties in academic achievement and social integration.

Neurosensory Outcome

Vision

Impaired visual function after neonatal encephalopathy can be due to (1) cortical visual impairment resulting from injury in the posterior visual pathway, including the primary visual cortex [60], or (2) injury in other CNS structures (e.g., optic radiation, basal ganglia, or thalamus [61]) that may then affect acuity, visual fields, or stereopsis. Severe visual impairment or blindness occurs in 11–25% of children after severe or moderate encephalopathy, most often in association with neurologic disability [62,63]. Abnormalities can be detected in the first years after birth and are related to the extent of cerebral injury on MRI, in particular, to basal ganglia involvement [61]. Visual abnormalities persist to school age and are highly related to early visual abnormalities [64].

Hearing

Children with neonatal encephalopathy are at increased risk for sensorineural hearing loss [41,62]. Hearing loss may be associated with neurologic disabilities but not necessarily [56,63,65]. The pathophysiology of sensorineural hearing loss after HIE is not fully understood and may be due to selective injury to brainstem [66] and dorsal cochlear nuclei [56]. It appears that hearing loss is not associated with gentamycin treatment or familial deafness [65]. While there is no increase in parental-reported hearing impairments in children with low Apgar scores and signs of encephalopathy [40], survivors of moderate encephalopathy without CP are at substantial risk of hearing loss, with up to 18% affected based on parental report [51].

Epilepsy

Postneonatal epilepsy frequently occurs after moderate or severe neonatal encephalopathy, affecting 20–50% of survivors [67,68]. Two recent studies reported a significantly lower incidence of epilepsy (9.4%) in infants who were treated for clinical *and* subclinical seizures in the neonatal period [69,70]. Following TH, brainstem injury appears to predict a high risk of infantile spasms, whereas cortical injury *alone* confers a lower risk for short-term postneonatal epilepsy relative to injuries in the basal nuclei [71]. The occurrence of postneonatal epilepsy is strongly related to the diagnosis of CP and developmental delay [70].

Cognitive Ability

General

A limited number of studies have presented results on cognitive abilities. Overall, cognitive functions may also be impaired in the absence of CP or major disability [39,41]. Overall, 30–50% of children with moderate (grade 2) HIE have mental deficits at follow-up

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[47]. Marlow et al. demonstrated that intellectual performance in children with severe encephalopathy without CP is significantly poorer than in controls, with a mean difference of 11 IQ points [39]. Another study including children after amplitude-integrated electroencephalography (aEEG)–detected neonatal seizures (moderate and severe encephalopathy) showed that 11% of children with moderate encephalopathy manifested global delay in the absence of CP at 5 years of age [70]. Robertson and Finer found that 42% of nondisabled children (that is, in the absence of CP, mental retardation, severe neurosensory deficits, or seizure disorders) in the moderate encephalopathy group were delayed on school-readiness tests [72].

In addition to generally diminished intellectual performance, children in the moderate encephalopathy group were more likely to have problems in reading, spelling, and arithmetic compared with those with mild encephalopathy or control children at 8 years of age [41]. No difference was found between mildly encephalopathic newborns and control newborns [41]. A large study by Moster et al. from Norway compared children with low Apgar scores (0–3) and signs of neonatal encephalopathy to those with normal Apgar scores and no neonatal signs. Neurodevelopmental and behavioral outcomes were assessed by parental questionnaire. Children with major neurologic disabilities were excluded. The authors found that children with low Apgar scores and signs of neonatal encephalopathy had a sevenfold increased risk of need for extra resources in kindergarten and a threefold increased risk of intervention at school. They also were judged by their parents to perform below average in reading, writing, spelling, and mathematics [40].

It appears that the proportion of children with cognitive deficits may rise with increasing age of follow-up and increasing intellectual demands: a study examining 28 children at ages 15–19 years detected definitive cognitive dysfunctions in 71% of the children [51]. These dysfunctions are coupled with educational problems, which may continue into adulthood, leading to a higher unemployment rate and a lower proportion of survivors obtaining a university degree [50]. This was confirmed in a Swedish study linking the Swedish Medical Birth Registry and the Swedish School Grade Registry. They showed that a low 5-minute Apgar score (<7) as an indicator of HIE was associated with a significantly increased risk of never receiving graduation grades, presumably because they went to special schools because of cognitive impairment or other special educational needs [73].

Because HIE can cause potential long-term neurocognitive impairments, studies examining the protective role of TH need to follow these children until adolescence in order to delineate whether a lasting neuroprotective effect of TH occurs and which modifying factors may play a role.

Memory and Executive Functions

Little information is available on specific neurocognitive deficits after neonatal encephalopathy. However, short- and long-term memory problems, in particular, auditory memory, are prevalent in survivors of moderate or severe neonatal encephalopathy. A study by Lindström et al. showed that 64% of parents of children with moderate encephalopathy reported short-term memory problems and problems with time perception interfering with the child's daily life [51]. Deficits in short- and long-term memory may not be detected following a mild encephalopathy [57]. However, Robertson et al. showed that cognitive function of children after moderate encephalopathy was particularly affected in areas of auditory memory, attention, and short-term recall. They also demonstrated for children after mild encephalopathy that visual attention for letters and objects (assessed by the Detroit Tests of Learning Aptitude) was significantly diminished compared with a neonatal and peer comparison group [45]. Marlow et al. confirmed these findings in a cohort of 65 children at 7 years of age, 50 of whom were free of motor disability. Although childhood survivors of moderate neonatal encephalopathy had similar overall IQ scores compared with control children, specific cognitive impairments were detected: language and auditory memory (narrative memory, sentence repetition) on a standardized neuropsychological assessment scale (NEPSY) [39].

A study by Van Handel M et al. examined a broad spectrum of neuropsychological outcomes including short-term memory, verbal working memory, and episodic long-term memory in children after HIE at the age of 9 to 10 years [53]. They show in children with HIE that overall intelligence was reduced, *and* there is a specific profile with impaired verbal working memory and verbal and visuospatial long-term memory. In this study, the severity of HIE was associated with more profound impairments in these domains, although memory problems occurred in children without CP.

Language

Language development may also be impaired after neonatal encephalopathy [65]. Children following moderate encephalopathy are reported to have more problems in speaking and listening and reading and spelling compared with those with mild encephalopathy or control children [39,41]. Similar results were reported for children with low Apgar scores and signs of neonatal encephalopathy at school age compared with children with normal Apgar scores and no neonatal encephalopathy [40]. Language impairment appears to be especially related to severity of injury in watershed regions [33,34].

Behavior

Childhood survivors of neonatal encephalopathy without motor disability are at increased risk for behavioral problems such as hyperactivity and emotional problems [39]. Children with low Apgar scores (0–3) and signs of neonatal encephalopathy were more likely to manifest behavioral problems such as aggressive behavior, passivity, and anxiety as assessed by parental questionnaire using the Yale Children's Inventory Scale [40]. They were also almost four times more likely to need follow-up by a special resource center for children with educational or behavioral problems [40]. However, from this study it is unknown whether these behavioral outcomes differed in individuals with mild or moderate encephalopathy. Other studies suggest that behavioral abnormalities may not be detected at early school age (7–8 years) in children after mild or no encephalopathy [57]. In contrast, studies show that behavioral problems following moderate encephalopathy may persist into late adolescence. Comparing adolescents after moderate neonatal encephalopathy with a sibling comparison group, significant differences are seen on the Conners scale ($p < 0.003$), the inattention subscale of the ADHD Rating Scale IV ($p < 0.006$) and on the Asperger Syndrome Screening Questionnaire [51].

Quality of Life

Quality of life is a multidimensional construct integrating an individual's subjective perception of physical and psychological health, social, emotional, and cognitive wellbeing [74]. Quality of life can be assessed by means of self-reports or proxy reports. No study has been published on long-term quality of life of children after neonatal encephalopathy using instruments that reflect the above-mentioned construct. One study examined social interaction using standardized questionnaires (Conners 10-Item Scale, Asperger Syndrome Screening Questionnaire) [51]. Difficulties making friends or interacting with peers were reported more frequently for teenage children with moderate neonatal encephalopathy compared with their siblings [51]. In a study of family stress and function in 7-year-old children after mild neonatal encephalopathy, no difference in the number of major life events (e.g., divorce, loss of job, etc) was found between affected children and control children [57]. This finding is not unexpected because major life events have been associated only with major child disabilities but not with minor neurocognitive problems.

It is, however, striking that there is a paucity of studies examining quality of life in recent HIE cohorts with or without TH treatment. This is a clear lack of outcome information and needs to be addressed in future studies.

We therefore propose that all children, regardless of TH or other treatment, need stringent and regular follow-up assessments until early adolescence in centers experienced in the examination of at-risk populations. In these assessments, the full spectrum of potential developmental problems needs to be evaluated. As children grow older, the assessment becomes more complex and may have to include specific assessments of memory and executive function as well as social competence and visuoperceptual functions (Table 47.3). Validated and standardized assessment tests should be used, and quality standards should be established for a follow-up center in case a patient registers with pooling of outcome data. The choice of appropriate assessment tools for specific cognitive testing should be discussed with an experienced pediatric neuropsychologist.

Neurodevelopmental Outcome Following TH

Several randomized, controlled trials demonstrated that TH reduces the mortality rate and the rate of CP in term-born infants with moderate and severe HIE at 18–24 month and 6–7 years of age. Importantly, the reduction in mortality was not associated with an increase in the rate of major disabilities in survivors. There is also evidence that TH has a favorable influence on cognitive and motor outcome

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Table 47.3 Proposed follow-up template and domains of neurodevelopmental assessment after discharge
Suggested examination ages, neurodevelopmental domains and proposed assessment tests. Intervals can be modified and increased depending on clinical indication, tests can be altered but should include standardized tests with normative values.

Domain	Test	1 y	2y	4-6 y	8-12 y
Neurology	Standardized neurological examinations (N) Assessment of vision and hearing	N	N	N	N
Cognition	Bayley- III (B) DAS-II (D) WPPSI – IV (WP) K-ABC-II (K) WISC-IV (W)	B	B	WP/D/K	W/D/K
Language	Bayley- III (B) REEL (R) Preschool Language Scale (P) Specific language tests (SL)	B/R	B/R	P/SL	SL
Fine/Gross Motor	Bayley-III (B) BOT-2 (BO) ZNA (Z) M-ABC –II (M)	B	B	W/BO/Z/M	W/BO/Z/M
Visuo-spatial/ Visual-motor	WRAVMA (W) Beery VMI (V) NEPSY-II (N)			W/V/N	W/V/B
Attention/ Behavior	Bayley-III (B) ADHD RS SDQ (S) CBCL (C)	B	B/C	BA/S/C	S/C
Social Functioning/ Autism	M-CHAT (M) SRS (S) SCQ (SC)		M	S /SC	S/SC
Executive Functions	BRIEF (BR) D-KEFS (D) NEPSY-II (N)			BR/N	BR/D/N
Specific learning problems	Specific tests examining reading/writing and mathematical skills (R/M)				R/M

at 18–24 months and 6–7 years of age (see Tables 47.1 and 47.2). However, studies on school age outcome showed that survivors of HIE with and without CP and independent of TH are at elevated risk for subnormal IQ and the need for educational services [54]. In the analysis of the NICHD NRN trial on whole-body hypothermia, it became evident that overall IQ was only slightly higher in those treated with TH than in those without treatment (median 83 versus 81) and that the rate of children performing in the moderately abnormal range (70–84) was similar (27% versus 21%) [54]. In contrast to that study, the TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trial demonstrated significantly better results for those

treated with TH. They showed that survival with an IQ score of 85 or higher among all children who could be tested was 52% in the treatment group versus 39% in the control group ($p = 0.04$). Compared with the NICHD trial, total IQs were higher both in treated and in nontreated children without a treatment effect [75].

Patterns of Brain Injury in Relation to Neurocognitive Outcomes

The severity of clinical encephalopathy in the first days of life is an important predictor of neurodevelopmental outcome [2,19]. Children with mild encephalopathy do not appear to have an increased risk of neurocognitive sequelae compared with normal children [45,76], even when selected motor functions, short- and long-term memory, and behavior were tested [57]. In contrast, the majority of children with severe encephalopathy die, and those who survive suffer from severe disabilities such as CP, mental retardation, or epilepsy [41]. Determining the outcome of moderate encephalopathy is more difficult because the spectrum of neurocognitive disability is broad. In this context, neonatal brain imaging with MRI in particular is a powerful tool to accurately predict neurocognitive outcomes, even in neonates receiving TH.

While it is accepted that the risk of an abnormal neurodevelopmental outcome increases with the severity of brain injury detected by MRI, the pattern of injury also conveys important prognostic information regarding the *pattern* of neurodevelopmental outcomes [29,77]. Abnormal signal intensity in the posterior limb of the internal capsule on MRI and injury predominantly in the basal ganglia and thalamus are associated with severely impaired motor and cognitive outcomes [29,78]. As noted earlier, when reviewing components of neurocognitive outcomes, the patterns of brain injury on MRI are often associated with specific profiles of neurocognitive impairments [15,29]. The predictive value of MRI when TH is administered does not change significantly (see below).

The basal nuclei– and watershed-predominant patterns of injury are associated with impairments in different developmental domains. Both the basal nuclei–predominant pattern and abnormal signal intensity in the posterior limb of the internal capsule on MRI have each been associated with severely impaired motor *and* cognitive outcomes [29,77–79]. Because the basal nuclei–predominant pattern of injury is frequently accompanied by cerebral cortical and white matter injury in a watershed distribution [29], and with cerebellar injury [80,81], cognitive deficits with this pattern of injury may result from damage to areas outside the deep gray nuclei themselves. In contrast, newborns with the watershed pattern have predominantly cognitive impairments that often occur without functional motor deficits when examined at 30 months [29]. The watershed injury pattern is also highly predictive of later outcome and particularly predicts verbal IQ at 4 years [34] and both full-scale and verbal IQ at 10 years of age [33] where, for each point increase in the watershed injury score, the IQ decreased by 4.9 IQ points. In this study, both smaller head circumference at birth and the diagnosis of a CP at the time of examination were independently associated with lower full-scale IQ.

Advanced quantitative brain imaging techniques such as MR spectroscopy and diffusion tensor imaging can now be applied to measure response to TH [82] and to detect subtle brain injuries such as white matter injuries and determine their association with long-term neurocognitive outcomes [35,83,84]. For example, in a case series using advanced volumetric techniques, five survivors of neonatal encephalopathy examined between 8 and 14 years with delayed recall, in the setting of intact semantic memory and motor function, were found to have bilateral hippocampal atrophy on MRI [30]. A recent meta-analysis on the use of MR spectroscopy demonstrated that measurements of *N*-acetylaspartate/lactate ratio and absolute NAA in the deep gray matter have a better prognostic value than conventional and diffusion-weighted MRI for the early prediction of outcome [85]. Another study was able to show that low apparent diffusion coefficient values in the posterior part of the corpus callosum were associated with poorer outcome after HIE [86]. TH treatment modified this association, showing that lower values were needed for an adverse outcome.

