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Foreword

William F. Rayburn, MD
Consulting Editor

This issue of the *Obstetrics and Gynecology Clinics of North America*, guest edited by Henry Galan, MD, pertains to emergencies that can occur in obstetrics and gynecology. An obstetrician-gynecologist may be confronted with a sudden emergency at any time, either at the hospital or in the outpatient setting. Prompt corrective action is necessary, whether it is severe postpartum hemorrhage, acute chest or abdominal pain, or an anaphylactic reaction to an injection in the office. Preparing for an emergency requires planning, provision of resources, awareness of early warning signs, and specialized trainees who are aware of what to do in an emergency.

Certain emergencies, such as a massive pulmonary embolus or a complete abruptio placentae, can be sudden and potentially catastrophic. Standardized responses will increase the efficiency and quality of care. A protocol should provide a full evaluation of the problem and clearly communicate the patient care issue. Periodic drills may lead to a more standard response with a favorable outcome.

Planning for potential emergency events such as anaphylactic shock or cardiopulmonary resuscitation can be complex. At a minimum, it should involve an assessment of suspected risks related to the underlying condition. All physicians should be familiar with the "crash cart." By placing necessary items in one place, time is not lost in gathering supplies. A small kit can be created for handling allergic reactions. As with a crash cart, this kit must be maintained regularly to ensure that supplies are current.

It becomes clear with any emergency when to call for help. Activation of a response team before a full arrest may lead to improved survival and less

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need for an intensive care admission. Rapid correction of problems is better met with a small emergency team whose members talk with each other and share information. Although a leader must coordinate the response, all members of the team should be empowered to practice together. By practicing together, barriers hindering communication and teamwork can be overcome.

Adult learning theory, as described in this issue by its distinguished panel of contributors, supports the value of experiential learning. Training can entail a sophisticated simulated environment or a customary work space with a mock event. Emergency drills allow physicians and others to practice principles of effective communication in a crisis. Our desire is that this issue will attract the attention of providers caring for those women at risk for emergencies. Practical information provided herein will hopefully aid in the development and implementation of more-specific and individualized treatment plans.

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Preface

Henry L. Galan, MD
Guest Editor

Every medical or surgical specialty has emergencies that are somewhat specific to that specialty. This is also true in obstetrics and gynecology. However, several characteristics set the specialty of Ob/Gyn apart from all others. Not only can nearly all of the emergencies seen in other specialties be seen in the field of Ob/Gyn, but pregnancy also brings a new and unique dimension to emergency situations in our specialty. Three primary characteristics of Ob/Gyn set it apart from other fields of medicine when it comes to emergencies: (1) it is the only specialty committed completely to women; (2) it is the only specialty in which a single emergent event can threaten the lives of two individuals, the mother and her fetus; and (3) an otherwise completely healthy patient may succumb purely to a pregnancy-related complication. It is these three general themes that drive the topics in this issue of the *Obstetrics & Gynecology Clinics of North America*.

The authors contributing to this issue were invited to cover topics that are of particular interest to them and in which they are considered leaders. They have utilized the best available evidence and their own experience to provide the reader with knowledge of and guidance through these emergency conditions. Considerable focus is given to the physiological changes in pregnancies that impact emergency conditions.

Several of the articles in this issue are related to hemorrhage, which, because of the 600 cc/min uterine blood flow at term, can be massive. Gyamfi and Berkowitz launch this issue by guiding us through the challenges of

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caring for the Jehovah's Witness patient who refuses the medically indicated blood transfusion. Fuller and Bucklin provide the basics of blood product transfusion and its application to the hemorrhaging patient. Teal and Mukul review first-trimester bleeding, which itself can be massive and without the benefit of having reached the full maternal expansion of blood volume seen later in pregnancy. Monga and Kilpatrick address the physiologic and physical changes of the abdomen and contents within related to pregnancy, which are dramatic and impact the differential diagnosis, diagnostic procedures, and thresholds for surgical exploration. Oyelese, Scorza, Mastrolia, and Smulian provide guidelines for the management of postpartum hemorrhage, including the newer B-Lynch and Bakri balloon procedures, followed by the expert descriptions by Banovac, Lin, Shah, White, Pelage, and Spies of interventional radiologic approaches to hemorrhage.

Of all the obstetric-related emergencies, few match the profound maternal cardiovascular collapse and disseminated intravascular coagulation of amntiotic fluid embolism, which is discussed in depth by Sheffield and Stafford. Gottlieb and I review risk factors and management of shoulder dystocia, which most often rears itself in without warning and carries risk for long-term fetal sequelae and medical-legal action. Muench and Canterino thoroughly review catastrophic and noncatastrophic trauma in pregnancy with emphasis on evaluation of the trauma patient and how physiologic changes impact the evaluation. Gardner and Atta conclude the emergencies articles with a review of cardiopulmonary resuscitation with a focus on the effect of physiologic changes in pregnancy and which may be an end result of any of the above-mentioned emergencies.

While not always presenting as acutely or urgently as some of the aforementioned emergencies, several medical conditions and social circumstances predispose pregnant patients to serious and life-threatening events. Guinn, Abel, and Tomlinson provide information on sepsis, the leading cause of death in the critically ill patient. Conway and Parker review the most serious condition in the diabetic patient, diabetic ketoacidosis. Pregnancy is a known thrombogenic state with great potential for adverse events; Lockwood and Rosenberg guide the reader through thromboembolic disease. Gunter draws our attention sharply to the prevalence, dangers, and the need for heightened awareness of domestic partner violence and provides us everyday tools with which to address this problem in our office practice. This issue concludes with an article by Shwayder reviewing the medical-legal implications of obstetric emergencies and strategies for prevention of legal action in the setting of an adverse event.

I would like to add a personal note of gratitude to all the gifted individuals contributing to this issue of the *Obstetrics & Gynecology Clinics of North America* and to Carla Holloway of Elsevier for her patience and professionalism. Most of all, on behalf of my fellow authors, I would like to thank our patients, students, nurses, and house staff, from whom we learn so much about our beautiful specialty. This gift allows us to push the

frontiers of knowledge and provide the best care possible for the next mom and unborn baby that we encounter.

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Management of Pregnancy in a Jehovah's Witness

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The refusal of blood products by Jehovah's Witnesses makes this group a unique obstetric population with the potential for disastrous perinatal outcomes secondary to hemorrhage. Obstetric hemorrhage is the second leading cause of maternal mortality in the United States after pulmonary embolism [1]. Singla and colleagues [2] reported on maternal mortality amongst Jehovah's Witnesses who refuse all blood products. When this group develops an obstetric hemorrhage, they have a 44-fold increased risk of death.

The care of these patients must be meticulously coordinated to achieve good pregnancy outcomes. This involves coordination of care with the patient's primary care provider, maternal–fetal medicine specialist, anesthesiologist, and possibly other subspecialists to reduce perinatal morbidity and mortality.