In the meta-analysis of Thayyil et al., it also became clear that the timing of conventional MRI is important when predicting outcome [85]. Early administration of conventional MRI (<day 7) had a higher specificity but lower sensitivity for poor outcome. Therefore, early MRI may miss abnormalities that may help in terms of outcome prediction. However, MRI may be helpful in the discussion of redirection of care and therefore needs to be administered early. With the introduction of TH, the discus-

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sion of redirection of care has become even more complex (for a review, see Bonifacio et al. [87]).

Predictors for Neurodevelopmental Outcome in Neonates Undergoing TH

Because TH has become a standard treatment for moderate and severe HIE, the questions about whether methods used to predict neurodevelopmental outcome in noncooled infants remain valid for infants who undergo TH are essential. Several reviews address this challenging topic [87-91].

Some clinical parameters reflecting the severity of compromise shortly after birth are less predictive in neonates who undergo TH than in noncooled neonates, and recovery during and after cooling is more important for predicting neurocognitive outcomes. For example, recovery of Sarnat scores under TH seems to be of greater importance than the score before initiation of TH [46]. This has also been demonstrated for the Thompson score, where a score between 7 and 16 at the beginning of cooling had a rather poor predictive strength for outcome. Only if encephalopathy is very severe at the start of TH (Thompson score > 16 within 6 hours of birth) does prediction remain strong regarding poor outcome in cooled infants [92]. A favorable course with few neurologic symptoms on day 7 has been associated with survival without severe handicap (Thompson score < 5 on day 7 associated with a survival without severe handicap [PPV 91%]) [93]. Attention should also be given to neurologic symptoms at discharge, such as the need for gavage feedings. The need for gavage feedings has been associated with a greater risk of death or disability at 18 months in cooled infants [94].

aEEG recording and cerebral MRI remain important tools for the prediction of neurodevelopmental outcome after TH. However, in cooled newborns, the early aEEG seems to be less predictive, but if the "cut-off" time point for predicting outcome is changed from 6 to 24–48 hours after birth [95] aEEG is still very useful. The time by which the background aEEG trace has recovered to a discontinuous normal voltage pattern remains highly predictive of outcome at 18 month [90].

Several studies have compared the prognostic utility of conventional cerebral MRI in neonates who were treated with TH and noncooled neonates. They all reported the ability of conventional MRI to predict adverse outcomes in newborns with HIE to be similar in infants who underwent TH and noncooled infants [94,96,97]. Imaging in the first week of life seems to provide optimal specificity for predicting adverse outcomes, whereas later imaging provides higher sensitivity for identifying the full extent of lesions that can signify risk for developmental sequelae

Conclusion

Childhood survivors of neonatal encephalopathy are at risk of a broad spectrum of neurocognitive and behavioral-social deficits. With sophisticated and detailed measures of cognition there appears to be an association between specific cognitive deficits, such as language and memory deficits, and the severity of neonatal encephalopathy and the pattern of brain injury. This recognition allows physicians and caregivers an opportunity to optimally care for infants following neonatal encephalopathy by identifying those who may benefit most from rehabilitative services and early intervention to maximize educational and social function and thus independent function throughout development. In this era of potential therapies for neonatal brain injury, including hypothermia, we need a better understanding of the full and long-term spectrum of all aspects of neurodevelopmental outcomes of survivors of neonatal encephalopathy. Importantly, we need to provide more information on the adolescent outcome of children, whether treated with TH or not. Aspects of quality of life, academic achievement, and social integration need to be studied carefully in order to be able to provide the necessary resources to improve the outcome of these children. Studies into the mechanisms that contribute to resilience and recovery from neonatal brain injury offer further promise to prevent neurocognitive deficits following neonatal encephalopathy. In addition, a better understanding of the postnatal factors affecting neurocognitive outcomes, including environmental and social influences, will ultimately lead to better interventions to improve the outcome of affected newborns.

References

1. Volpe J. *Neurology of the Newborn*, 4th edn. Philadelphia: Saunders, 2001.
2. Miller SP, Latal B, Clark H, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. *Am J Obstet Gynecol* 2004; **190**: 93–9.
3. Ferriero DM. Neonatal brain injury. *N Engl J Med* 2004; **351**: 1985–95.

4. Vannucci RC, Perlman JM. Interventions for perinatal hypoxic-ischemic encephalopathy. *Pediatrics* 1997; **100**: 1004–14.
5. Finer NN, Robertson CM, Richards RT, et al. Hypoxic-ischemic encephalopathy in term neonates: perinatal factors and outcome. *J Pediatr* 1981; **98**: 112–17.
6. Nelson KB, Lynch JK. Stroke in newborn infants. *Lancet Neurol* 2004; **3**: 150–8.
7. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 2010; **340**:c363.
8. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013; **1**:CD003311.
9. Tagin MA, Woolcott CG, Vincer MJ, et al. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2012; **166**: 558–66.
10. Juul SE, Ferriero DM. Pharmacologic neuroprotective strategies in neonatal brain injury. *Clin Perinatol* 2014; **41**: 119–31.
11. Thoresen M. Cooling after perinatal asphyxia. *Semin Fetal Neonatal Med* 2015; **20**:65.
12. Dammann O, Ferriero D, Gressens P. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters. *Pediatr Res* 2011; **70**:1–2.
13. Volpe JJ. Neonatal encephalopathy: an inadequate term for hypoxic-ischemic encephalopathy. *Ann Neurol* 2012; **72**: 156–66.
14. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998; **317**: 1554–8.
15. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003; **361**: 736–42.
16. Gano D1, Chau V, Poskitt KJ, Hill A, Roland E, Brant R, Chalmers M, Miller SP. Evolution of pattern of injury and quantitative MRI on days 1 and 3 in term newborns with hypoxic-ischemic encephalopathy. *Pediatr Res* 2013 Jul; **74**(1): 82–7. doi: 10.1038/pr.2013.69. Epub 2013 Apr 25.
17. Barkovich AJ, Miller SP, Bartha A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *AJNR Am J Neuroradiol* 2006; **27**: 533–47.
18. McKinstry RC, Miller JH, Snyder AZ, et al. A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns. *Neurology* 2002; **59**: 824–33.
19. American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol* 2014; **123**:896–901.
20. Myers RE. Four patterns of perinatal brain damage and their conditions of occurrence in primates. *Adv Neurol* 1975; **10**: 223–34.
21. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol* 1972; **112**: 246–76.
22. Childs AM, Cornette L, Ramenghi LA, et al. Magnetic resonance and cranial ultrasound characteristics of periventricular white matter abnormalities in newborn infants. *Clin Radiol* 2001; **56**: 647–55.
23. Felderhoff-Mueser U, Rutherford MA, Squier WV, et al. Relationship between MR imaging and histopathologic findings of the brain in extremely sick preterm infants. *AJNR Am J Neuroradiol* 1999; **20**: 1349–57.
24. Hope PL, Gould SJ, Howard S, et al. Precision of ultrasound diagnosis of pathologically verified lesions in the brains of very preterm infants. *Dev Med Child Neurol* 1988; **30**: 457–71.
25. Schouman-Claeys E, Henry-Feugeas MC, Roset F, et al. Periventricular leukomalacia: correlation between MR imaging and autopsy findings during the first 2 months of life. *Radiology* 1993; **189**:59–64.
26. Barkovich AJ, Hajnal BL, Vigneron D, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. *AJNR Am J Neuroradiol* 1998; **19**: 143–9.
27. McQuillen PS, Ferriero DM. Selective vulnerability in the developing central nervous system. *Pediatr Neurol* 2004; **30**: 227–35.
28. Sie LT, van der Knaap MS, Oosting J, et al. MR patterns of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. *Neuropediatrics* 2000; **31**: 128–36.
29. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005; **146**: 453–60.
30. Gadian DG, Aicardi J, Watkins KE, et al. Developmental amnesia associated with early hypoxic-ischaemic injury. *Brain* 2000; **123**(Pt 3):499–507.
31. Ramaswamy V, Miller SP, Barkovich AJ, et al. Perinatal stroke in term infants with neonatal encephalopathy. *Neurology* 2004; **62**: 2088–91.
32. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA* 2005; **293**: 723–9.

.048

33. Perez A, Ritter S, Brotschi B, et al. Long-term neurodevelopmental outcome with hypoxic-ischemic encephalopathy. *J Pediatr* 2013; **163**: 454–9.
34. Steinman KJ, Gorno-Tempini ML, Glidden DV, et al. Neonatal watershed brain injury on magnetic resonance imaging correlates with verbal IQ at 4 years. *Pediatrics* 2009; **123**: 1025–30.
35. Miller SP, Newton N, Ferriero DM, et al. Predictors of 30-month outcome after perinatal depression: role of proton MRS and socioeconomic factors. *Pediatr Res* 2002; **52**: 71–7.
36. Gonzalez FF, Miller SP. Does perinatal asphyxia impair cognitive function without cerebral palsy? *Arch Dis Child Fetal Neonatal Ed* 2006; **91**:F454–9.
37. Barnett A, Mercuri E, Rutherford M, et al. Neurological and perceptual-motor outcome at 5–6 years of age in children with neonatal encephalopathy: relationship with neonatal brain MRI. *Neuropediatrics* 2002; **33**: 242–8.
38. Dixon G, Badawi N, Kurinczuk JJ, et al. Early developmental outcomes after newborn encephalopathy. *Pediatrics* 2002; **109**:26–33.
39. Marlow N, Rose AS, Rands CE, Draper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**:F380–7.
40. Moster D, Lie RT, Markestad T. Joint association of Apgar scores and early neonatal symptoms with minor disabilities at school age. *Arch Dis Child Fetal Neonatal Ed* 2002; **86**:F16–21.
41. Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr* 1989; **114**: 753–60.
42. Goodwin TM, Belai I, Hernandez P, et al. Asphyxial complications in the term newborn with severe umbilical acidemia. *Am J Obstet Gynecol* 1992; **167**: 1506–12.
43. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981; **68**:36–44.
44. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; **33**:696–705.
45. Robertson CM, Finer NN. Long-term follow-up of term neonates with perinatal asphyxia. *Clin Perinatol* 1993; **20**:483–500.
46. Gunn AJ, Wyatt JS, Whitelaw A, et al. Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. *J Pediatr* 2008; **152**: 55–8.
47. de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**:F220–4.
48. Diamond A. Executive functions. *Annu Rev Psychol* 2013; **64**: 135–68.
49. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. *Eur J Paediatr* 2007; **166**: 645–54.
50. Kjellmer I, Beijer E, Carlsson G, et al. Follow-up into young adulthood after cardiopulmonary resuscitation in term and near-term newborn infants. I. Educational achievements and social adjustment. *Acta Paediatr* 2002; **91**: 1212–17.
51. Lindstrom K, Lagerroos P, Gillberg C, Fernell E. Teenage outcome after being born at term with moderate neonatal encephalopathy. *Pediatr Neurol* 2006; **35**: 268–74.
52. Viggedal G, Lundalv E, Carlsson G, Kjellmer I. Follow-up into young adulthood after cardiopulmonary resuscitation in term and near-term newborn infants. II. Neuropsychological consequences. *Acta Paediatr* 2002; **91**: 1218–26.
53. van Handel M, de Sonneville L, de Vries LS, et al. Specific memory impairment following neonatal encephalopathy in term-born children. *Dev Neuropsychol* 2012; **37**:30–50.
54. Dilenge ME, Majnemer A, Shevell MI. Long-term developmental outcome of asphyxiated term neonates. *J Child Neurol* 2001; **16**: 781–92.
55. Badawi N, Felix JF, Kurinczuk JJ, et al. Cerebral palsy following term newborn encephalopathy: a population-based study. *Dev Med Child Neurol* 2005; **47**: 293–8.
56. Volpe JJ. *Neonatal Neurology*, 4th edn. Philadelphia: Saunders, 2001.
57. Handley-Derry M, Low JA, Burke SO, et al. Intrapartum fetal asphyxia and the occurrence of minor deficits in 4- to 8-year-old children. *Dev Med Child Neurol* 1997; **39**: 508–14.
58. van Kooij B, van Handel M, Uiterwaal C, et al. Corpus callosum size in relation to motor performance in 9- to 10- year-old children with neonatal encephalopathy. *Pediatr Res* 2008; **63**:1–6.
59. van Schie PE, Schijns J, Becher JG, et al. Long-term motor and behavioral outcome after perinatal hypoxic-ischemic encephalopathy. *Eur J Paediatr Neurol*. 2015; **19**: 354–9.
60. Van Hof-van Duin J, Mohn G. Visual defects in children after cerebral hypoxia. *Behav Brain Res* 1984; **14**: 147–55.