To provide comprehensive care to patients who are Jehovah's Witnesses, the care provider should understand the background of their belief system. Charles Russell founded the group in 1872 in Pennsylvania [3]. Many of the followers' beliefs are based on literal translations of the Bible. Genesis 9 and Leviticus 17 state that one cannot eat the blood of life; these passages are interpreted to include the exchange of blood products [4]. For the Jehovah's Witness, receiving blood products may lead to excommunication and eternal damnation [3], and an individual who offers to transfuse blood is considered by many members of the sect to be acting through the devil's influence. Understanding these facts is crucial when caring for patients who are Jehovah's Witnesses.

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Addressing the risk of hemorrhage

As the editors of Williams Obstetrics have reemphasized over many editions, ''Obstetrics is 'bloody business'!'' [5]. The incidence of postpartum hemorrhage is difficult to quantify because of varying definitions. However, it has been estimated to occur in 4% of vaginal deliveries and 6% to 8% of cesarean deliveries [5]. The need for blood transfusion is fairly common. Klapholz [6] reported a 2% transfusion rate for women who delivered at Beth Israel Hospital in 1986. Rouse and colleagues [7] reviewed over 23,000 primary cesarean deliveries and found that the rate of transfusion in that population was 3.2%. Among patients with a previous cesarean delivery, Landon and colleagues [8] found that transfusion was more likely with a trial of labor than with an elective repeat cesarean, 1.7% versus 1.0%, respectively (odds ratio: 1.71; 95% CI, 1.41–2.08, $P < .001$).

Because the risk of requiring blood transfusion is not negligible, the potential for transfusion should be discussed with all obstetrical patients during their prenatal care. The policy at Columbia University Medical Center is to ask all new obstetrical patients whether they will accept a blood transfusion in an emergency situation. Without specifically asking about religion, this serves to open the dialog about transfusion and can identify patients who hold fast to the beliefs of the Jehovah's Witnesses.

The authors have previously shown that there are varying degrees of adherence to the doctrine of blood refusal amongst Jehovah's Witnesses [9]. In a study of pregnant Jehovah's Witnesses, almost 50% indicated, when a review of health care proxies was undertaken, that they would accept some form of blood or blood products [9]. This means that, rather than assuming that a Jehovah's Witness will not accept any blood products, the clinician must inquire as to the specific beliefs of the individual patient. Strong familial and church pressures can influence a patient's decision in the presence of others. This is why it is important for the clinician to be alone with the patient when discussing her wishes. At the very minimum, the patient should be asked about whether she will be willing to accept any or all of the following: whole blood, fresh frozen plasma, cryoprecipitate, albumin, isolated factor preparations, nonblood plasma expanders, hemodilution, and cell-saver. At the authors' institution, this inquiry is presented in the form of a checklist, which is then signed by the patient and included in the patient's chart. Additionally, a statewide health care proxy is signed.

Prenatal care

For a variety of reasons, identification of a patient who will not accept blood, and the discussion about which products, if any, she is willing to accept, should be undertaken at the first prenatal visit. First, most obstetric patients are young and healthy and may not consider themselves to be at risk to hemorrhage. It is important to explain to the patient what puts her

in this category. A discussion of the health care proxy and blood product checklist requires extensive education because the average person is not familiar with the terms "nonblood plasma expanders" or "cell-saver." In most cases the patient will want to discuss this with her family and/or church leaders, so there will be a delay in signing the checklist. An early discussion allows the patient a chance to make an informed decision. Second, identification and treatment of an existing anemia are very important in the care of these patients. Because the treatment of anemia is a slow process, aggressive early management may obviate the need for transfusion later. Finally, a physician has to be both willing and able to allow a properly educated patient to die once she has indicated that she prefers death over transfusion. It is always difficult for a physician, who has been trained to save lives, to accept a patient's decision that can lead to her death. If a physician does not want to participate in the care of such a patient, she should be transferred to the practice of a physician associated with a tertiary care center, and consultation should be obtained with a maternal–fetal medicine specialist. The transferring physician is obligated to ensure that another physician has agreed to accept the patient. This may be difficult to arrange in an emergency situation, so early transfer of the patient's care is extremely prudent.

Evaluation and treatment of anemia

When a Jehovah's Witness presents for her first prenatal visit, a complete blood count with platelets should be included in the routine prenatal laboratory tests, and the patient should be started on iron and folic acid supplementation. The goal should be to maintain her hematocrit above 40% [10]. Once that level has been achieved, a patient can sustain a 2-L peripartum blood loss, and is unlikely to require transfusion. If the initial hematocrit is below this level, a workup for potential causes of anemia should be initiated. If iron deficiency is documented, the dose of iron supplementation can be adjusted accordingly, and a stool softener should be prescribed. Iron is best absorbed through the gastrointestinal tract in an acidic medium, so vitamin C, or simply orange juice, should be taken along with the iron pills. Foods high in heme content, such as meat, poultry, and fish, should be encouraged [4]. Vegetarian diets are low in heme, and tannins found in tea and phylates in bran can decrease the absorption of iron [11]; so it is important to supplement this subgroup.

Many patients complain of constipation while taking iron supplementation. This can lead to noncompliance. An easy way to assess whether a patient is taking her iron supplements is to ask her about the color of her stool, which should be markedly darker if iron is being consumed. One strategy to encourage compliance is to prescribe a stool softener in addition to iron. In women who cannot or will not take oral iron, parenteral iron is a reasonable alternative. Intravenous iron has traditionally been discouraged because

iron dextran can lead to anaphylactoid reactions. Iron sucrose, however, is considered a safer alternative, with hypersentivity reactions estimated at 0.005% compared with 0.2% to 3% for iron dextran [12]. A test dose is not required before administration of iron sucrose, but it should not be considered the first-line agent for treatment of anemia because adverse drug events other than hypersensitivity are common [12].

Erythropoietin may also be administered to an obstetrical patient with a hematocrit of less than 40% who has not responded to iron supplementation [10]. Erythropoietin stimulates the bone marrow to maximize red blood cell production. Recombinant erythropoietin is available either in the form of epoetin alfa or darbepoetin alfa. Both of these drugs are erythropoesis-stimulating agents (ESAs) that increase hemoglobin in a similar fashion. Darbepoetin is more expensive, but can be dosed less frequently than epoetin alfa [13]. ESAs should be stopped once the hemoglobin is greater than 12 g/dL because adverse cardiovascular events can occur above that level [14]. Not all Jehovah's Witnesses accept these medications because each is packaged with 2.5 mL of albumin per dose. To help the patient make an informed decision, a discussion should ensue about how the medication works and how it is constituted.

Review blood products and their alternatives

Another key element in the initial prenatal visit is a comprehensive discussion about what blood products the patient may be willing to accept and the available alternatives. As mentioned earlier, this conversation should occur in the absence of outside influences that may alter the woman's responses. This is the appropriate time to review the checklist of blood and blood products, described earlier, to see which of these, if any, is acceptable.

Next, a discussion of autologous blood donation should ensue [4]. Autologous blood donation involves optimizing the patient's hematocrit with oral iron supplementation (or erythropoietin, if this is acceptable) [4] and then having her donate her own blood at least 72 hours (but ideally, 2 weeks) before elective cesarean delivery or the estimated date of confinement. After appropriate testing, the blood is stored and held for the patient. It will be discarded if not used at the time of delivery [15]. This process is somewhat tedious, but if the patient is willing to accept her own blood, it could be lifesaving [15].

In addition to allogenic blood or blood products, other options should also be discussed with the patient. Cell salvage systems can be employed as a form of intraoperative autologous blood donation [4,16]. Cell-saver systems allow for free blood in the abdomen to be aspirated, filtered, and then reinfused into the patient perioperatively [16]. Such systems use centrifugal cell separators that segregate the red cells from the plasma, wash the red cells with normal saline, and prepare them for reinfusion. Clotting is prevented by using a double-lumen tube with one lumen providing suction

and the other providing a constant flow of anticoagulant [16]. Using a cell-saver system during a cesarean delivery carries the potential risk that fetal cells, amniotic fluid, and debris may enter the maternal circulation if they are not properly filtered by the system, theoretically predisposing the patient to amniotic fluid embolism (AFE) [17]. However, researchers have shown that the filtration system used by these devices can limit the amount of particulate matter in the blood to be reinfused to a concentration equal to that of maternal venous blood [18–20].

Although the use of cell salvage systems has been shown to be safe and potentially life-saving, they are unfortunately still underused in obstetrics because of the theoretical risk of AFE [18,21,22]. The obstetric literature contains hundreds of cases where a cell-saver system was used safely [22], and an American College of Obstetrics and Gynecology (ACOG) technical bulletin advocates the use of these systems during cesarean delivery associated with major hemorrhage such as that which occurs with placenta accreta [21]. An extensive MEDLINE search from 1966 to the present using the key words "cell salvage," "cell saver," "obstetrics," and "amniotic fluid embolism" in various combinations revealed only one case report containing a possible association with cell salvage and maternal death [23]. The patient was a Jehovah's Witness with hemolysis–elevated-liver-enzymes–low-platelets (HELLP) syndrome. Preoperatively, she was anemic and thrombocytopenic with a hemoglobin of 7.1 g/dL and a platelet count of 48,000/mL. Intraoperatively, she developed clinical signs of disseminated intravascular coagulopathy (DIC). The estimated blood loss was 600 mL, and she received 200 mL of salvaged blood. She died 10 minutes later from a cardiac arrest, and an autopsy never confirmed AFE. It is likely that the combination of severe anemia and DIC was the cause of that death, but this cannot be verified.

Techniques employed by anesthesiologists

To complete the overview of alternatives to blood and blood products, an anesthesia consult should be obtained to discuss some additional techniques available to combat massive blood loss. Ideally, there should be a core group of obstetric anesthesiologists involved in the patient's care who are familiar with the relevant therapeutic options and well versed in the implementation of intraoperative alternatives to blood administration in women experiencing massive intraoperative bleeding. All the anesthesiologists involved should be comfortable with the management plans because the patient's refusal to accept blood may result in her death on the operating table. If a member of that group does not feel that he or she can withhold a transfusion, a covering physician should be immediately available to take over if needed. This arrangement prevents confusion and conflict in the case of an emergency situation.

Intraoperative techniques to combat massive hemorrhage include normovolemic hemodilution, controlled hypotensive anesthesia, sedation, and muscle paralysis. Normovolemic hemodilution involves removing whole blood in the immediate preoperative period and replacing it with crystalloid or colloid [4]. This causes a decrease in the viscosity of the patient's circulating blood and increases tissue perfusion. Because the circulating blood contains a reduced number of red cells, there is a shift of the oxygen dissociation curve to the right, which optimizes the oxygen-carrying capacity of those cells [16]. Once the perioperative blood loss has been curbed, the patient's whole blood can be replaced. This technique has been used safely in some pregnant patients [18]. Controlled hypotensive anesthesia involves reducing the mean arterial pressure to 50 mm Hg [4]. This is the minimum requirement for tissue perfusion, and reduces the amount of blood loss by lowering the arterial pressure in the setting of substantial intraoperative hemorrhage. Sedation and muscular paralysis have also been used both peri- and postoperatively to decrease oxygen consumption [4].

If the pregnant Jehovah's Witness is scheduled for a cesarean delivery with the potential for more than average blood loss (eg, in the case of a previous myomectomy or a known placenta accreta) consultation with interventional radiology for preoperative pelvic placement of balloon catheters is an option to be considered.

Blood substitutes

An ideal substitute for blood would be a compound that could both act as a volume-expander and have a high oxygen-carrying capacity. Such compounds exist, but are in limited use in the United States because of several shortcomings. Perfluorocarbons are under investigation for the delivery of oxygen to tissues [24]. These compounds have a 10- to 20-fold increase in oxygen-carrying capacity when compared with water, but they are very unstable at room temperature, and there is limited information on their use in pregnancy [25]. Stroma-free hemoglobin is another potential blood substitute. However, it has been shown to cause hypertension and renal damage, and there are no reports of its use in pregnancy [26].

Recombinant activated factor VIIa has been used to treat obstetric hemorrhage. This clotting factor is indicated for patients with demonstrated factor VII deficiency, and its use in obstetrics remains controversial. Factor VIIa promotes hemostasis by ultimately leading to the formation of fibrin through an increase in thrombin formation [27]. Although there are case reports of successful use in the treatment of obstetric hemorrhage [27,28], recombinant activated factor VIIa has been associated with the development of thromboembolic events [29]. Considering the hypercoagulable state of pregnancy, one should only use this drug as a last resort.

Once the various therapeutic options have been discussed, the patient should also be made aware that, in the case of a significant postpartum hemorrhage, a hysterectomy might be necessary. This should be performed much earlier than would be the case in women who accept blood transfusions. The potential need for hysterectomy is part of a routine consent once any patient is admitted to a labor floor, but in the case of a Jehovah's Witness, there should be a much lower threshold for definitive surgical management if hemorrhage ensues [10]. At the authors' institution, obstetric patients who refuse blood transfusion are not candidates for elective procedures, such as tubal ligation, and they are informed of this during the antepartum period. Additionally, women who refuse to accept blood or blood products are not considered to be candidates for attempted vaginal birth after cesarean because of the increased risk for blood transfusion in this group of patients [8].

End of life decisions

Once a Jehovah's Witness has declared what forms of management are acceptable to her, the next step involves making end-of-life decisions and assigning next of kin to her children [10]. This serves not only to convey to the patient the importance and potential consequences of blood refusal, but also to prevent a court order reversal of such refusal. It is important that the patient understands that the refusal to accept blood or blood products substantially increases her risk of both morbidity and mortality if major hemorrhage occurs. She should feel comfortable that with appropriate early prenatal care her condition can be optimized before the intrapartum period; but she must also know that even with the best "alternatives" to blood transfusion, she still could bleed to death.