61. Mercuri E, Atkinson J, Braddick O, et al. Basal ganglia damage and impaired visual function in the newborn infant. *Arch Dis Child Fetal Neonatal Ed* 1997; **77**: F111–14.
62. Robertson C, Finer N. Term infants with hypoxic-ischemic encephalopathy: outcome at 3.5 years. *Dev Med Child Neurol* 1985; **27**: 473–84.
63. Shankaran S, Woldt E, Koepke T, et al. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. *Early Hum Dev* 1991; **25**: 135–48.
64. Mercuri E, Anker S, Guzzetta A, et al. Visual function at school age in children with neonatal encephalopathy and low Apgar scores. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**:F258–62.
65. D'Souza SW, McCartney E, Nolan M, Taylor IG. Hearing, speech, and language in survivors of severe perinatal asphyxia. *Arch Dis Child* 1981; **56**: 245–52.
66. Roland EH, Hill A, Norman MG, et al. Selective brainstem injury in an asphyxiated newborn. *Ann Neurol* 1988; **23**:89–92.
67. Brunquell PJ, Glennon CM, DiMario FJ Jr, et al. Prediction of outcome based on clinical seizure type in newborn infants. *J Pediatr* 2002; **140**: 707–12.
68. Clancy RR, Legido A. Postnatal epilepsy after EEG-confirmed neonatal seizures. *Epilepsia* 1991; **32**:69–76.
69. Hellstrom-Westas L, Blennow G, Lindroth M, et al. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. *Arch Dis Child Fetal Neonatal Ed* 1995; **72**:F97–101.
70. Toet MC, Groenendaal F, Osredkar D, et al. Postneonatal epilepsy following amplitude-integrated EEG-detected neonatal seizures. *Pediatr Neurol* 2005; **32**: 241–7.
71. Jung DE, Ritacco DG, Nordli DR, et al. Early Anatomical Injury Patterns Predict Epilepsy in Head Cooled Neonates With Hypoxic-Ischemic Encephalopathy. *Pediatr Neurol* 2015; **53**(2): 135–40.
72. Robertson CM, Finer NN. Educational readiness of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Dev Behav Pediatr* 1988; **9**:298–306.
73. Stuart A, Otterblad Olausson P, Kallen K. Apgar scores at 5 minutes after birth in relation to school performance at 16 years of age. *Obstet Gynecol* 2011; **118**: 201–8.
74. Koot HM. The study of quality of life: concepts and methods. In: Koot HM, Wallander JL, eds., *Quality of Life in Child and Adolescent Illness*. Hove: Bunner-Routledge, 2001.
75. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; **361**: 1349–58.
76. Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. *Acta Paediatr* 1995; **84**: 927–32.
77. Roland EH, Poskitt K, Rodriguez E, et al. Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. *Ann Neurol* 1998; **44**: 161–6.
78. Rutherford MA, Pennock JM, Counsell SJ, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. *Pediatrics* 1998; **102**: 323–8.
79. Krageloh-Mann I, Helber A, Mader I, et al. Bilateral lesions of thalamus and basal ganglia: origin and outcome. *Dev Med Child Neurol* 2002; **44**: 477–84.
80. Le Strange E, Saeed N, Cowan FM, et al. MR imaging quantification of cerebellar growth following hypoxic-ischemic injury to the neonatal brain. *AJNR Am J Neuroradiol* 2004; **25**: 463–8.
81. Sargent MA, Poskitt KJ, Roland EH, et al. Cerebellar vermian atrophy after neonatal hypoxic-ischemic encephalopathy. *AJNR Am J Neuroradiol* 2004; **25**: 1008–15.
82. Bonifacio SL, Saporta A, Glass HC, et al. Therapeutic hypothermia for neonatal encephalopathy results in improved microstructure and metabolism in the deep gray nuclei. *AJNR Am J Neuroradiol* 2012; **33**: 2050–5.
83. Nagy Z, Lindstrom K, Westerberg H, et al. Diffusion tensor imaging on teenagers, born at term with moderate hypoxic-ischemic encephalopathy. *Pediatr Res* 2005; **58**: 936–40.
84. Rutherford M, Counsell S, Allsop J, et al. Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time from birth. *Pediatrics* 2004; **114**: 1004–14.
85. Thayyil S, Chandrasekaran M, Taylor A, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics* 2010; **125**: e382–95.
86. Alderliesten T, de Vries LS, Khalil Y, et al. Therapeutic hypothermia modifies perinatal asphyxia-induced changes of the corpus callosum and outcome in neonates. *PLoS One* 2015; **10**:e0123230.
87. Bonifacio SL, deVries LS, Groenendaal F. Impact of hypothermia on predictors of poor outcome: how do we decide to redirect care? *Semin Fetal Neonatal Med* 2015; **20**: 122–7.

88. Massaro AN. MRI for neurodevelopmental prognostication in the high-risk term infant. *Semin Perinatol* 2015; **39**: 159–67.

89. Merchant N, Azzopardi D. Early predictors of outcome in infants treated with hypothermia for hypoxic-ischaemic encephalopathy. *Dev Med Child Neurol* 2015; **57**(Suppl 3):8–16.

90. Sabir H, Cowan FM. Prediction of outcome methods assessing short- and long-term outcome after therapeutic hypothermia. *Semin Fetal Neonatal Med* 2015; **20**: 115–21.

91. Shankaran S. Outcomes of hypoxic-ischemic encephalopathy in neonates treated with hypothermia. *Clin Perinatol* 2014; **41**: 149–9.

92. Shankaran S, Pappas A, McDonald SA, et al. Predictive value of an early amplitude integrated electroencephalogram and neurologic examination. *Pediatrics* 2011; **128**:e112–20.

93. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics* 2010; **126**:e771–8.

94. Shankaran S, Laptook AR, Tyson JE, et al. Evolution of encephalopathy during whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 2012; **160**: 567–72.

95. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* 2010; **126**:e131–9.

96. Cheong JL, Coleman L, Hunt RW, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy: substudy of a randomized trial. *Arch Pediatr Adolesc Med* 2012; **166**: 634–40.

97. Rutherford M, Ramenghi LA, Edwards AD, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol* 2010; **9**:39–45.

Chapter

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Neonatal Neuroethics

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Introduction

The provision of care in the perinatal period brings medical practice to the essence of what it means to be human: fertility, birth, death, dignity, personhood, parenthood, and beyond. The shifting technological and moral landscape of such care necessitates that practitioners possess an adaptable ethical framework with which to address complex, emotionally charged, value-laden decisions with care. As the border of viability is pushed earlier and earlier in gestational life, and as we improve the treatment of conditions that were once considered untreatable, the areas for ethical inquiry and potential moral distress grow.

Prognostic uncertainty places many fetuses and neonates in a gray zone where not only the likelihood of survival but also associated physical and neurologic morbidity are unclear. Unfortunately, throughout the breakthroughs made in the treatment of disease, our ethical examinations of such advances often lag behind, evolving as the shortcomings of those leaps become apparent. Projected neurologic function often lies at the heart of ethical questions that emerge in the neonatal period, and yet despite rigorous efforts in research, there remains a paucity of reliable evidence-based guidance. In an effort to provide just and equitable care to the smallest, most vulnerable patients, we must investigate many elements of the decision-making process as it pertains to medical practitioners, families, and the courts. To that end, we must balance the rights of the patient and surrogate decision makers, the duties of the physician and care team, legal precedent, and questions revolving quality and quantity of life. The fervent research efforts in neonatology have played an enormous role in improving the care of this population. Recent controversies in such research highlight the challenge of communicating with desperate parents, the delicate balance involved in respecting patient preferences today and research that yields valuable evidence for superior care tomorrow. Our ultimate goals should include making treatment decisions that are both evidence based and morally grounded.

Legal Background

Many ethical decisions take place at the beginning of life, especially in scenarios where the beginning may also constitute the end of life. Care of the very young has been the focus of several significant legal cases that served as precedents used in addressing neonates today. Two key concepts have played major roles in shaping the law: *vitalism*, which holds that the value of life itself is paramount and must be maintained at almost all cost, and the *best interests standard*, which allows for parents and caregivers to weigh the burdens and benefits of continued living to the infant.

Baby Doe

The matter of Baby Doe has been so influential that many authors categorize the timeline of neonatal ethics into pre– and post–Baby Doe eras [1]. In 1982, Baby Doe was born with trisomy 21 with tracheoesophageal fistula and duodenal atresia. The parents were advised by their obstetrician not to proceed with treatment. His chances of mortality were high, and should he live, he would have severe intellectual disabilities. The patient's pediatrician and family physician disagreed and recommended surgical intervention. The physicians caring for the child could not reach a consensus regarding how to proceed, and the family was offered transfer to another hospital for treatment or to remain at the birth hospital and allow the child to die.

This case took place during the term of a pro-life president, Ronald Reagan, and his like-minded appointed Surgeon General, C. Everett Koop. In the wake of the Baby Doe case, the White House sent a memo to the Secretary of the Department of Health and Human services to notify healthcare providers

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that Section 504 of the Rehabilitation Act of 1983 "forbids recipients of federal funds from withholding from handicapped citizens simply because they are handicapped, any benefits or services that would ordinarily be provided to persons without handicaps" [2]. After significant legal debate, President Regan amended the Federal Child Abuse Prevention and Treatment Act (CAPTA) of 1984 to include what became known as the "Baby Doe Rule." The amendment required that life-sustaining treatment be provided to severely ill infants unless the following exceptions were met: the infants was "chronically and irreversibly comatose"; situations when providing treatment would not save the infant's life but merely prolong dying; or when "the provision of such treatment would be virtually futile in terms of the survival of the infant and the treatment itself under such circumstances would be inhumane" [3].

In 1986, the Supreme Court struck down part of the Reagan's Baby Doe Rule as a means to withhold federal funds. In the Court's opinion, Justice John Paul Stevens stated, "Section 504 does not authorize the secretary [of Health and Human Services] to give unsolicited advice either to parents, to hospitals or to state officials who are faced with difficult treatment decisions concerning handicapped children" [4]. However, the legacy of the Baby Doe era lives on in the amendments to federal CAPTA regulations. The Americans with Disabilities Act of 1990 provides that persons with disabilities are entitled to treatment by physicians as a part of the 'public accommodations' provision of the ADA [5].

The Baby Doe case brought the issue of care of critically ill infants, and especially the idea of intellectual disability as reason to forego life-sustaining therapies, into public discourse. In the hands of vitalists such as Surgeon General Koop, to withhold potentially life-prolonging therapies from a child with a potential future was unthinkable. While his view was not pervasive, his work in this area laid the foundation for a major shift in public opinion on the matter. Society's views surrounding persons with intellectual disabilities have changed dramatically over the past several decades. The influence of the Baby Doe case is still felt today, where the birth of a child with a similar presentation (and without further major congenital anomalies that would affect prognosis) results in near-universal surgical palliation. A diagnosis of trisomy 21, in and of itself, has disappeared as a reason for withholding medical treatment. This societal revolution in perceptions of the value of persons with intellectual and physical disabilities (i.e., trisomy 21, autism spectrum disorders, etc.) has continued to evolve. The increased openness to caring for persons with disabilities has led to more research and public interest into the long-term follow-up of such patients and their particular diseases.

Technically speaking, physicians and families using the best interests standard may find themselves in direct conflict with the Baby Doe standards (as embedded in CAPTA), given the highly restrictive language in the law. In Loretta Kopelman's analysis of Baby Doe's influence, she argues that the law "thwarts compassionate and individualized decision making, undercut[ting] duties to minimize unnecessary suffering" [6].

Baby K

In 1992, an anencephalic infant was born, and the child's mother demanded aggressive medical treatment despite dissuasion by the child's doctors. The patient's physicians attempted to refuse to provide life-sustaining treatment to the child, claiming that the "standard of care" for anencephalic infants was for provision of nutrition, hydration, and warmth and that provision of more advanced technologies was not. The US Court of Appeals for the Fourth Circuit ruled in favor of the patient's mother, citing that the Emergency Medical Treatment and Active Labor Act (EMTALA, also referred to as the *antidumping law*) offered no standard-of-care exception [7]. The child eventually died after two years and six admissions for emergency medical treatment [8]. There are several unusual aspects of the Baby K case, including the fact that it was a federal rather than state court where the case was heard. Despite the outcome of this case, the following decades witnessed continued evolution of "futility" or "medically ineffective care" as a basis of declining treatment.

Texas Advanced Directives Act

Texas attempted to preemptively address the issue of "futile" cases in its 1999 law, the Texas Advanced Directives Act, also known as the *Texas futility law* [9]. The law provides that if a physician refuses to honor a patient's (or his or her surrogate's) request for life-sustaining treatment because he or she determines it to be medically ineffective, then the physician

may put into motion a series of steps to resolve the issue. Until the process has been completed, the patient continues to receive treatment.

1. The physician's decision is reviewed by an ethics committee.
2. The patient or surrogate must be notified of the committee meeting at least 48 hours in advance and supplied with relevant written policies and procedures.
3. The patient or surrogate is entitled to be given a list of potential alternative providers, attend the ethics meeting, and receive a written copy of the decision made by the committee (which also becomes part of the medical record).
4. If any party disagrees with the recommendations of the committee review, then the attending physician must attempt to transfer the patient to a physician who is willing to comply with the decision.
5. If the patient is in a healthcare facility, the facility must assist in arranging such a transfer to another physician, another unit in the same facility, or another facility.
6. The patient or family has 10 days to arrange for such a transfer at their expense. Life-sustaining treatment is provided in the waiting period, but after the tenth day, there is no obligation to continue such treatment. The family is able to request a time extension from the court.

The Texas law inspired other many other states to create their own such futility laws, attempting to define mechanisms to address such disputes [10]. California, for example, allows physicians to refuse to comply with healthcare instructions or directives for treatments that are contrary to generally accepted standards or are "medically ineffective." Patients or their surrogates must be told of the basis of the refusal, and care must be continued until a transfer can be affected or it appears a transfer will not take place [11].

Born-Alive Infants Protections Act

In 2002, the Born-Alive Infants Protections Act (BAIPA) was approved by then President George W. Bush. The act states that any infant born at any developmental stage, by any form of expulsion (vaginal delivery, cesarean, inducted abortion, etc.), is considered an alive human person with inherent rights [12]. The Centers for Medicare and Medicaid Services (CMS) provided a memo regarding the interaction of BAIPA with EMTALA [13]. The memo includes a "prudent layperson" as a person who could identify that a "born-alive infant" may need emergency medical care and that if such care is not provided, the provider would be in violation of EMTALA. In response to the law, the American Academy of Pediatrics (AAP) Neonatal Resuscitation Program Steering Committee stated that it did not believe the law should in any way affect the physician decision-making process and that the care of critically ill newborns is "clearly not relevant in the context of this law" [14]. While the law was designed to address abortions and confer legal status to infants, it runs the risk of influencing the treatment of infants on the border of viability, as well as infants born with marginal chances of survival due to severe congenital diseases. Despite the AAP's position, it is not outside the realm of possibility that the law will be interpreted far more narrowly than the AAP predicts in some future test case.

Brain Death

The concept of brain death emerged in response to the increasing availability of intensive care technologies that usurped some cardiopulmonary function, thereby complicating the pronouncement of death by traditional criteria. In 1968, an Ad Hoc Committee of the Harvard Medical School published "A Definition of Irreversible Coma," proposing that the definition of death include the loss of certain basic neurologic functions, independent of the loss of heart and lung function [15]. This definition of death has become widely accepted socially and deeply entrenched in the law. In considering that brain function is necessary to essentially all aspects of human existence, it is not unreasonable for brain death to be considered as profoundly final as cardiopulmonary death in its severing an individual from interaction with the living.

The recent case of Jahai McMath in Oakland has reignited public controversy surrounding brain death. Although she was pronounced brain dead by multiple independent neurologic examinations in December 2013, her family refused to accept the diagnosis and sought a court order to maintain their daughter's ventilatory support. She was ultimately transferred to a long-term care facility in New Jersey in January

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2014. At this time, her family is seeking to have Jahi's death certificate revoked [16].

In the ethics literature, debate continues over whether "brain death" truly represents the cessation of the organism as an integrated whole [17] or whether it is a "legal fiction" analogous to defining someone as legally blind when he or she has 20/200 vision (rather than total blindness) [18] or as an adult on his or her eighteenth birthday. A third option is to reject the idea that life and death name "natural kinds" of distinctly occurring natural categories. Death does not occur at a singular distinct moment but as a biologic process along a continuum. On this view, the establishment of criteria to define brain death was made based on many factors, including policy considerations, and virtually no false positives when followed correctly [19].