The remainder of the patient's prenatal care involves reassessment of her hematocrit at least once a trimester with treatment of anemia as indicated. As stated, the goal is to maintain a hematocrit above 40% so that even a relatively large amount of peripartum blood loss will be better tolerated. Appropriate consultation should be completed in the antepartum period, with an initial maternal–fetal medicine consult obtained before 28 weeks. The blood products checklist and health care proxy should be signed and placed in the patient's chart.

Summary

In the successful management of a pregnant Jehovah's Witness, many issues must be addressed beyond those normally required for routine prenatal care. The clinician who undertakes such care should be well versed in the potential complications related to blood refusal, the antepartum management of anemia, and the intrapartum management of obstetric hemorrhage. Furthermore, these patients should be delivered in a tertiary care center because this increases their options for obtaining alternative management

of hemorrhage. A woman who is well informed about her options can then decide exactly what she wants done in the event of a life-threatening obstetrical hemorrhage.

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Intimate Partner Violence

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Intimate partner violence (IPV) is a pattern of psychological, economic, and sexual coercion of one partner in a relationship by the other that is punctuated by physical assaults or credible threats of bodily harm [1,2]. It is a universal health crisis affecting women of every economic, social, cultural, and racial background. The World Health Organization (WHO) Multi-Country Study of Women's Health and Domestic Violence Against Women indicates that the lifetime prevalence of IPV varies significantly by country and region, ranging from 13% to 71% [3]. Estimates of the prevalence in the United States vary significantly because of underreporting and differences in methods of collection with the lifetime prevalence ranging from 23% to 60%, with an annual prevalence of up to 17% and an estimated 5.3 million IPV incidents per year [4–10]. IPV is the most common cause of nonfatal injury for women with 21% of the female population reporting ever receiving some type of injury and 9% reporting a severe injury [6,11]. IPV is truly an obstetrics gynecology emergency as 50% of murdered women are killed by a current or previous partner. Murder is among the five most common causes of death for women ages 15 to 34 and is the leading cause of maternal mortality [12,13].

The scope of the problem

The definition of IPV, also known as domestic violence, encompasses both physical and sexual violence in addition to psychological abuse, economic coercion, stalking, and threats of violence both sexual and nonsexual. There are many misperceptions concerning personality or socioeconomic status of women who are victimized; every woman who has ever been partnered in a heterosexual or same-sex relationship is at risk [7].

IPV is characterized by what has become known as the cycle of violence that starts with tension-building or arguing that escalates into battering,

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followed by a ''honeymoon phase,'' which is characterized by excuses, gifts, and/or denial (Fig. 1). Many ask: ''Why don't women just leave?'' The reasons are complex and involve both intangibles and barriers to leaving, such as shame, guilt, love, self-esteem, hopelessness, depression, economic dependency, lack of support systems, social isolation, fear, and negative experiences with medical professionals and the legal system. In addition, changing behavior is a dynamic process. A continuum of predictable stages has been identified as individuals attempt to change behavior (Fig. 2) [14–17]. These stages account for such responses as denial, acknowledgment of the problem, planning for action, enacting the plan, and maintenance. Returning to a previous stage is a frequent occurrence and many women leave a harmful relationship as many as eight times before securing a permanent break [14,17].

The lifetime prevalence of IPV in the United States ranges from 25% to 60% with an annual prevalence of 4% to 17% [4–8,18–21]. IPV is the most common cause of nonfatal injury for women. In a given year, approximately 1.5 million women in the United States are victimized. On a global scale, millions of women are assaulted every day [3–5,11,19,21]. The two most common forms of abuse are emotional (84%) and psychological (68%). However, 43% to 60% of women report physical violence. The most common violent act is a slap [3,18,19].

IPV has subclassifications based on risk of injury and potential lethality [1,3,11,19]. Severe IPV involves being hit with a fist, kicked, dragged, choked, threatened, burned, or injured with a weapon with a lifetime prevalence among ever-partnered women ranging from 4% to 49% [1,3,11]. In the United States, at least 21% of women report an injury as the result of IPV and up to 46% of women seen in the emergency room for violence-related injuries are injured by a current or former partner [19,22,23]. Underreporting of these injuries is common because many women do not seek care and screening for IPV is suboptimal, even in emergency room settings, so

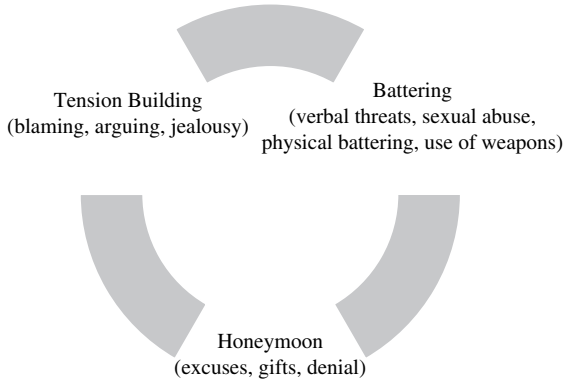

Fig. 1. IPV cycle of violence.

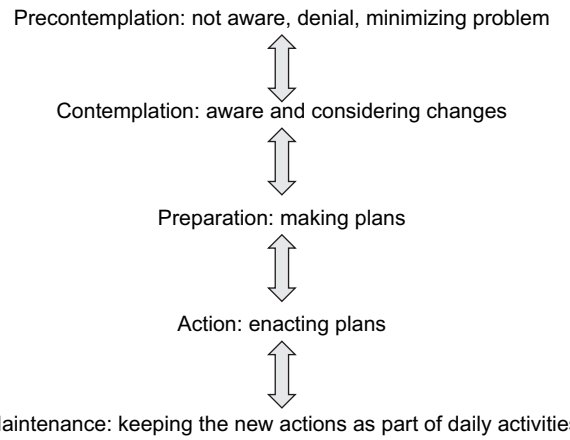

Fig. 2. Stages of change. Returning to a previous stage is expected, is not a failure, and may happen several times as people learn more about their problems and how best to approach them. (*Data from* Refs. [14–17].)

many assaults are unrecognized [21–23]. The lifetime prevalence of sexual abuse by a current or previous partner ranges from 10% to 50%. Among ever-abused women, 40% to 80% report a sexual assault, which may have been the result of direct physical force or of fear of implied violence [3,24]. Femicide, the murder of a woman, is a leading cause of death for women and 40% to 50% of these murders are perpetrated by a current or previous intimate partner [12,18,25,26].

At-risk populations

While any woman who has ever been partnered is at risk for IPV, some populations are at increased risk, including pregnant women, adolescents, and the disadvantaged. Women who are at increased risk often have additional barriers to leaving, such as a greater degree of financial and emotional dependency and greater social isolation [14,27].

Up to 45% of pregnant women report a history of IPV and the prevalence of IPV during pregnancy ranges from 6% to 22% [3,28–35]. It is important for clinicians to include women seeking pregnancy termination in this high-risk population because 22% of women seeking pregnancy termination report a history of abuse in the preceding 12 months and 24% to 35% report a history of substantial conflict and fights with the man involved with the current pregnancy [32–34]. Of all the assault-related injuries reported for women of reproductive age, 10% occurred during pregnancy and women who are assaulted during pregnancy are three times more likely to be hospitalized as compared with women who are assaulted and not pregnant [36]. Women who are pregnant are three times more likely to be a victim

of an attempted or successful femicide as compared with abused nonpregnant controls [37]. Trauma is the leading cause of maternal death and femicide is the most common cause of injury-related death, most often perpetrated by an intimate partner [37–43].

The increased incidence of IPV-related abuse, assaults, and femicide during pregnancy is most likely multifactorial. Pregnancy is associated with increased personal, medical, and financial stress. Pregnancy is also a period when attention is focused on the pregnant woman, which means the partner, and potential batterer, gets less attention. Furthermore, pregnancy may also mark a change in the relationship. Unplanned pregnancy may be a marker for sexual assault as a significant percentage of women who are victimized by IPV are raped by their partners. Meanwhile, many other women become pregnant out of fear of implied violence, they fail to ask their male partner to use a prophylactic, or are afraid or unable to see a health care provider for a prescription contraceptive [3].

Adolescents

The incidence of IPV is highest among younger women, particularly between the ages of 15 and 19 [3,44–47]. Dating violence is a significant problem in this population with more than 90% of teens reporting verbal abuse, 25% reporting physical abuse, and 14% victimized by sexual abuse [14, 44–47]. Femicide, most often perpetuated by an intimate partner, is the number-one cause of death for African American women ages 15 to 24 and the second most common cause of death for white women ages 15 to 24 [12,18,47]. In addition to injuries, the consequences of IPV for adolescent women include anxiety, anger control issues, suicide ideation, substance abuse, unsafe sex, and unhealthy weight control behaviors [48–51]. Young maternal age is an independent risk factor for IPV during pregnancy and, among adolescents who are pregnant, IPV is associated with a more-than-threefold increased risk of repeat pregnancy within 12 months [52].

Disadvantaged populations

IPV affects women of every race and ethnicity, regardless of socioeconomic status. However, some women have additional vulnerabilities and greater barriers to leaving based on social, economic, or physical factors. In the United States, victimization rates are highest for African American women, women who live in urban areas, and those with lower household incomes [53]. In urban areas, the exposure to violence in general is greater and it has been hypothesized that this may cause desensitization, leading to acceptance or rationalization of IPV by both victim and perpetrator [14,49,54,55]. Poverty, higher in inner-city regions and among minority women, increases financial dependency on an abusive partner and creates additional barriers to leaving, such as difficulties in finding new housing and obtaining resources for civil litigation. Minority women report a higher prevalence of negative experiences,

including racism, with institutional resources and law enforcement. These negative experiences further inhibit IPV reporting because these women assume they will not get the type of assistance they need or they fear that their partner may be victimized by racism [14,55–58].

The prevalence of IPV varies among cultures. However it is more prevalent in some societies and in some cultures many women report that the violence is justified [3]. Acceptance of battering is higher among women from provincial and rural settings and among those who have previously experienced abuse, suggesting that some women may learn to adapt to their violent situations and, either because of societal pressure or because of acceptance of their situation, do not recognize themselves as victims [3]. This is an important consideration for immigrant women who may have different understandings of what constitutes IPV as it is "normalized" in some cultures. Communication barriers, social isolation, lower awareness of IPV-related services, and lack of direct questioning by clinicians add further barriers for immigrant women [14,58–61]. Women with no family in the United States are three times more likely to be physically injured by their partner as compared with women with family in the country. Immigration laws further increase the risk of victimization; IPV is higher among women who report that their partners refuse to change their immigrant status, among those who are threatened by their spouse with deportation, and for women on spousal visas who are unable to work [60,61].

Aboriginal women–that is, women descended from indigenous peoples of North America, report a higher prevalence of IPV and in some communities it is estimated that 60% to 90% of women are battered and up to 57% sexually abused [14,62–65]. Aboriginal women are more likely to be victims of severe IPV with more than 40% reporting injuries and are eight times more likely to be a victim of femicide as compared with non-aboriginal women [63–66]. Like women in other minority populations, aboriginal women experience double discrimination—as a woman and as a minority [14]. In addition, for many minority women, regardless of race, ethnicity, country of origin, culture, or aboriginal status, culturally appropriate services for victims of IPV often do not exist.

Women with disabilities are more vulnerable to abuse and face more barriers in attempting to escape abuse. Challenges encountered by women with disabilities include an inability to physically defend themselves, a high dependency on partners for physical needs, difficulties in reporting abuse because of communication barriers, an inability without assistance to physically leave a dwelling and go to a shelter, and a high economic dependency on their partner. The prevalence of IPV is likely significantly underestimated in this population. However, it is believed to be at least 40% higher than in the general population with the risk of severe IPV and sexual assault also significantly higher [14,67–69].

Women who are economically disadvantaged are at increased risk of violence independent of other risk factors, such as race, aboriginal status,

pregnancy, age, and immigrant status [7,49,54,63,70–72]. The associations between income and IPV are complex, and are most likely different for each woman. However, economically disadvantaged women, compared to women with average financial means, have more difficulty hurdling financial barriers to health care, are less likely to have access to health care, and therefore are less likely to be screened for IPV.

Consequences of IPV

The consequences of IPV are far-reaching and range from injuries to the perpetuation of gender inequality [3,14,73]. The immediate medical sequelae of IPV include trauma, sexually transmitted diseases, unplanned pregnancy, and death. Abused women, compared to other women, have a higher incidence of headaches, back pain, vaginal bleeding, vaginal infections, pelvic pain, dyspareunia, urinary tract infections, eating disorders, abdominal pain, gastrointestinal disorders, depression, suicide, substance abuse, anxiety, and chronic somatiform disorder [39,73–78]. Medical consequences that may not be immediately appreciated include the psychological harm of shame or guilt, stress-related illness, and post-traumatic stress disorder. Other issues of concern include noncompliance with medical recommendations and lack of treatment or exacerbation of medical conditions because of insufficient access to health care either due to shame, fear of discovery, or restriction of access to health care by an abuser to maintain control [14,72].

It is estimated that IPV costs $5.8 billion annually in the United States, with $4.1 billion for direct medical care and mental health services; a study conducted in a closed-model health maintenance organization indicates that IPV increases the cost per member per year by $1700 [9,79]. Costs increased most among women who reported physical abuse. However, elevated costs are also associated with sexual and emotional abuse, and cost of care increased both for women currently experiencing abuse and for those who reported a history of IPV [79].