Parental Rights

The goal of shared decision making with parents is an important one given that physicians need guidance on the values of the family in the context of illness and parents need education and advice regarding the alien nightmare of having a critically ill child. It is in this context that the child's "best interests" may be assessed and prioritized. As legal guardians of their infants, parents are often deferred to for decision making. It stands to reason that parents are the most emotionally and physically invested in the well-being of their child and have the most intimate understanding of that child's place and influence as an individual on the rest of the family. At times, it may feel as though the autonomy that is so prized in American medical decision making comes at a price, giving parents too much leeway to make decisions for which they are not adequately prepared. Racine et al. eloquently note that "parental proxy decision makers are often caught between the emotional crushing of hopeful parental expectations for their child and the dehumanized technical environment of a neonatal intensive care unit." There are any number of daily decisions that the care team makes for which the parents are not generally consulted – medication changes, ventilator adjustments, and so on. There is variation among practitioners as to where the shift occurs between notification and consultation. For instance, Singh et al. found that only one-third of neonatologists would resuscitate infants on the border of viability based on parental preference [20]. Once the patient is in the neonatal intensive care unit (NICU), larger decisions regarding overarching care plans often include parents. There are, however, times when the autonomy granted to parents must be limited.

Nurses, physicians, social workers, and other bedside caregivers are constantly forming perceptions of parental interactions with the child, attempting to determine whether they are bonding with the child, how they are coping emotionally, or if they have "given up." If parental behavior or discussions imply that they do not have the child's best interests at heart, the team must explore those concerns further and help the family either to regain its ability to advocate for the child or offer alternatives such as adoption. At times, it is necessary to consult with local child protective service agencies for the assumption of legal guardianship.

Fiduciary Obligations

While physicians may not technically be obligated to initiate or continue treatment that they deem to be inappropriate (depending on local law), such a determination is inherently subjective because these decisions are linked to treatment goals, which may differ between the physician and the family [21]. The provider may feel uncomfortable with acting in a manner that damages trust with family and increases strife with family and within the NICU. If the care team and parents are at an impasse, the physician is obligated to offer that the patient be transferred to the care of another physician within the institution or another hospital that is willing and able to provide such treatment (see the section "Texas Advanced Directive Act"). This can be a dicey process, and one should explore the various options with colleagues and other resources before unilaterally imposing this path. Additionally, there are times when physicians are compelled, either by the demands of parents, internal pressure from colleagues, or, in the case of Baby K, by the court, to provide therapy beyond what they determine to be medically effective. When in doubt, personal reflection on the issue, candid discussions with one's colleagues, and transparent and compassionate interactions with families may serve to minimize these conflicts.

Quality of Life versus Quantity of Life

Advances in neonatal intensive care, such as improved respiratory support, the development of

surfactant, the fine tuning of artificial nutrition, and the treatment of infections, have lowered the age of viability approximately 1 week each decade since the 1960s [22]. Today, where the borderline of viability may confer a survival of greater than 50%, the corresponding projected level of disability and quality of life often remains undetermined.

There is inherent subjectivity in determining a patient's projected quality of life compared with quantity of life. Such determinations are naturally value laden and will be influenced by the individual convictions and beliefs of each family, as well as those of the healthcare providers. In using the best interest standard, a combination of data, physician expertise, and parental values is used to assess the various benefits and burdens to the child. While the patient must be treated as an individual, the values and resources of the family are inextricably linked. The outcome for each child will mold the future of the family in which he or she is born – emotionally, socially, and financially. Unless there is significant evidence to indicate that the parents are not acting in the child's best interests, generally, parents are granted great latitude to make decisions for their children.

The projected neurologic outcome for a neonate is often a major influencing factor in deciding whether to continue aggressive treatment [23,24]. Parents and providers must weigh quality-of-life assessments that may never come to fruition, unable to predict exactly how much suffering the child and family might endure [25]. Even moderate to late preterm infants have demonstrated altered white matter microstructure in many of the brain's major tracts when compared with term-born controls [26]. In patients who are projected to require surgical intervention, especially patients with complex congenital heart disease, there are additional concerns regarding the developing brain. Injury to white matter is a known complication of cardiac surgery in term neonates, and this may be exaggerated in preterm children. Yet, knowing that many of these children will grow up with limited (or perhaps no discernible) disability, it is difficult to know how much information is useful to parents in the decision-making process. The repercussions of such decisions may last for many years because more and more NICU graduates are surviving into adulthood.

Both quality- and quantity-of-life decisions rely heavily on the decision maker's predictive capacity, that is, ability to imagine a particular future scenario in the context of information provided. Statistical information is often confusing, and the general public, as well as physicians, frequently do not have an accurate understanding of what these numbers mean [27]. Physicians must first ensure their own understanding of any objective data that may be available. Appropriate counseling relies on frequent assessment of short- and long-term outcomes, locally and beyond. This information must then, in turn, be provided to parents in an understandable fashion. Additionally, families will need assistance in navigating the social and financial resources that may be available, often coordinated initially by NICU social workers. They also deserve time to synthesize this flood of knowledge so that they may ultimately be functional members in the decision-making process.

Given the quandaries in addressing such uncertain prognoses, it is essential to ensure that parents understand that while the child remains alive, any decisions made will not be static. Not only do the decisions have an impact on the immediate future of the patient, but each decision is likely a branch point to further questions. A critical element in this level of care is that although intensive care may be used initially, as the infant's condition develops and more information is learned, there may be multiple points at which it may be appropriate to either escalate treatment or redirect care toward less invasive measures.

Providers each have stories of patients who have defied expectations to survive with limited morbidity and, conversely, patients who should by all statistical probability have done well, only to suffer terrible consequences. Such experiences influence physicians' ability to provide objective information. In a study by Singh et al., physicians reported that they provide or withhold treatment for extremely premature infants based on appearance in the delivery room. However, their data suggest that neonatologists' ability to predict individual outcomes based on appearance may be clouded by overconfidence [28]. While it is not possible to (nor should one attempt to) remove such experiential knowledge from one's mind, it is imperative to recognize the difference between objective data, high-quality research results, and personal experience. Each is a valuable tool, when used prudently.

There are certain diseases in the modern age that were once considered uniformly lethal (e.g., anencephaly, trisomies 13 and 18, and renal agenesis, among others), and it was believed that providing aggressive

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medical treatment to such patients was unethical in that it caused continued suffering without any benefit. However, modern technology in resource-rich intensive care units has made survival past the neonatal age period possible. Population studies demonstrate that children with such congenital malformations are surviving longer, with greater than 50% surviving more than 1 week and upwards of 20% to 1 year [29,30]. In discussing such diseases, the language used to describe them has evolved, shying away from terms such as *lethal* and moving toward *life-limiting* and conferring a *poor prognosis*. Wilkinson et al. outline a suggested counseling approach based on five key questions to help parents understand their child's prognosis [31]:

1. What is the diagnosis, and how certain is it?
2. What is the likelihood of survival beyond the newborn period if life-sustaining treatment is offered?
3. What is the likely duration of survival if life-sustaining treatment is provided?
4. What is the range of possible physical or cognitive impairments if the newborn survives?
5. What is the burden of treatment required to keep the baby alive?

In the digital age, another element that may complicate counseling families is the development of peer support Internet sites, many of which are of questionable quality. In their analysis of nine highly trafficked advocacy websites for neurodevelopmental disorders, Di Pietro et al. discovered an unsettling percentage of unsubstantiated claims, with incorrect or irrelevant peer-reviewed citations [32]. Online resources can be credited with assisting patients and their families in better understanding their respective diseases and treatments and in finding social and emotional support. However, it often falls to the treating physician to assist in separating valuable, evidence-based information from the rest [33]. Such resources may lead parents to request information regarding alternative therapies with unproven efficacy and/or safety. The physician will be inclined to evaluate the scientific merits of the therapy and determine if there is any evidence to support its use, balancing ethical principles of beneficence and nonmaleficence, and ultimately making a recommendation [34].

Vital to the shared decision making process are the early establishment of trust with the family and the continued maintenance of that trust through transparent and compassionate transmission of information. In the alien environment of the hospital, parents are in need of allies in the care process. In attempting to provide options to families, it can be incredibly challenging for physicians to provide objective information that prepares a family for potential outcomes without also completely overwhelming them. Fostering an environment of empathy and understanding is as important to the budding relationship between the family and the care team as the content of available information. While the creation of such an environment is the expectation, it can be difficult to achieve in practice. Janvier and Lantos suggest the practical application of an etiquette-based approach in which we remind ourselves to use commonsense communication tools to interact with NICU parents [35].

In resource-limited environments, such as in the developing world, questions regarding quality and quantity of life are deeply informed by available technologies. Providing space for infants with marginal likelihood for long-term survival may mean that there is not space for a neonate with greater probability of survival with less morbidity [36]. Treatments such as hypothermia protocols for patients with hypoxic-ischemic encephalopathy (HIE) have been the standard course in resource-intense environments but are not widely available in poorer countries. Such limitations place economically disadvantaged neonates at a greater risk for devastating outcomes. Further work is needed to increase the availability of the most efficacious treatments to such locations. Currently, such treatment-availability discussions are often avoided in the United States, but resources are not limitless, and the future of neonatology in resource-rich environments will have to make room for such questions of judicious allocation of treatment.

Withholding/Withdrawing Life-Sustaining Treatment

When a diagnosis is devastating, curative measures have failed, or the child's suffering appears to be overshadowing potential benefits, a discussion regarding the treatment goals with the family is warranted. Sometimes the only outcome available that holds any certainty is that withholding all invasive treatment will result in the patient's death. Up to 50% of treatment-limitation discussions in NICUs occur in light of low predicted quality of life for the child, the majority of whom suffer some brain injury [37,38]. In a retrospective study of neonates with severe brain

injury (HIE and grade III/IV intraventricular hemorrhage) in Australia, treatment-limitation discussions were documented in 54% of the infants. Of the infants studied, 39% died before discharge. For the high-risk infants who survived, most suffered from severe long-term impairment, although there were some infants who were not impaired [39].

For infants born at the border of viability (currently 22–24 weeks' gestation), it can be difficult to decide whether to proceed with aggressive treatment. In this "gray zone," one study found that the high disability rate in outborn infants was "attributable to suboptimal perinatal care . . . secondary to a failure or a delay in initiating intensive care" [40]. In light of such findings, it seems prudent to aggressively treat most infants and scale back treatment after seeing the response. Alternatively, a study of neonates born at 22–23 weeks' gestation found that although survival did not change appreciably between 1993–7 and 2003–7, the median age of death increased significantly, from 11 hours to nearly 4 days [41]. The implication is that although this population did not have an overall improvement in survival, they were subjected to intensive care measures – many of which contribute to suffering – for a longer period of time before their demise. Of course, long-term survival is the hope when treatment is initiated, but it is difficult to align this result with a respect for the dignity of the child.

There are times when the decision to withhold or withdraw medical therapies is easier than others, when prognosis is clearly poor and the team and family agree that continuation of medical treatment is no longer in keeping with the goals of care.

Should there be any discord between the caregivers and the family, the decisions become progressively more difficult. More often than not, families and/or physicians will need to take time to come to terms with a decision to redirect care toward palliative and/or comfort care. It should be anticipated that it may take more than one discussion to come to consensus. In the NICU, the medical team is accustomed to quick changes in care, but in the case of end-of-life care, it is important to give families some leeway in determining when any deescalation of treatment will occur, giving them sufficient time to address their grief and potentially religious arrangements should the child die. It can be helpful to set a date one or more days in advance before any irrevocable changes are made in treatment. There are times when the family comes to determine before the medical team that the continuation of aggressive care is not in their child's best interests. This can pose a unique challenge to physicians who are more accustomed to introducing the concept of redirection of care goals to less intrusive means. Physicians, in their attempts to also strive for the child's best interests, may feel that such determinations by the family are in haste or misinformed, in which case a renewed discussion regarding the family's understanding of the situation should be confirmed. However, it may simply take the physician more time to come to the same conclusion.

Resources

The physician need not explore this bioethical territory in a vacuum because there are many resources at one's disposal. First, morally charged discussions can be held in partnership with one's colleagues and the patient's parents/decision maker to determine where commonality might be found. When approached with thoughtfulness, care, and compassion, these discussions can be opportunities for shared strength and demonstration of the special value of the individual child. As with many other skills, each discussion is also a learning opportunity. Second, the clinician should always feel welcome to consult with the hospital's risk-management services or other legal counsel. Such hospital resources are frequently available to partner the clinician's medical expertise with applicable legal advice.

The development and use of next-generation sequencing has the potential to dramatically affect the care of critically ill newborns. While prematurity is a major source of critical illness, increasingly, genetic findings are correlated with diseases previously thought to be congenital. Some of these findings may provide welcome information and insight to aid in decision making. But in other cases they may be a source of unanticipated conflict as options that might otherwise be made available are not offered due to findings associated with future neurodevelopmental delay or other perceived contraindications to aggressive life-sustaining treatments [42,43].

A bioethics consultation or committee meeting may be a valuable resource and can be helpful in discussing a clinician's concerns by providing a fresh perspective. Since 1984, the American Academy of Pediatrics has endorsed the formation and use of hospital-based bioethics committees, consisting of physicians and nonphysicians, to assist clinicians in

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addressing difficult ethical questions formed at the bedside [44]. The Joint Commission requires that each of its accredited hospitals offers some modality to address the ethical concerns of patients and clinicians [45].

In cases where the need for hospice or palliative care may be foreseen, such consultants can be brought to the table early, helping parents to understand the many services that are available to assist in the process of caring for a neonate who may, unfortunately, have a short life. If the family has a particular spiritual practice, the introduction of a chaplain or the invitation to bring their own spiritual representative may be helpful in navigating emotionally labile times, especially if the family needs to make specific arrangements for religious rites.

Moral Distress as a Guide

Any moral distress among team members or family members should be taken seriously and explored. As a physician who may be leading such decision-making endeavors, it is especially important to explore any of your own misgivings on a particular topic. It is important to resist any urge to make an unnecessarily quick decision when there is a voice expressing a significant concern, or perhaps your own nagging gut instinct, that the decision on the table may be the "wrong" one. Any distress within the healthcare team ideally will be discussed separately and before such a discussion with the family. Nurses are often especially attuned to moral distress in the NICU because they often have a unique position within the care team given that they are positioned to develop intimate relationships with both the patient and parents. To mitigate such distress, as well as to build the team relationship around these issues, the group should work to communicate effectively and collaboratively, participate in debriefing sessions around sensitive topics, and pursue interprofessional educational opportunities [46]. In doing so, it is possible to avoid additional strife as each patient's goals of care are clarified.

Special Considerations in Research

The tremendous efforts in research in neonatology have reaped amazing benefits and advances in the care of critically ill infants, leading to the rapid decrease in the border of viability and significant improvements in morbidity and mortality. The Neonatal Research Network (a branch of the Department of Health and Human Services) was formed in 1987 [47], and the international consortium the Vermont Oxford Network closely followed in 1988 [48]. These groups, along with the work of other researchers, have been instrumental in examining the long-term effects of intensive care, including physical and neurodevelopmental outcomes, and in exploring the adverse effects of NICU care on the family [49–51].