The maternal sequelae of IPV during pregnancy include maternal morbidity from injuries, exacerbation of medical conditions due to restricted access, depression, and mortality because pregnant women are more likely to die as victims of femicide than from any obstetric cause [13,14,39–43,80]. Women who are victimized by IPV during pregnancy have an increased risk of spontaneous abortion and an increase in perinatal complications, such as low birth weight, preterm labor and delivery, preterm rupture of membranes, insufficient weight gain, and urinary tract infections [14,29,31,80–84]. One quarter to one half of women who are physically abused during pregnancy report that they were kicked or punched in the abdomen. These women had increased rates of placental abruption and antepartum hemorrhage [3,14,29,37,80–84]. In addition, violence during pregnancy results in delayed entry into prenatal care [14,29,80–84].

The medical sequelae of IPV also extend to children; in homes with IPV, child abuse occurs in up to 70% of families. Thirty-nine percent of victimized women report that their children witnessed the attack and during 61% of these attacks the mother was injured [85–87]. Children who witness violence not only are at risk of injury, but are also more likely to have behavioral problems, problems in school, and such problems as substance abuse, anxiety, aggression, enuresis, depression, and suicidality [74,85–89]. In addition, batterers often use child custody as a forum to continue the abuse with harassing and retaliatory legal actions [86,90].

Women victimized by IPV experience significant economic hardship. They may miss work because of injuries, fear, stalking, court appearances, custody hearings, and litigation and they may incur more expenses with new housing and legal bills from divorce and child custody petitions. Women who leave violent situations are four times more likely to report housing instability, such as late rent or mortgage payments and frequent moves, because of the inability to obtain affordable housing or lack of own housing [91]. Housing ramifications can be severe as 50% to 60% of homeless women report a history of IPV [92,93].

Diagnosing IPV

Whom to screen?

With a lifetime prevalence of 25% to 60% and a 21% lifetime risk of injury, women who are currently victims of IPV and those who have previously been abused are likely to be encountered regularly in both acute-care and office-based settings [4–8,18–23]. Accordingly, the American College of Obstetrics and Gynecology (ACOG) recommends routine screening at annual exams, family planning visits, and preconception visits [29,94,95]. Routine screening for IPV is also endorsed by the Society of Obstetricians and Gynecologists of Canada, the American Medical Association, the American Academy of Family Physicians, and numerous other national medical associations and government agencies [10,14,96,97]. The Joint Commission, formerly the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), initiated standards for IPV screening in 2004 (JCHAO standard PC.3.10 on victims of abuse).

Factors that increase a woman's risk for IPV include young age, previous episodes of IPV, and disability. This means that some patients may require more frequent screening. Enhanced surveillance is specifically recommended during pregnancy because of the increased risk of IPV and its association with both maternal and fetal morbidity and mortality [14,29,40,94,98]. Screening in pregnancy should occur at the first prenatal visit, at least once a trimester, and at the postpartum visit [14,29,94,99,100]. In addition, there are "red flags" that should raise suspicion of IPV and prompt screening. These "red flags" include injuries that are inconsistent with the history,

frequent missed appointments, repeated visits with vague complaints, and chronic pain [14,29,95,98].

The US Preventative Services Task Force and the Canadian Task Force on Preventative Health Care do not recommend routine screening for IPV because of "limited evidence as to whether interventions reduce harm to women," because few studies have addressed the negative sequelae of screening, and because few interventions have proven successful [101–103]. However, support for screening, both routine and when symptoms suggest possible abuse, is high among women who have been victimized by IPV [104,105]. In addition, many variables affect how a patient responds to screening for IPV. Such variables include the stages of change, fear of reprisal, self-esteem, previous experiences with the medical and legal systems, skill of the provider, and format used to screen [14,98,104–107]. The evidence for the efficacy of specific interventions for IPV are unclear and the most appropriate outcome measures have not been identified. Such measurements could track access to advocacy services, frequency of abusive episodes, or injury rates. Such measurements would vary depending on stages of change and many other unique factors for each woman [14,104–108]. Many women identify the act of screening itself as helpful and possibly useful in helping a woman move forward in the stages of change [3,14,104–107]. Barriers to leaving are multifactorial and unique for each woman. Health care professionals do not necessarily have the ability to provide the desired health outcome because freedom from violence for many women involves complex financial, social, and legal issues. Furthermore, leaving a violent partner does in guarantee freedom from further violence as many women are stalked, abused, assaulted, and even murdered by former partners [4,5,12,109]. Many significant health problems have ineffective interventions. One such problem is smoking, which is the most common preventable cause of death in the United States with only a 14% to 20% long-term quit rate. Yet the US Preventative Services Task Force recommends that clinicians screen all adults for tobacco use and provide tobacco cessation interventions [102,110].

How to screen?

Screening involves not only asking the right questions, but also documenting findings and providing information to victims about safety, options, and interventions. A useful pneumonic developed by the Massachusetts Medical Society is RADAR with each letter representing one of its five directives: R—Routinely inquire about violence; A—Ask direct questions; D—Document findings; A—Assess safety; and R—Review options and referrals. To ensure both safety and accuracy A woman must not be in the vicinity of a partner or family member when screened, and questions should be posed in a nonjudgmental manner. A sound universal policy is to make sure every patient has time alone with his or her health care

professional. Also, it is best to routinely use a medical interpreter and not a family member if there are language barriers. As staff and patients alike become familiar with these routines, patients will be less likely to be anxious about being singled out for questioning and a perpetrator who presents with his or her partner will be less likely to become suspicious.

A variety of questionnaires, both oral and written, have been designed. How a patient is screened significantly affects response rates, with a 12-month prevalence of IPV ranging from 1% to 19%, depending on the method used [4–8,10,19,21]. The most common ones cited include the Partner Violence Screen (PVS), the Women Abuse Screening Tool (WAST), the SAFE tool, a two-question emergency department tool, and the Conflicts Tactics Scale (CTS), which is considered the gold standard (Box 1) [10,14,111–114]. All of these questions are closed-ended with yes–no or short responses; only the WAST asks about violence in an indirect manner and then progresses to direct abuse-related questions. In addition, there is a verbal, less structured patient-centered approach that involves picking up on verbal and nonverbal cues, such as a patient comment about stress, a chronic pain complaint, or another issue. Then questions can be framed using the patient's own description: ''You have described a lot of stress. How is that handled at home?'' The response may lead to further questions and responses that uncover serious problems [114]. Single questions about being afraid produce lower results, with only 8% of victims correctly identified; only 50% of women who survive an attempted homicide by partner perceived their risk and women who are precontemplative may not perceive risk at all [113,115].