The development of protocol-based care in NICUs has made it possible to provide more uniform care and has increased the ability to ascertain local outcomes. Despite these successes, recent controversy in neonatology has surrounded research to improve practice, particularly the controversy of the SUPPORT trial [52]. One of the main challenges in neonatology has been determining the correct oxygen saturation targets for premature newborns. Early on (as far back as the 1950s), it had been established that the high oxygen treatments thought to be necessary to save the lives of these infants was producing significant occurrences of retinopathy of prematurity (ROP) or blindness as a result of oxygen toxicity. At the same time, it was known that insufficient oxygen would result in potential neurologic damage and death. Determining the optimal range for targeting was a challenge. Practice had begun to shift toward higher oxygen targets (with accompanying higher rates of ROP) as neonatologists began successfully treating younger patients. A prospective, nonrandomized study in Great Britain, published in 2001, evaluated 295 babies born before 28 weeks' gestation and determined that there were significantly lower levels of ROP with no differences in mortality or cerebral palsy at relatively low oxygen saturation levels (70–90%) [53]. A survey of NICUs published in 2001 found some practice variation and lower reported rates of ROP in institutions with lower oxygen target levels [54]. As a result of these data, leaders in the field tentatively concluded that moderately lowering the oxygen saturation targets had the potential to reduce the prevalence of ROP without negatively affecting the children. However, the existing data were far from definitive, and different practices were common (the previously cited survey indicated target ranges from 82–100% at different NICUs). Consensus standards in the early 2000s that emerged were that target levels between 85–95% were acceptable and within recommended standards. In practice, some institutions were aiming at the low end of that target range (e.g., Texas

Children's Hospital), others aimed at the high end (a plurality according to the survey), some in between (Tufts targeted 88–92%), and many institutions allowed a wide fluctuation anywhere within the 85–95% saturation target. Neonatologists hypothesized that aiming for the lower end within that range would reduce the incidence of ROP without adversely affecting the infants. An international call for a large clinical trial that would answer the question took place and resulted in clinical trials conducted in parallel throughout the decade. The Canadian Oxygen Trial (COT) included 25 institutions in Canada, the United States, Argentina, Finland, Israel, and Germany. The Benefits of Oxygen Saturation Targeting (BOOST) trials included NICUs in the United Kingdom, New Zealand, and Australia. In the United States, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) involved an additional 23 NICUs. The studies focused on comparing "high" (91–95%) and "low" (85–89%) oxygen targets. The studies all demonstrated that there were significant differences in rates of ROP (higher at higher oxygen targets). The COT study suggested no increase in mortality in either arm; SUPPORT suggested that there was a small increase in mortality in the lower range ($p = 0.04$); the BOOST further supported the increase in mortality at the lower range. Combining the data, the neonatal community has concluded that there is a small increase in mortality at the lower oxygen saturation targets and a decrease in ROP. The trial seemed to be a success and has led to changes in practice.

SUPPORT was a complicated trial. It was a 2 × 2 study that not only randomized patients between the two oxygen target levels but also randomized the infants between two different approaches to treatment. While traditionally these premature infants were intubated and given surfactant at birth, new evidence raised the possibility that the infants would do better if they were initially given continuous positive airway pressure (CPAP) and only intubated if necessary. Thus the infants who were enrolled would be randomized between both differences in treatment protocol.

Several years after the conclusion of the study, Public Citizen, a self-identified watchdog group, attacked SUPPORT (and later BOOST), claiming that the research failed to minimize risks to subjects and that researchers failed to disclose reasonably foreseeable risks to the parents of the children who were enrolled. An Office of Human Research Protection (OHRP) investigation resulted in a letter to the University of Alabama Birmingham (lead site on SUPPORT) notifying them of a determination that investigators had failed to adequately disclose reasonably foreseeable risks. They did not find (and have continued to deny) any problems with the research design.

In their determination letter, OHRP particularly highlighted the claims made by the researchers that because the arms of the high and low oxygen targets are within the standard of practice, they do not expose the infants to any increase in risk. The informed consent forms do spell out that there was an anticipated difference in ROP between the two arms – though they state it in the positive (there is evidence that ROP will be lower at lower oxygen target levels) rather than the negative (there is evidence that ROP will be higher at higher oxygen targets). And the form template also states that "some unknown risks may be learned during this study."

A number of bioethicists were unhappy with the OHRP letter and defended the SUPPORT investigators [55–57]. A large number of bioethicists and research ethicists published a letter critical of OHRP in the *New England Journal of Medicine*, shortly followed by a group of lawyers and ethicists who defended OHRP and found fault with the study. OHRP suspended its finding [58,59], HHS held a one-day hearing on the topic, and views from both sides have started to be developed and more fully articulated. This resulted in a controversial draft guidance from OHRP [60–62]. No final guidance has yet been issued.

A number of issues have emerged from this debate that go beyond the details of SUPPORT. First, for research within the range of standard practice, how should the risk of being enrolled be understood? If there is little to no evidence about what is best among standard practices, does that mean that there is no difference in risk between being enrolled in research and clinical care? Is it always better (for patient participants) to have decisions made by a physician, exercising his or her clinical judgment about what is best for them, in contrast to being randomized on a protocol? When the common rule says that all reasonably anticipated risks should be disclosed, are those the risks of the research (as opposed to the risks of the clinical interventions that they would be exposed to anyway) or the risks of any interventions to be

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undertaken on the protocol (including those that they would be exposed to if not enrolled in research). Has too much emphasis been placed on consent forms (as opposed to the process of communicating with patients or parents)? Has too much emphasis been placed on consent in this type of research?

Conclusion

Neonatology is challenged by its dynamic nature. The state of knowledge is constantly changing, the edge of viability continues to move down, and this dynamic applies at the micro level to individual patients, whose course and prognosis may change in unpredictable ways. At the same time, exhausted and often desperate parents are asked to process and understand complicated and uncertain information to fully participate in decision making. In this situation, awareness of the limitations, challenges, and options for good ethical practice is critical to successful practice.

> The most important human endeavor is the striving for morality in our actions. Our inner balance and even our very existence depend on it. Only morality in our actions can give beauty and dignity to life.
>
> – *Albert Einstein*

References

1. Placencia FX, McCullough LB. The history of ethical decision making in neonatal intensive care. *J Intensive Care Med* 2011; **26**(6): 368–84.
2. Section 504 of the Rehabilitation Act of 1983, Pub. L. No. 93–112, 87 Stat. 355. 29 USC § 701. Available at www.usbr.gov/cro/pdfsplus/rehabact.pdf (accessed June 8, 2015).
3. Child Welfare Information Gateway. What is child abuse and neglect? Recognizing the signs and symptoms, 2015. Available at www.childwelfare.gov/pubpdfs/whatiscan.pdf (accessed July 8, 2015).
4. Elsasser G. Reagan loses Baby Doe case. *Chicago Tribune*, June 1986. Available at http://articles.chicagotribune.com/1986–06-10/news/8602110374_1_handicapped-infant-rehabilitation-act (accessed July 8, 2015).
5. USC, Title 42 – The Public Health and Welfare, Chapter 67 – Child Abuse Prevention and Treatment and Adoption Reform. Available at www.gpo.gov/fdsys/pkg/USCODE-2010-title42/html/USCODE-2010-title42-chap67.htm (accessed July 8, 2015).
6. Kopelman, L. Rejecting the Baby Doe rules and defending a "negative" analysis of the best interests standard. *J Med Philos* 2005; **30**(4): 331–52.
7. *In re: Baby "K,"* 16 F.3d 590 (4th Cir.), cert. denied, 115 S. Ct. 91, 1994.
8. Brown K. In the matter of Baby K: the Fourth Circuit stretches EMTALA even further. *Mercer Law Rev* 1996; **47**: 1173–79.
9. Texas Health and Safety Code, Chapter 166, Section 46, 1999. Available at www.statutes.legis.state.tx.us/Docs/HS/htm/HS.166.htm (accessed August 5, 2015).
10. Bassel A. Order at the end of life: establishing a clear and fair mechanism for the resolution of futility disputes. *Vanderbilt Law Rev Notes* 2010; **63**(2). Available at www.vanderbiltlawreview.org/2010/03/order-at-the-end-of-life-establishing-a-clear-and-fair-mechanism-for-the-resolution-of-futility-disputes/ (accessed August 5, 2015).
11. California Probate Code, Sections 4735 and 4736.
12. Chabot S., H.R. 2175 – 107th Congress (2001–2): Born-Alive Infants Protection Act of 2002. Available at www.congress.gov/bill/107th-congress/house-bill/2175/text (accessed July 8, 2015).
13. Centers for Medicare and Medicaid Services. Memo 05–26: Interaction of the EMTALA and the Born-Alive Infants Protection Act of 2002, April 2005. Available at www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/SCletter05-26.pdf.
14. American Academy of Pediatrics Neonatal Resuscitation Program Steering Committee. Resources: Born-Alive Infants Protection Act of 2001, Public Law No. 107–207, January 2003. Available at www2.aap.org/nrp/inst_resources-resources-bornalive_act.html (accessed August 5, 2015).
15. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA* 1968; **205**(6): 337–40.
16. Debolt D. Jahi McMath: family breaks silence on brain-dead girl's condition. *San Jose Mercury News*, October 2014. Available at www.mercurynews.com/ci_26659381/jahi-mcmath-family-breaks-silence-brain-dead-girls (accessed August 5, 2015).
17. Bernat JL. Whither brain death? *Am J Bioethics* 2014; **14**(8).
18. Truog RD, Miller FG. Changing the conversation about brain death. *Am J Bioethics* 2014; **14**(8).
19. Magnus D, Wilfond B, Caplan AL., Perspective: Accepting Brain Death. *N Engl J Med* 2014; **370**(10): 891–4.
20. Singh J, Fanaroff J, Andrews B, et al. Resuscitation in the "gray zone" of viability: determining physician preferences and predicting infant outcomes. *Pediatrics* 2007; **120**(3): 519–26.
21. Di Pietro NC, Whiteley L, Mizgalewicz A, Illes J. Treatments for neurodevelopmental disorders:

evidence, advocacy, and the Internet. *J Autism Dev Disord* 2013; **43**(1): 122–33.

22. Vavasseur C, Foran A, Murphy JFA. Consensus statements on the borderlands of neonatal viability: from uncertainty to grey areas. *Ir Med J* 2007; **100**(8): 561–4.
23. Verhagen AAE, Janvier A, Leuthner SR, et al. Categorizing neonatal deaths: a cross-cultural study in the United States, Canada, and The Netherlands. *J Pediatr* 2010; **156**(1): 33–7.
24. Weiner J, Sharma J, Lantos J, Kilbride H. How infants die in the neonatal intensive care unit: trends from 1999 through 2008. *Arch Pediatr Adolesc Med* 2011; **165**(7): 630–4.
25. Kuschel CA, Kent A. Improved neonatal survival and outcomes at borderline viability brings increasing ethical dilemmas. *J Paediatr Child Health* 2011; **47**(9): 585–9.
26. Kelly CE, Cheong JLY, Gabra Fam L, et al. Moderate and late preterm infants exhibit widespread brain white matter microstructure alterations at term-equivalent age relative to term-born controls. *Brain Imaging Behav* 2015; **10**(1): 41–9.
27. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, et al. Helping doctors and patients make sense of health statistics. *Psychol Sci Public Interest* 2007; **8**(2): 53–96.
28. Singh J, Fanaroff J, Andrews B, et al. Resuscitation in the "gray zone" of viability: determining physician preferences and predicting infant outcomes. *Pediatrics* 2007; **120**(3): 519–26.
29. Tennant PWG, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *Lancet* 2010; **375** (9715): 649–56.
30. Wang Y, Hu J, Druschel CM, Kirby RS. Twenty-five-year survival of children with birth defects in New York State: a population-based study. *Birth Defects Res A Clin Mol Teratol* 2011; **91**(12): 995–1003.
31. Wilkinson DJC, Thiele P, Watkins A, De Crespigny L. Fatally flawed? A review and ethical analysis of lethal congenital malformations. *BJOG* 2012; **119**(11): 1302–8.
32. Di Pietro NC, Whiteley L, Mizgalewicz A, Illes J. Treatments for neurodevelopmental disorders: evidence, advocacy, and the Internet. *J Autism Dev Disord* 2013; **43**(1): 122–33.
33. Akins RS, Angkustsiri K, Hansen RL. Complementary and alternative medicine in autism: an evidence-based approach to negotiating safe and efficacious interventions with families. *Neurother J Am Soc Exp Neurother* 2010; **7**(3): 307–19.
34. Bell E, Wallace T, Chouinard I, et al. Responding to requests of families for unproven interventions in neurodevelopmental disorders: hyperbaric oxygen "treatment" and stem cell "therapy" in cerebral palsy. *Dev Disabil Res Rev* 2011; **17**(1): 19–26.
35. Janvier A, Lantos J, POST Investigators. Ethics and etiquette in neonatal intensive care. *JAMA Pediatr* 2014; **168**(9): 857–8.
36. Ali Z. Selection criteria in the NICU: who should get effective critical care? *Indian J Med Ethics* 2009; **6**(2): 103–4.
37. Verhagen AAE, Janvier A, Leuthner SR, et al. Categorizing neonatal deaths: a cross-cultural study in the United States, Canada, and the Netherlands. *J Pediatr* 2010; **156**(1): 33–7.
38. Wilkinson DJ, Fitzsimons JJ, Dargaville PA, et al. Death in the neonatal intensive care unit: changing patterns of end of life care over two decades. *Arch Dis Child Fetal Neonatal Ed* 2006; **91**(4): F268–71.
39. Brecht M, Wilkinson DJC. The outcome of treatment limitation discussions in newborns with brain injury. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**(2): F155–60.
40. Yu VYH. Is neonatal intensive care justified in all preterm infants? *Croat Med J*. 2005; **46**(5): 744–50.
41. Swamy R, Mohapatra S, Bythell M, Embleton ND. Survival in infants live born at less than 24 weeks' gestation: the hidden morbidity of non-survivors. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**(4): F293–4.
42. Char D, Cho M, Magnus D. Whole genome sequencing in critically ill children. *Lancet Respir Med* 2015; **3**(4): 264–6.
43. Richards C, Crawley L, Magnus D. Use of neurodevelopmental delay in pediatric solid organ transplant listing decisions: inconsistencies in standards across major pediatric transplant centers. *Pediatr Transplant* 2009; **13**(7): 843–50.
44. American Academy of Pediatrics Infant Bioethics Task Force and Consultants. Guidelines for infant bioethics committees. *Pediatrics* 1984; **74**(2): 306–10.
45. McGee G, Spanogle J, Caplan A, et al. Successes and failures of hospital ethics committees: a national survey of ethics committee chairs. *Camb Q Healthc Ethics* 2002; **11**(1): 87–93.
46. Molloy J, Evans M, Coughlin K. Moral distress in the resuscitation of extremely premature infants. *Nurs Ethics* 2015; **22**(1): 52–63.
47. Hack M, Horbar JD, Malloy MH, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics* 1991; **87**(5): 587–97.
48. What is Vermont Oxford Network? Available at https://public.vtoxford.org/about-us/ (accessed August 4, 2015))
49. Malkar MB, Gardner WP, Mandy GT, et al. Respiratory severity score on day of life 30 is predictive

of mortality and the length of mechanical ventilation in premature infants with protracted ventilation. *Pediatr Pulmonol* 2015; **50**(4): 363–9.

50. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009; **123**(1): 313–18.
51. Hoffman L, Bann C, Higgins R, et al. Developmental outcomes of extremely preterm infants born to adolescent mothers. *Pediatrics* 2015; **135**(6): 1082–92.
52. Magnus D. The SUPPORT controversy and the debate over research within the standard of care. *Am J Bioeth* 2013; **13**(12): 1–2
53. Tin W, Milligan D, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**(2): F106–10.
54. Anderson CG, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol* 2004; **24**(3): 164–8.
55. Magnus D, Caplan AL. Perspective: risk, consent, and SUPPORT. *N Engl J Med* 2013; **368**(20): 1864–5.
56. Drazen JM, et al. Support for SUPPORT. *N Engl J Med* 2015; **373**: 1469–70.
57. Wilfond B, Magnus D, et al. Letter: The OHRP and SUPPORT. *N Engl J Med* 2013; **368**: e36.
58. Wilfond B, Magnus D, et al. Letter: "The OHRP and SUPPORT." *N Engl J Med.* 2013; **368**: e36
59. Macklin R, Shepherd L, Dreger A. The OHRP and SUPPORT: another view. *N Engl J Med* 2013; **369**(2):e3.
60. Lantos JD. Vindication for SUPPORT. *N Engl J Med* 2015; **373**: 1393–5.
61. Magnus D, Wilfond B. Research on medical practices and the ethics of disclosure. *Pediatrics* 2015; **135**(2): 208–10.
62. Cho MK, Magnus D, Constantine M, et al. Attitudes toward risk and informed consent for research on medical practices: a cross-sectional survey. *Ann Intern Med* 2015; **162**(10): 690–6.

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Chapter 49

Medicolegal Issues in Perinatal Brain Injury

David Sheuerman

Introduction

Perinatal hypoxic-ischemic brain injury is an important and often troublesome medicolegal problem for practicing physicians. Brain injury to infants occurring during the perinatal period is a frequent cause of severe long-term neurologic deficit in patients, and consequently, the incentive for legal action is high.

Although vast advances in care have taken place during the past several decades in the practice of perinatal medicine, the incidence of brain injury and its sequelae has not seen a significant decline. Litigation involving these types of injuries has remained a constant over many years despite endeavors in education of both physicians and patients and improvements in care. Some would argue this is evidence that the actions of the labor and delivery teams are not likely causes of the injuries. This chapter attempts to explore and explain the manner in which legal principles are applied to complex medical issues in the medicolegal examination of perinatal brain injury. The rules of law in this chapter refer either to California law or to general medical negligence principles in the United States.

The term *medical malpractice*, often misused and frequently misunderstood, refers to any professional act or omission to act that encompasses or represents an unreasonable lack of knowledge, care, or skill in carrying out one's professional duties. As used herein, the term *malpractice* is synonymous with *negligence*.

Although there are a number of legal theories that may be brought against a physician for allegedly faultworthy conduct in perinatal or other medical contexts, the vast majority of such legal actions are based on allegations that a physician or other practitioner was negligent – that is, that he or she did not perform in a reasonable manner as compared with other practitioners of similar standing acting under the same or similar circumstances.

Duty

The first element of the theory of negligence as malpractice is establishing that a duty was created by the practitioner-patient relationship. In certain instances, whether such a "duty" has been created is a contested legal issue. Such circumstances might include where an informal communication that might be construed as a consultation takes place or where a physician volunteers to help in an emergency situation. Once a sufficient relationship has been established, the practitioner has a duty to possess and use that degree of knowledge, care, and skill exercised by a reasonable and prudent physician under the same or similar circumstances. A physician owes the patient a duty to act in a manner consistent with the standards established by his or her profession, commonly referred to as the *standard of care*.

There is no clear or precise definition of the duty of a particular physician under each factual scenario. Thus, because most medical malpractice cases, especially those in the perinatal area, are highly technical, the standard of care is defined by witnesses who profess to carry special medical qualifications and who are asked to provide guidance to the judge or jury. In general, the finder of fact is instructed to base its decision solely on the opinions of such experts in deciding whether the physician in question acted with ordinary prudence [1] (Box 49.1). Instructions are also given to the jury on physician duty [2] (Box 49.2). (Instructions may vary significantly in different venues.)

Breach of Duty

The second element of a cause of action for medical malpractice is proof, only more likely than not, that the physician did not comply with the duty described earlier. It is thus alleged that the physician breached his or her duty by failing to act within the applicable

BOX 49.1 Medical Negligence: Standard of Care Determined by Expert Testimony

You must determine the standard of professional learning, skill, and care required of the defendant only from the opinions of the physicians (including the defendant) who have testified as expert witnesses as to such standard.

You should consider each such opinion and should weigh the qualifications of the witness and the reasons given for his or her opinion. Give each opinion the weight to which you deem it entitled.

(You must resolve any conflict in the testimony of the witnesses by weighing each of the opinions expressed against the others, taking into consideration the reasons given for the opinion, the facts relied on by the witness, and the relative credibility, special knowledge, skill, experience, training, and education of the witness.)

Source: California BAJI 6.30 [1]

BOX 49.2 Duration of Physician's Responsibility

Once a physician has undertaken to treat a patient, the employment and duty as a physician to the patient continue until the physician withdraws from the case after giving the patient notice and a reasonable time to employ another doctor or until the condition of the patient is such that the physician's services are no longer reasonably required.

A physician may limit his or her obligation to a patient by undertaking to treat the patient only for a certain ailment of injury or only at a certain time or place. If the employment is so limited, the physician is not required to treat the patient for any other ailment or injury or at any other time or place.

Source: California BAJI 6.05 [2]

BOX 49.3 Duty of Physician

A physician performing professional services for a patient owes that patient the following duties of care:

(1) The duty to have that degree of learning and skill ordinarily possessed by reputable physicians, practicing in the same or a similar locality and under similar circumstances.
(2) The duty to use the care and skill ordinarily exercised in like cases by reputable members of the profession practicing in the same or a similar locality under similar circumstances.
(3) The duty to use reasonable diligence and his or her best judgment in the exercise of skill and the application of learning.

A failure to perform any one of these duties is negligence.

Medical Perfection Not Required

A physician is not necessarily negligent because he or she errs in judgment or because his or her efforts prove unsuccessful. The physician is negligent if the error in judgment or lack of success is due to a failure to perform any of the duties as defined in these instructions.

Source: California BAJI 6.00.1, 6.02 [3]

standard of care. This is obviously a vigorously contested issue in each medicolegal case, with a variety of criteria to be examined in supporting the plaintiff or the defense case, mostly surrounding the opinions of the various experts. In the perinatal arena, consensus statements and guidelines such as those published by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) are frequently used to clarify the standard of care in the community. Of course, it is not possible for any consensus statement or clinical practice guideline to encompass or anticipate each clinical scenario or to speak to the important aspect of physician judgment employed in each case. The jury is instructed by the court to use a specific framework in evaluating whether the physician deviated from the standard of care [3] (Box 49.3).

Physicians asked to consult on a given case and to render their opinion whether the practitioner(s) met the standard of care commonly apply very different standards in the application of the *standard of care* to a given set of facts and circumstances. Many consultants are misled into believing that if the practitioner in question acted in a manner that deviated from the treatment the consultant believes he or she would have given, the standard must have been breached. This is clearly an incorrect application of the law, which provides that different methods may be employed by different practitioners, and where no uniformity of opinion exists, the physician is not negligent merely because he or she chooses a method different from or not favored by other physicians [4] (Box 49.4).

A generally accurate description by a testifying expert witness is "a physician must use the care a

BOX 49.4 Alternative Methods of Diagnosis or Treatment

Where there is more than one recognized method of diagnosis or treatment and no one of them is used exclusively and uniformly by all practitioners of good standing, under the same or similar circumstances, a physician is not negligent if, in exercising his or her best judgment, he or she selects one of the approved methods, which later turns out to be a wrong selection or one not favored by certain other practitioners.

Source: California BAJI 6.03 [4]

reasonable physician might employ in the same or similar circumstances." An error in judgment does not constitute negligence. Intentionally, and by necessity, the legal definition of the *standard* to be met is vague. I propose that if one may logically surmise that the practitioner has demonstrated adequate knowledge to apply the necessary skills and has used that knowledge in a logical manner in an attempt to achieve the desired result, the physician has met the standard of care regardless of the outcome of the treatment.

Causation

The third element that must be proved by the plaintiff, again by a preponderance of the evidence, is that the act or omission said to be negligent by the physician was a cause of the resulting injury. The closeness of this connection is described as *legal* or *proximate cause*. In the law, the concept of causation differs markedly from the concept of etiology in medicine. The law requires only that a particular act or omission be a "substantial factor" and not necessarily the major or most immediate cause of the injury, as a physician would apply the term to describe the etiology of an injury.

Physicians involved in the legal process, whether as defendants, retained experts, or treating physicians, often confuse (or allow themselves to be confused) when they are being cross-examined regarding their opinions on causation. Plaintiffs' burden of proof to show something did or did not happen by a "preponderance" of the evidence requires only that the "likelihood" of the occurrence or nonoccurrence is greater than 50%. Thus words such as "probably" and "likely" have critical meaning in the legal forum. Physicians are to be cautioned that use of these words in an answer (or a response linked to a question containing these words) constitutes a medical opinion that may make or break the legal case. The jury receives instruction on causation [5] (Box 49.5).

BOX 49.5 Cause: Substantial Factor Test

The law defines cause in its own particular way. A cause of injury, damage, loss, or harm is something that is a substantial factor in bringing about an injury, damage, loss, or harm.

There may be more than one cause of an injury. When negligent or wrongful conduct of two or more persons contributes concurrently as (a) cause(s) of an injury, the conduct of each is a cause of the injury regardless of the extent to which each contributes to the injury. A cause is concurrent if it was operative at the moment of injury and acted with another cause to produce the injury. It is no defense that the negligent or wrongful conduct of a person not joined as a party was also a cause of the injury.

Source: California BAJI 3.76, 3.77 [5]

Causation is a critical element in the evaluation of most perinatal brain injury cases. Numerous criteria are evaluated in an attempt to prove the likelihood or lack of causation in the perinatal period, including epidemiology, indicators of intrauterine injury, evaluation of fetal heart monitor tracings, consideration of alternative causes of brain injury to those occurring in the perinatal period, and correlation of clinical findings and timing of the hypoxic-ischemic event by use of Apgar scores, blood gases, brain imaging, placental pathology, hematologic markers such as nucleated red blood cells [6], and the like.

Informed Consent

All patients must give *informed consent* prior to medical treatment. Generally, the courts have stated that in order to give informed consent, the patient must be informed of (1) the nature of the procedure, (2) the risks, complications, and expected benefits or effects of the procedure, and (3) any alternatives to treatment and their risks and benefits.

The scope of the physician's communications to the patient must be measured by the patient's needs, and those needs are whatever information is material to the decision. The test for determining whether a potential peril must be divulged is its materiality to the patient's decision. *Material information* has been described as that which the physician knows or should

know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended procedure; to be material, a fact must also be one that is not commonly appreciated. If the physician knows or should know of a patient's unique concern or lack of familiarity with medical procedures, this may expand the scope of required disclosure [7].

The patient's *informed* consent, as distinguished from the general concept of consent to treatment, is not required for all procedures. Procedures or treatments that are complex generally require the patient's informed consent as earlier. Procedures that are somewhat common, for instance, insertion of an intravenous (IV) line for access or fluids, do not require informed consent, although they do require consent. Use of medications such as Pitocin would most certainly require informed consent rather than the simple general consent to treat.

It is the treating physician's responsibility to obtain informed consent. Hospital personnel should not be involved in providing the information necessary to secure the patient's informed consent or in responding to the patient's questions concerning the procedure. The duty to provide this information and informed consent is the exclusive duty of the treating physician. How that physician obtains his or her informed consent is within the discretion of the physician.

It is highly recommended that the physician carefully and fully document in the hospital medical record and other records including the prenatal chart that full discussions were had with the patient and that informed consent was obtained. As indicated in the section on documentation, this writing in the record is critical to the defense of any malpractice case. I recommend that the physician not only include a brief statement that informed consent was obtained but that the physician includes the major and most substantial serious risks of the procedures or treatments. In this manner, one can defend by saying if the patient was willing to accept the risk of stroke, nervous system damage, death and the like, it is unlikely that he or she would have refused the procedure because of the risk of infection. It is also recommended that the patient sign and, if possible, initial forms documenting informed consent. It is generally a duty of the hospital and the nursing staff to see that these forms are signed. These forms do not substitute for the communications between physician and patient for informed consent. This holds true even if the informed consent form used by the hospital lists specific risks of procedures, generally such as infection, bleeding, neurologic injury, damage to adjacent organs, or death.

Damages

The fourth element of the medical malpractice lawsuit is plaintiffs' proof of the nature and extent of damages. During a perinatal brain injury case, damages may include a wide range of financial, physical, and emotional injury to the patient.

General or noneconomic damages are awarded for pain and suffering, mental anguish, grief, and emotional conditions that are thought to flow inevitably from the injury caused by the defendant as a natural and foreseeable consequence of the injury. *Special* or *economic damages* in a perinatal brain injury case are presented by a team of experts on each side, which has grown into a cottage industry, often thought by the defense to represent extreme departures from reason. The plaintiffs' bar, however, argues that defense experts are hired to unreasonably reduce just compensation for legitimate injuries. Economic damages in a severe perinatal injury case will generally include

- Healthcare services, often including those of a pediatrician, internist, dentist, podiatrist, nutritionist, vision specialist, occupational and physical therapist, speech therapist, psychological services, and behavioral intervention, therapeutic recreation, laboratory, emergency room, case manager, financial manager, and acute hospitalization
- Medical supplies, including medications, bowel and bladder supplies, gastrostomy supplies, respiratory supplies and equipment, and medical equipment including wheelchair, orthotics, mechanical bedding, bedside equipment and supplies.
- Diagnostic testing; chest, hips, spine, and other x-rays; neurodiagnostic studies such as magnetic resonance imaging (MRI)/computed tomography (CT) of the head, electroencephalograms (EEGs), and various laboratory work are claimed as intermittent needs.
- Attendant care, often alleged to be necessary around the clock, can alone easily generate damages of several hundred thousand dollars per year for life. The level of care required is a

frequently contested issue, often involving millions of dollars depending on whether the jury finds that care should be provided by a trained attendant, a licensed vocational nurse, or a registered nurse.

- Home modifications, such as access ramps, widened hallways, lowered cabinets, and specialized bathroom facilities, are commonly prescribed.

In many cases, such lifetime damages are funded by the purchase of an annuity, generally at a small fraction of the expenses projected by the plaintiffs. An exemplar of such damages can be found as part of a typical life-care plan (Box 49.6). The courts have yet to reach any consensus on the possible role of the Affordable Care Act (ACA) in determining actual damages.