When compared with the gold standard CTS the three-question PVS has a 71% sensitivity and an 85% specificity. The PVS and WAST have similar sensitivities. However, the written WAST may yield a lower prevalence [10,111]. Studies are conflicting as to the optimal method of screening with some suggesting that patients prefer a written questionnaire and others supporting the less structured, individually tailored, patient-centered approach, which appears to be preferred, although non-direct screening may have a lower sensitivity [3,10,104–107,114,116,117]. Women report that they want their physician to be sympathetic and caring, so it is possible that health care professionals who do not have the same training as IPV researchers may ask direct questions with a different tone and manner or they respond differently to positive screens, thus reducing satisfaction with this approach [104,105,116].

Barriers to screening

Voluntary screening by verbal questions and subsequent documentation in the medical record are often considered ''usual care.'' However, this method results in the lowest screening rates with only 8% to 45% of women in the emergency room and 10% to 42% in office-based settings screened

Box 1. IPV screening tools

Partner Violence Screen
1. Have you been hit, kicked, punched, or otherwise hurt by someone within the past year? If so, by whom?
2. Do you feel safe in your current relationship?
3. Is there a partner from a previous relationship who is making you feel unsafe?

Antenatal Psychological Assessment
1. Within the past year, or since you have become pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone?
2. Are you in a relationship with a person who threatens or physically hurts you?
3. Has anyone forced you to have sexual activities that made you feel uncomfortable?

SAFE tool
S for spouse: How would you describe your spousal relationship?
A for arguments: What happens when you and your partner argue?
F for fights: Do fights result in you getting hit, shoved, or hurt?
E for emergency: Do you have an emergency plan?

Emergency department screening tool
1. Have you ever been hit, slapped, kicked, or otherwise physically hurt by your partner?
2. Have you ever been forced to have sexual activities?

The Woman Abuse Screening Tool
1. In general, how would you describe your relationship? A lot of tension? Some tension? No tension?
2. Do you and your partner work out arguments with great difficulty? With some difficulty? With no difficulty?
3. Do arguments ever result in you feeling down or bad about yourself? Often? Sometimes? Never?
4. Do arguments ever result in hitting, kicking, or pushing? Often? Sometimes? Never?
5. Do you ever feel frightened by what your partner says or does? Often? Sometimes? Never?
6. Has your partner ever abused you physically? Often? Sometimes? Never?
7. Has your partner ever abused you emotionally? Often? Sometimes? Never?

according to ACOG guidelines, with more than 50% of providers not screening at all for IPV and one third screening only if a patient presents with a bruise or laceration; younger women, who are at greatest risk for IPV and subsequent injury, are screened the least [10,21,112,118–122]. The low screening rates for IPV imply that significant barriers for health care professionals impede routine screening. Attitudes toward IPV, training in residency, and comfort with screening vary significantly and screening for IPV by health care professionals is related to their preparedness, both educational and experiential [119–121,123,124]. Studies using oral screening for IPV use a trained professional (physician, nurse, or research assistant) who has background in the area, is trained to screen, and is surveying many patients and thus is well prepared both by education and experience. Additional barriers for health care professionals include brevity of visits, lack of access to services, misconceptions about typical victims, frustration because the victim may not leave dangerous situation, and lack of understanding of mandatory reporting laws [119–124].

Women who have been or who currently are victims of IPV have significantly more frequent contacts with the health care system as compared with woman who have never been abused. This means that barriers to screening for IPV translate into many missed opportunities for detection and intervention [125,126]. In a study of identified female IPV victims, 64% presented at least once to an emergency department in the year of the index assault (with the median number of visits four), but only 23% were correctly identified as victims of IPV [125]. Among women murdered by a current or previous intimate partner, 40% sought medical care in the emergency room within the preceding 12 to 24 months. Thus, there are many potential opportunities to offer intervention for many of the women who are at the greatest risk [127,128].

There are also patient barriers to identification, including denial, past failures with medical and legal systems, shame, cultural and language barriers, fear of reprisal, low self-esteem, and desire to protect the perpetrator [3,14,15,17,98,104–107]. Many women do not recognize that they are victims of abuse or they underestimate their risk; violence becomes normalized through exposure and psychological abuse leaves many women with shame and self-doubt [14–17,27,98,113–116]. If a woman does not recognize her situation as abusive, it is important to raise the issue but to not push too far to prevent alienation [14,104–107,114]. Posters in bathrooms and printed material in waiting rooms can also help raise awareness among women who are precontemplative.

How to respond

If a patient responds yes to screening for IPV the following four steps should occur: (1) show support, (2) perform a risk assessment, (3) document injuries, and (4) discuss solutions [10,14,29,74,95–99]. Statements of support

might vary if the patient is screening positive for current abuse versus past or lifetime abuse. For patients currently in violent relationships, statements may include:

"I believe what you are saying."
"No one deserves to be treated that way."
"I am so sorry. I would like to help."
"It must be hard to be treated that way."
"It's not your fault." [14,74,98]

For patients who are no longer in a violent situation, examples of useful statements include:

"That must have been a difficult time."
"Some women have health consequences from such stress."
"Do you have any ongoing concerns regarding a previous relationship?" [14,74,98]

The next step is to perform a risk assessment. A variety of factors have been identified that are associated with increased risk of injury and lethality (Box 2) [4,11,14,25,40,74,109,115,128–131]. Factors associated with an increased risk of femicide include the perpetrator's access to a gun, previous

Box 2. Risk factors for injury and lethality

Demographic factors
- Age 15–24
- Minority population
- Pregnant
- Women with disabilities

Assault factors
- Perpetrators threats of suicide or homicide
- Gun in house
- Choking
- Stalking
- Previous or current injury with a weapon
- Sexual assault
- Abuse of family pets
- Increase in severity or frequency of violence
- Fear for personal safety or life
- Violence outside the house

Relationship factors
- Recent separation
- Separation for a new partner
- Perpetrator stepchild living in the house

threat with a weapon, abuse during pregnancy, stalking, choking, forced sex, perpetrator's stepchild living in the home, estrangement from a controlling partner, victim having left the relationship for another partner, and perpetrator threats of suicide [4,11,14,25,40,74,109,115,128–131]. Abuse does not always escalate in a predictable pattern and many women are severely injured or murdered without any known risk factors. However, if a patient screens positive, there is a significant increased risk of injury and death [14,25,74,98,115,128,130,132]. Women often underestimate the risk of their situation, a factor probably compounded by many factors, including stages of change, fear, and lack of alternatives to leaving; almost 50% of women who are severely injured or murdered by their partner did not appreciate that they were at risk [25,37,115,129,130]. If any risk factors are present for injury or lethality, be clear that the patient may be in imminent danger, be clear about the need to leave, and document the conversation and recommendations in the medical record.