BOX 49.6 Exemplar: Future Medical Needs, Neonatal Brain Injury

I. Future medical care

A. *Physicians*

1. Internist: four times a year over life expectancy after age 18.
2. Pediatrician: 4–6 times a year until age 18.
3. Other (neurologist, ophthalmologist, immunologist, gastroenterologist, hematologist, pulmonologist, rehabilitation medicine, orthopedist, etc.): 10–12 visits per year over the patient's life expectancy.

B. *Ancillary medical care*

1. Dentist: cleaning 3–4 times per year. Currently, seeing a special pediatric "special needs" dentist. Because of oral tactile defensiveness, as patient ages, will likely need examination and cleaning under anesthesia.
2. Podiatrist 1–2 times per year over the patient's life expectancy.
3. Nutritionist: 2 times per year over the patient's life expectancy.
4. Low-vision specialist: 1 time per year until age 18.

C. *Counseling*

1. Individual counseling for mother 6 times per year over the patient's life expectancy.
2. Family counseling for parents as a couple 6 times per year over the patient's life expectancy.
3. Sibling (5-year-old brother) 4 times per month for 3 months, then 1 time per month until age 18.

D. *Behavioral intervention*

1. A behavioral specialist to assist with a program of environmental and behavioral modification to extinguish negative self-mutilating behavior and the behavior of kicking, pinching, and biting others. Initial intervention at 6–12 sessions for the first 6 months, supervised by a psychologist. Thereafter, 2 visits per year over the patient's life expectancy.

II. Diagnostic testing

A. *Routine blood chemistry*

1. Complete blood count: 6 times per year on average over the patient's life expectancy, exclusive of inpatient lab.
2. Sequential multiple analyzer count (SMAC) 20: 2 times per year over the patient's life expectancy.
3. Valproic acid levels: 2 times per year over the patient's life expectancy.
4. Immunoglobulin G levels.

III. Neurodiagnostic studies

A. *Magnetic resonance imaging/computed tomographic head scans*

4–6 more times over the patient's life expectancy.

B. *Electroencephalogram*

4–6 more times over the patient's life expectancy.

IV. Radiologic studies

A. *Chest x-ray*

2–4 per year over the patient's life expectancy. Based on this track record thus far, this is a conservative estimate.

B. *Joint x-ray/spine x-ray*

Approximately 1–2 per year over the patient's life expectancy to follow scoliosis; rule out fractures/dislocation secondary to anticipated falls.

V. Gastrointestinal studies

A. *Upper gastrointestinal endoscopy*

4–6 per year over the patient's life expectancy for recurrent obstruction, gastrointestinal bleeding, and vomiting.

BOX 49.6 (cont.)

VI. Rehabilitation therapy

A. *Physical therapy*

One time per week until age 18. Then 4 times per year over the patient's life expectancy to reevaluate lower-extremity range of motion, mobility status, and equipment.

B. *Occupational therapy*

Two times per week until age 18. Thereafter, 4 times a year to reevaluate equipment, upper-extremity range of motion, and self-care potential.

C. *Speech therapy*

One time per week until age 18. Thereafter, reevaluations are appropriate once every 3–5 years.

D. *Therapeutic recreation*

One time per year over the patient's life expectancy to assist with the selection of developmentally appropriate recreational activities.

VII. Equipment

A. *Feeding supplies*

1. Gastrostomy tubes (Mic Key buttons with adapters for both J-tube site and separate G-tube site). Buttons are changed every 3–4 months.
2. Feeding bags with tubing.
3. Intravenous pole.
4. Feeding pump.
5. Syringe.
6. 2 × 2 dressings for both G-tube and J-tube sites.
7. Stockinette (wrapped around abdomen to secure G-tube and J-tube dressings).

B. *Incontinence supplies*

1. Diaper wipes.
2. Diapers (approximately 8 per day).
3. A&D ointment.
4. Gloves.
5. Bactroban ointment.

C. *Respirator equipment*

1. Suction machines, portable.
2. Yangauer suction handle.
3. Pulse oximeter.
4. Pulmoaide.

BOX 49.6 (cont.)

D. *Mobility aids*

1. Wheelchair: pediatric manual Quickie wheelchair with head rest, lateral trunk and lateral thigh supports, hip abduction wedge, detachable foot rests, antitip bars, heavy-duty wheels, back support with lumbar insert, chest and lap belts, handles on back for parents to push chair.
2. Bilateral ambulatory foot orthotics: will require a new pair every 12 months until age 18. Thereafter, replace every 2–3 years.

E. *Equipment*

1. Hospital bed.
2. Bath equipment: shower chair and hand-held shower hose will be needed after age 8–10 years. Currently, parents lift him in and out of bathtub.

F. *Safety equipment*

1. Restraint jacket to use in any bad conditions (traveling).
2. Helmet.
3. Vail bed enclosure.
4. Bilateral arm splints to hold elbows in extension to prevent self-mutilation.
5. Other: Porto-Cath, implanted. Change? How often?

VIII. Medications

A. *See attached.*

In addition, is frequently on antibiotics several times per year. These include Keflex, Septra, etc., per J-tube, and Rocephin, intramuscularly as an outpatient.

IX. Tube feeding

A. *Vivonex* via J-tube at 65 mL/h × 24 h/day.

Documentation

No discussion of medicolegal issues in any area of medicine can ignore the critical importance of careful and accurate charting. One must recognize that the practitioner's primary responsibility is to provide quality care to the patient, even if that endeavor detracts from accurate charting. The ability to time precisely particular events or to record all "significant" information greatly depends on clinical

circumstances. However, when trying to defend one's actions years after an event has taken place, failure to record, as recommended by obstetric and nursing organizations, makes it far more likely that a lay jury will infer that a negative event is represented by lack of documentation. Often the issue in a perinatal case brought years after the event involves when the status of the fetus was compromised. Long time periods of undocumented fetal heart rates often simply reflect long periods of fetal well-being. Plaintiffs will argue, perhaps supported by suboptimal blood gases or low Apgar scores, that the lack of documentation reflects lack of adequate monitoring. Both ACOG and NAACOG (the organization for obstetric, gynecologic, and neonatal nurses) have published standards requiring specific frequency of recording as well as specifying the characteristics required to be noted. For instance, the ACOG indicates that auscultated fetal heart rates should be recorded in the chart after each observation [8]. The practitioner must recognize that the events of labor, delivery, and neonatal care often are not even examined by lawyers or consulting experts until several years after the events. Substandard record keeping alone, where the actual care was adequate, has led to many malpractice suits.

Terminology Matters

Accurate and consistent use of terms (or the reverse) is often the difference between the filing or the successful prosecution of cases alleging substandard perinatal care. The term *fetal distress* is most commonly misapplied in medical charts to the reaction of the fetus to the stress of labor, and the term's indiscriminate use can lead to confusion or worse. The ACOG has stated, "Terms such as asphyxia, hypoxia, and fetal distress should not be applied to continued electronic fetal monitoring or auscultations" [9].

Practitioners have been cautioned by the ACOG against indiscriminate use of the term *fetal distress*. Instead, the term *nonreassuring fetal status* is recommended [10]. Another term used with consistent imprecision is *perinatal asphyxia*. According to the ACOG, "long usage prevents its abandonment" [11]. The current AAP and ACOG guidelines state that *asphyxia* should be reserved to describe neonates with all the following conditions:

1. Acidemia, pH below 7.0 on arterial cord blood
2. Apgar score of 0–3 for longer than 5 minutes
3. Objective neonatal neurologic signs and symptoms (seizures, coma, hypotonia, etc.)
4. Multisystem organ dysfunction (cardiovascular, gastrointestinal, hematologic, pulmonary, or renal) [12]

It should be noted, effective in 1998, the International Classification of Diseases (ICD) dropped "all inclusion terms" for "fetal distress" except *metabolic acidemia*.

Similarly, the term *hypoxic-ischemic encephalopathy* (HIE) is frequently applied indiscriminately by perinatal providers because it occurs with other such "diagnoses." Once the term is applied to the patient by one practitioner, it is commonly repeated in subsequent chart entries by others, without appropriate consideration of whether the neonate displaying neurologic depression actually had evidence antepartum or intrapartum of events likely to compromise oxygen supply to the fetus. Once the term is used in the chart (and frequently buttressed by multiple entries simply parroting it), it is extremely difficult for the defense team to demonstrate to a jury of laypeople that the infant's depression is more likely a result of perinatal ischemic stroke, congenital metabolic condition, infectious etiologies, or placental vasculopathies. Litigation experience shows that once discovery ensues, comparison of records of the neonate's siblings can uncover similar developmental delays, demonstrating a likely genetic cause of the original neurologic compromise and subsequent delay. However, because these causes are often difficult to prove, the diagnosis of HIE is often applied by default. A more complete review of the factors to be considered in the "cause and effect" analysis of perinatal depression can be found in Chapter 1.

Authorities, including Nelson, have advocated that when encephalopathy and/or later cerebral palsy occurs in a term or near-term infant without the obvious antecedent asphyxial events, a diagnosis of *neonatal encephalopathy* (NE) is the appropriate term [13]. This appears to be a preferred approach from both the therapeutic and the medicolegal perspective.

The absence of subsequent markers of HIE, including positive findings on MRI, should also be noted as significant in the diagnostic process and accompanying documentation.

Case Study: Obstetrics/Labor and Delivery

In a case alleging negligent care by two obstetricians, the hospital nursing staff, and the anesthesiologist, the minor plaintiff brought this action for severe brain injury following uterine rupture:

The mother of the baby was a 25-year-old gravida 3 para 1 with a relatively uncomplicated prenatal course admitted to the subject hospital for induction at 40 + 4/7 weeks' gestational age due to a low amniotic fluid index. The patient had no known risk factors for the eventual complication, a uterine rupture. She had previously delivered a 3,500+ g infant by uncomplicated vaginal delivery.

The patient was in the hospital for induction for approximately 12 hours on the day prior to delivery. During that time, she received oxytocin augmentation, which was discontinued around midnight to allow her to rest overnight. On the following day, the obstetricians began a trial of misoprostol for induction. After approximately 7 hours of relatively normal, albeit slow progress of labor (there was dispute whether the fetal monitors reflected fetal well-being and whether there was evidence of hyperstimulation), the mother requested her labor epidural. She testified, as compared with her previous pregnancy, that she felt thast delivery was imminent.

The external fetal monitor belt was removed for placement of the epidural. A few minutes after the epidural was in, the mother reported a tearing sensation and severe pain, which the experienced nursing staff interpreted as labor pain. The fetal monitoring Doppler was being reattached; however, the nurses had not obtained a fetal heartbeat since attempting to replace the external fetal monitor belt following the epidural. The next 6–8 minutes passed as the nursing staff attempted to obtain a fetal heart rate, without success. The obstetrician was called, arrived within 5 minutes, and delivered the baby from the abdomen by cesarean section within 20 minutes of her arrival.

Allegations against Prenatal Obstetrician

Plaintiff alleged that the prenatal care was negligent in that the position of the baby at 29 weeks was confirmed as transverse and that no accurate testing regarding presentation was done thereafter until the uterine rupture occurred. Plaintiff complained that the obstetricians did not assess the position of the fetus sonographically on several visits leading up to the delivery and failed to document that the fetus was in the vertex position throughout the period of induction at the hospital.

Plaintiff complained that various drugs were used to promote cervical ripening and dilation without any descent of the fetus and without dilation in the mother. Plaintiff claimed that these drugs, rather than promoting ripening, induced hypercontractility. Plaintiff alleged that the prenatal obstetrician was negligent in failing to confirm a vertex presentation during the last few prenatal visits. That obstetrician testified that he most probably conducted a Leopold's maneuver to determine fetal presentation, given the mother's excessive weight gain and the fact that the first baby was nearly macrosomic. However, that obstetrician failed to document in the medical record that he had performed a Leopold's maneuver, nor did he document fetal presentation. Plaintiff alleged that had the examination been performed, it would have likely diagnosed a transverse lie requiring cesarean rather than vaginal delivery.

Plaintiff further claimed that the patient was not adequately informed concerning the risks and benefits of oxytocin under the circumstances of having a low amniotic fluid index and that the obstetricians further failed to explain the risks involved in the use of misoprostol.

Allegations against Labor Obstetrician

Plaintiff complained that the obstetrician managing the labor and delivery was negligent in failing to consider the potential for uteroplacental insufficiency and thereby discontinue the use of misoprostol; failing to confirm fetal presentation before ordering the use of misoprostol; and failing to observe the patient adequately to "insure" normal fetal heart rate and uterine contraction patterns in a patient laboring under misoprostol induction. Plaintiff alleged that the mother of baby was hyperstimulated and that according to misoprostol protocols, the patient's dosage should have been reduced or discontinued.

Allegations against Anesthesiologist

Plaintiff claimed that the anesthesiologist was negligent in ignoring complaints of severe pain at the time the epidural was administered despite two preceding doses of narcotic medications without relief; plaintiff alleged that removal of the fetal monitor during epidural administration was negligent in the face of "abnormalities" present on the fetal heart rate monitor and with contractions occurring every 1–2 minutes.

Plaintiff contended that it was the responsibility of the anesthesiologist practicing in the labor and delivery department to know the status of both mother and fetus and to be "sure" that both were stable at all times.

Plaintiff complained of the anesthesiologist that he made no inquiries of the status of the fetus and that he prematurely left the patient's room shortly after giving the epidural. Plaintiff alleged that the standard of care required the anesthesiologist to remain in the room for 15–20 minutes following epidural administration. Had he done so, plaintiff alleged, he would have been aware of the report by the mother of baby that she felt a rip or tearing pain and that this would have alerted him to the occurrence of a uterine rupture. Plaintiff complained that when the nurse, following the epidural, was unable to obtain a fetal heart rate, the anesthesiologist should have immediately contacted the obstetrician rather than allowing the nursing staff to evaluate the reasons for loss of fetal heart rate.

Allegations against Hospital (Nursing Staff)

Plaintiff alleged that the hospital nursing staff failed to determine fetal position on vaginal examinations, failed to contact the obstetrician to report decelerations in the absence of uterine contraction, failed to detect hyperstimulation, failed to administer terbutaline to reduce the frequency of contractions, failed to evaluate the patient's complaints of pain described as hallmarks of uterine rupture, and delayed contacting the obstetrician once the fetal heart tones were found to be undetectable.

The prenatal obstetrician defended his actions by arguing that he did in fact determine that this fetus was in a vertex presentation based on the fact that he had written in his record the location of the fetal heart rate and had performed an abdominal examination. An ultrasound examination was done shortly before admission for the primary purpose of determining the amniotic fluid volume. He argued that he certainly would not have scheduled the patient for an induced labor had there been a transverse lie at the time of his examination. He testified that he used four methods to determine the vertex presentation on his final prenatal visit: (1) location of the fetal heart rate in the lower quadrant, (2) palpating the fetal back through the abdominal wall, (3) vaginal examination with palpation of vertex, and (4) ultrasound confirmation of vertex presentation. However, only heart sound location was documented.

He testified that misoprostol is a synthetic prostaglandin E_1 analogue that can be administered intravaginally or orally for cervical ripening and induction; it had been studied in randomized clinical trials and had been found to be an effective agent for induction of labor. Reports of uterine rupture in the use of misoprostol had occurred, he argued, only in patients with prior cesarean section.

The labor and delivery obstetrician argued that she most likely did discuss the risks of induction with the patient despite the fact that she had made no note of such. She also argued that fetal presentation was vertex at the time of her initial evaluation, although, again, she did not make a note of that. She argued that the fetal heart rate and contraction patterns were adequate and reassuring. She saw no evidence of hyperstimulation. She argued that she was paged stat and that she arrived in 5 minutes' time. The baby was delivered within 20 minutes of her arrival.

The anesthesiologist defended his case by responding to the plaintiff's contention that he should have "questioned the indication for the epidural" by pointing to the mother's own testimony that she did feel as though she was in labor at the time of the epidural and had compared this labor to her previous delivery. He argued that the nursing staff, far more experienced in managing labor than he, also felt that the patient was in labor.

The anesthesiologist responded to the plaintiff's criticism that the fetal heart monitor should not have been moved during epidural administration by pointing to the fact that there is no standard or guideline requiring such monitoring in the face of many hours of a reassuring heart rate pattern. He argued that it would be substandard either not to remove or to move the fetal monitor strap to place the epidural and such would violate the sterile field. The nursing staff would then have been free to position the Doppler on the patient's abdomen during placement of the epidural if that was felt to be warranted.

The anesthesiologist argued that he did not prematurely exit the patient's bedside and that his chart reflected he recorded the patient's blood pressures every 5 minutes from the time he first saw her until the time of delivery. Thus, he argued, the plaintiff's testimony that he left the room and did not return was due to faulty memory.

The anesthesiologist responded to the allegation that he had failed to contact an obstetrician under emergency circumstances by arguing that the nurses were making constant attempts to locate the fetal heart rate and that the normal interaction between the obstetrician and the staff is that the notification to

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obtain an obstetrician for a problem is made by the nurses, not the anesthesiologist. He argued that it is not the role of the anesthesiologist to assume the tasks of the labor and delivery nurses, whose roles are carefully coordinated, with certain responsibilities assigned to them.

Discussion

This case points out several common areas in which plaintiffs may make allegations of substandard care. First, failure to adequately document fetal presentation by the obstetricians left them open to claims that the baby was inappropriate for induction despite the logical inference that trained obstetric personnel, including physicians and nurses, would not induce a patient for vaginal delivery in a transverse lie. In fact, the prenatal obstetrician would not have even been in the case had he documented fetal position. The physicians' and nurses' failure to document their informed-consent discussions or even the fact that such discussions took place with the patient left them open for criticism that they had not advised the patient as to the risks of induction with a low amniotic fluid index. Informed consent should always be documented. In many jurisdictions, the jury is instructed that a failure to give informed consent may subject the physician to liability for any injury caused by the treatment, even if the treatment itself is provided appropriately [14] (Box 49.7).

BOX 49.7 Duty of Disclosure

It is the duty of the physician to disclose to the patient all material information to enable the patient to make an informed decision regarding the proposed treatment.

Material information is information that the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject a recommended medical procedure. To be material a fact must also be one that is not commonly appreciated.

When a procedure inherently involves a known risk of death or serious bodily harm, it is the physician's duty to disclose to the patient the possibility of such outcome and to explain in lay terms the complications that might possibly occur.

Even though the patient has consented to a proposed treatment or operation, the failure of the physician to inform the patient as stated in this instruction before obtaining such consent is negligence and renders the physician subject to liability for *any* injury caused by the treatment if a reasonably prudent person in the patient's position would not have consented to the treatment if he or she had been adequately informed of all the significant perils [italics added].

Source: California BAJI 6.11 [14]

Serious questions arose in this case as to the time of the uterine rupture and the ability of the team to respond to this catastrophic event. The defendants argued that the baby and the placenta were both extruded into the abdomen at the time of the rupture. Thus, regardless of whether the baby had a heart rate at that time, the rupture of the placenta resulted in complete and total asphyxia of the child from the point of rupture. Using the mother's testimony and the chart to establish this timing, it became difficult to conceive of a scenario where this child could have been delivered without having suffered severe brain damage unless an obstetrician was present at the time of the rupture.

Demonstrating their awareness of this weakness in their case, the plaintiffs were highly motivated to find flaws in the prenatal care and in the early labor pattern to circumvent the causation defense that became operative at the time of rupture. Thus the plaintiff was motivated to focus less on the delay in diagnosis after the rupture had occurred. This was an area that was problematic for the defense, where substantial delays took place between the time of the apparent rupture and notification of the obstetrician.

This case also illustrates how allegations of negligence may shift in focus if, for instance, at a particular time causation cannot be proven to be linked with a particular act or mission. Here it was likely that the infant suffered severe irreparable brain damage within 8–10 minutes of the rupture, making a therapeutic response to the event virtually impossible. Delay in notification of the obstetrician was thus less significant. The focus of the case therefore shifted to the weaker negligence arguments, such as the allegation that a 29-week prenatal ultrasound showing the baby was transverse indicated that the baby was transverse at the time of induction.

The case against the hospital and the anesthesiologist settled before trial with approximately 80% of the payment coming from the hospital. The case went to trial against the two obstetricians. There was a finding of negligence by the jury, which also concluded that this negligence (by the prenatal

obstetrician) was not a cause of injury to the child. The resulting judgment was for the physicians.

Case Study: Obstetric Discharge/ Pediatric Follow-Up

This action was brought by a 5-year-old child with severe athetoid cerebral palsy from bilirubin encephalopathy that developed between 3 and 5 days after birth. Plaintiff alleged that "early discharge" resulted in missed hyperbilirubinemia.

Plaintiff was delivered with Apgars of 9/9 at approximately 36 weeks' gestational age (a few days short of the AAP definition of *term*). The child was observed for approximately 32 hours in the hospital without any indication of jaundice. During that time, the child voided and stooled normally; had normal feeding habits and normal laboratory values, including hematocrit and hemoglobin levels; and had frequent normal vital signs, normal skin color, normal activity, and normal tone. A cephalohematoma of unspecified size was noted.

Mother and child were discharged by the obstetrician with instructions to the mother to observe for color, feeding, activity, sleep, voiding, stools, and signs of illness. The mother was shown a videotape with similar instructions, which included a section on jaundice. At the time of discharge, the mother was instructed to return to the pediatrician's office in "1–2 days."

The medical records and the mother's deposition testimony reflect that the child did well at home until approximately 3 days following discharge. The medical records and the mother's testimony also reflected that the child exhibited symptoms of opisthotonos, the hallmark of bilirubin encephalopathy, on the third evening following discharge. The testimony demonstrated that the mother had not returned to the pediatrician's office during that 1- to 2-day period as instructed at the time of discharge.

The records indicated that the mother called the pediatrician's office for the first time 4 days post-discharge. The child was seen by the pediatrician at approximately midday on the fifth day of life. The pediatrician charted a relatively benign newborn examination, except that the child was jaundiced to the midabdomen. The pediatrician sent the patient to the hospital laboratory for a bilirubin level, which came back in approximately 2.5 hours, revealing a bilirubin level of 32 mg/dL. In light of the relatively benign physical examination, the pediatrician elected to order a retest stat to determine if there was laboratory error. The entire process between completion of the pediatrician's first examination and completion of the second blood test was approximately 4 hours. When the retest came back at the same level, the parents were sent immediately to the nearest neonatal intensive care unit. In the meantime, the pediatrician called the neonatologist at the neonatal intensive care unit for the purpose of preparing the staff for accepting the child for treatment. The neonatologist in charge ordered blood from the blood bank and began preparations for treatment. Because of the time required to obtain the blood, the transfusion did not take place for approximately an additional 4 hours.

Allegations against Obstetrician

Plaintiff's experts alleged the obstetrician had violated the standard of care in the "early" discharge because the patient was at increased risk for potential elevated concentration of free ("toxic") bilirubin due to (1) prematurity, (2) cephalohematoma, (3) breastfeeding, (4) mother's receipt of oxytocin during labor, and (5) Asian ancestry. Plaintiff also alleged that the obstetrician deviated from the standard of care in failing to educate the mother "vigorously" regarding her need to watch for jaundice, contending that the baby had a 50% increased risk of hyperbilirubinemia at the time of discharge. Plaintiff relied heavily on ACOG and AAP literature advocating against "early discharge."

Allegations against Pediatrician

Plaintiff alleged that the pediatrician was negligent because he failed to (1) obtain a complete history of symptoms in a baby at "very high risk" for hyperbilirubinemia and therefore did not conduct the appropriate physical examination; (2) did not order the initial bilirubin test stat; (3) did not inform the laboratory to phone with the results of the bilirubin in the initial order; and (4) that he reordered the bilirubin test after receiving the result of 32 mg/dL without having the mother stay at the hospital to receive the results.

The plaintiff's attorney retained two experts on the subject of hyperbilirubinemia. One, a nationally recognized expert in the pathophysiology of hyperbilirubinemia, with extensive writings on the subject,

was called to express opinions only on causation. This physician gave testimony that contradicted much of the causation testimony of the second plaintiff expert. The defense argued that had the mother followed the obstetrician's instructions to return the baby to the pediatrician in 1–2 days, the treatment would have been available. Plaintiff expert 1 admitted that had this child been treated with the standard therapies in the 3 days following discharge, she would have had no great injury whatsoever. Plaintiff expert 1 also acknowledged that based on the serum bilirubin laboratory value taken at the time of the first test, the child's level had either peaked or was on its way down when the pediatrician first examined the child. This expert further admitted that if the child was truly exhibiting opisthotonic movements, characterized by back arching on the previous evening, this would be an indication of bilirubin brain toxicity even before the pediatrician saw the child.

Plaintiff expert 2, a retired physician, clearly was an advocate for the plaintiff. Causation was strenuously contested throughout the cross-examination of this expert. Plaintiff expert 2 refused to acknowledge that the back-arching movements witnessed by the parents before the child was seen at the pediatrician's office were characteristic of opisthotonos. This expert claimed that most, or all, of the brain damage would have been avoided and/or reversed if treatment had been initiated by the pediatrician on the first visit. Plaintiff expert 2 produced a self-generated "table" of neonatal signs of bilirubin-induced neurologic dysfunction progressing to kernicterus, purporting to correlate clinical signs in three stages, with those stages being (1) reversible, (2) partially reversible, and (3) irreversible. This table was not the product of any controlled studies, nor had it been submitted for publication. Both plaintiff experts admitted that bilirubin encephalopathy does occur at levels over 20%. Expert 1, along with the defense experts, testified that the bilirubin level had peaked or was on the way down at the time the mother presented the child to the pediatrician's office. Thus the bilirubin level on the morning before the child arrived at the pediatrician's office was approximately 30 mg/dL. Bilirubin toxicity to the brain cells, it was acknowledged, may occur even before clinical symptoms are present. Following the expert depositions, the plaintiff dismissed the case and refiled it in a different jurisdiction before the statute of limitations expired. Plaintiff's expert 1 was not to be called in the refiled case. Thereafter, the case was settled for a small fraction of the proffered damages.

Discussion

The defense had legitimate fears of how the jury might react to specialty society (e.g., ACOG and AAP) guidelines advocating against early discharge. While the practitioners here sought to balance the discharge with early pediatric follow-up, deviations from such guidelines can be devastating at trial.

The hospital staff had documented (twice) the discharge instructions to the mother to return the child to the pediatrician's office in 1–2 days. Moreover, they had the mother sign the discharge instructions, acknowledging receipt and understanding. That follow-up instructions were given is frequently denied by plaintiffs. Signed instructions are a valuable and effective way to rebut such denials. However, the doctor is protected from liability only for injury resulting solely from the negligent failure of the patient to follow instructions [15] (Box 49.8).

This case illustrates the enormous impact a thorough analysis of the causation elements of a case may have on the ultimate result. Objective evidence using the natural progression of the bilirubin levels led to a strong conclusion that the child's encephalopathy had occurred before the visit to the pediatrician's office. This strong causation defense again caused the plaintiffs to focus arguments against the obstetrician, which may not have been made otherwise. The fact of the serious contradictory testimony between

BOX 49.8 Patient's Duty to Follow Instructions

A patient has a duty to follow all reasonable and proper advice and instructions regarding care, activities, and treatment given by such patient's doctor.

A doctor is not liable for any injury resulting *solely* from the negligent failure of the patient to follow such advice and instructions.

However, if the negligence of the doctor is a cause of injury to the patient, the contributory negligence of the patient, if any, in not following such advice and instructions does not bar recovery by the patient against the doctor, but the total amount to which the patient would otherwise be entitled shall be reduced in proportion to the negligence attributable to the patient [italics added].

Source: California BAJI 6.28 [15]

the two plaintiff experts also weighed heavily on the ultimate outcome of the case.

References

1. *California BAJI* (Book of Approved Jury Instructions), 6.30.
2. *Ibid.*, 6.05.
3. *Ibid.*, 6.00.1, 6.02.
4. *Ibid.*, 6.03.
5. *Ibid.*, 3.76, 3.77.
6. Altshuler G. Placental insights into neurodevelopmental and other childhood diseases. *Semin Pediatr Neurol* 1995; **2**: 90–9.
7. *Truman v. Thomas* (1980) 27 Cal. 3d 285, California Supreme Court.
8. American College of Obstetricians and Gynecologists. Fetal heart rate patterns: monitoring, interpretation, and management (ACOG Technical Bulletin No. 207, July 1995 (replaces No. 132, September 1989). *Int J Gynaecol Obstet* 1995; **51**: 65–74.
9. American College of Obstetricians and Gynecologists. *Intrapartum Fetal Heart Rate Monitoring* (ACOG Technical Bulletin No. 132). Washington, DC: American College of Obstetricians and Gynecologists, 1989.
10. American College of Obstetricians and Gynecologists. *The Intrauterine Device* (ACOG Technical Bulletin No. 104). Washington, DC: American College of Obstetricians and Gynecologists, 1987.
11. American College of Obstetricians and Gynecologists. *Fetal and Neonatal Neurologic Injury* (ACOG Technical Bulletin No. 163). Washington, DC: American College of Obstetricians and Gynecologists, 1992.
12. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Relationship between perinatal factors and neurologic outcome. In Poland RL, Freeman RK, eds., *Guidelines for Perinatal Care*, 3rd edn. Elk Grove Village, IL: AAP, 1992: 221–4.
13. Nelson KB. Is it HIE? And why that matters. *Acta Paediatr* 2007; **96**: 1113–14.
14. *California BAJI* (Book of Approved Jury Instructions). 6.11 (revised), Duty of Disclosure.
15. *Ibid.*, 6.28, Duty of Patient.

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