Patients should be asked if they have any injuries as a result of IPV. If so, such injuries should be documented because this is important for legal follow-up. Injuries should be photographed. If a camera is not available, draw the injuries. Common injury patterns include defensive wounds; central injuries; multiple injuries; bruises in various stages of healing; and injuries to head, neck, and mouth. During pregnancy, the abdomen is more likely to be involved [14,29,31,74,99]. Document size of lesions, color, bruising, and who the patient identified as the perpetrator; it is important to be as specific as possible and to use quotations, such as "John Smith hit me on March 3rd in the afternoon." [2,14,74,98]. This is an important legal point as the medical record is not hearsay, and a well-documented chart can be very helpful with orders of protection, prosecution, and child custody. Unfortunately, documentation of risk and safety assessment is often neglected; in one study, only 4% of identified victims had any IPV documentation in the medical record and less than 2% had documentation of risk assessment [132]. Documentation is also essential for those working in a hospital setting because screening for IPV is a Joint Commission measure and failure to screen or to document risk assessment and recommendations has resulted in exposure to medical malpractice claims [132,133].

Many health care providers are uncomfortable dealing with IPV; they may be unfamiliar with best screening practices, uncomfortable responding to those who screen positive, and unaware of available and appropriate interventions. To raise the comfort level of medical staff and improve screening rates, educational programs are available that incorporate specific training and tools for response [14,98,118–121,123,124]. When a woman screens positive for IPV, the provider, after acknowledging the positive response, should asked directly how he or she can help. It is important to frame provider responses and interventions in consideration of the stages of change and not to alienate patients who are precontemplative. However, discussing IPV can provide important validation for many victims and may

help them move forward to a contemplative phase. Posters and flyers in bathrooms with the number for the National Domestic Violence Hotline (1-800-799-SAFE) can also raise awareness and provide information for women about interventions [3,14,16,17,98,104–107,116,134–136]. Women who screen positive for IPV benefit from safety strategies and information on local resources, legal steps, and advocacy [16,98,104–107,135,136]. A personal safety plan, both for work and home, should be developed; some considerations are money, medications, extra keys, and copies of important documents with a trusted friend or in a safe deposit box, and a code word for friends and coworkers to trigger help [14,98]. Contact numbers for local advocacy services and other resources should be provided and, if available, the services of a social worker should be offered. Many victims of IPV indicate that legal information would also be helpful and so reporting of IPV to the police and orders of protection should also be discussed [98,135,136].

Mandatory reporting

Many states have injury reporting requirements for assault-related injuries and for injuries resulting from firearms, knives, or other weapons. California, Colorado, Kentucky, New Hampshire, and Rhode Island each have specific mandatory reporting laws for IPV [137,138]. In Rhode Island, reporting is for data collection purposes only with no identifying information passed along. In New Hampshire, a patient can object to the release of the information to the police unless there was a gunshot wound or serious bodily injury [137]. In California, Colorado, and Kentucky, IPV must be reported regardless of patient objections. However, in all states health care providers should encourage women to report the violence to law enforcement.

While support for universal IPV screening is very high among women with and without a history of abuse, concerns have been raised that mandatory reporting affects patient autonomy and confidentiality, may deter victims from disclosing IPV or seeking medical care, and may possibly increase the risk of retaliation [104,135,136,139,140]. In one state with mandatory reporting, 12% of women attending an inner-city emergency department indicated that, with mandatory reporting, they would be less likely to seek care for an IPV-related injury while 27% said they would be more likely to seek care [141]. Studies show that survivors of IPV have very high support for universal screening and physician reporting with patient approval, but have mixed support for mandatory reporting with 44% to 68% of women with a history of abuse opposing mandatory reporting that does not allow for consideration of patients wishes [139,140]. In states with mandatory reporting, if a patient objects, it is important to ask why, to try to address any concerns, and to relay the patient's objections and reasons to the authorities. In many states, the witnessing of IPV by a child is considered child abuse and as such requires mandatory reporting. Because definitions of witnessing

domestic violence vary significantly by state and may change, it is important to know the local statute information [142]. State-specific reporting requirements are available from the US Department of Health and Human Services Administration for Children and Families (www.childwelfare.gov/systemwide/laws_policies/search/index.cfm).

Do interventions work?

A woman increases her likelihood of accessing an intervention and improving her health by talking with a health care provider about abuse [143]. Interventions that have proven to be effective in reducing subsequent abuse include a stay by the woman for at least one night in a shelter with advocacy, the issuance of permanent restraining orders, and the arrest of the perpetrator [108]. Therapies targeting the batterer, such as cognitive behavioral therapy, mandatory counseling, and rigorous monitoring, have not proven effective. Therefore, the main focus of the intervention should be helping the patient recognize the abuse and providing assistance to leaving [144,145]. Executing interventions is out of the hands of the medical provider and access to advocacy, shelters, and response from the legal system varies by community. In addition, the current legal system relies more on batter intervention than on victim support to prevent future violence. While women can obtain orders of protection, such orders do not prevent batterers from purchasing guns. There are also many complicating factors, such as denial, social isolation, language barriers, finances, children, pets, housing, employment, self-esteem, and fear. So, in many studies, screening does not translate into change. However, most victims of IPV report a high degree of satisfaction with screening because it acknowledges the problem [3,104,105,107,140]. Interventions frequently fail because the problem of IPV is complex and the solution involves much more than just walking out the door.

Summary

IPV has a lifetime prevalence of approximately 60% and is a leading cause of morbidity and mortality for women of all reproductive ages, especially among younger women and during pregnancy. Providers should recognize that every woman who has ever been partnered is at risk for IPV and should screen appropriately, with increased surveillance during pregnancy and the postpartum period. Despite these recommendations, most providers do not screen according to ACOG guidelines. However, educational efforts improve provider confidence in screening. When a woman screens positive for IPV, it's important to consider the stages of change; to frame the response appropriately; to perform a risk assessment; to discuss interventions, including a safety plan; and to document in the medical record accordingly.

Those providers in states with mandatory screening must also report positive screens as indicated. Screening has yet to translate into reduced rates of abuse, indicating that IPV is not simply a medical problem, but involves complex psychological, financial, familial, cultural, and legal issues. Regardless, victims of IPV appreciate screening by medical professionals and indicate that simply asking the questions is helpful and supportive. Society's approach to IPV can be also be framed by the stages-of-change model; only recently has society moved past the precontemplative phase as IPV is now recognized as a major health problem for women. However, society is still trying to understand how best to approach the problem and offer the most effective interventions.

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Approach to the Acute Abdomen in Pregnancy

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Assessment of the pregnant woman with abdominal pain should be undertaken in an expedient and thorough manner. An acute abdomen may be the result of one of many gastrointestinal, gynecologic, urologic, or obstetric causes. These situations often require surgical intervention, and delay in diagnosis and intervention only worsens the outcome for the mother and her fetus.

Physiologic changes in pregnancy

Certain anatomic and physiologic changes specific to pregnancy may make the cause of the pain difficult to ascertain. As the gravid uterus enlarges, it becomes an abdominal organ at around 12 weeks' gestation and compresses the underlying abdominal viscera. This enlargement may make it difficult to localize the pain and may also mask or delay peritoneal signs [1]. The laxity of the anterior abdominal wall may also delay peritoneal signs. Alterations in gastrointestinal function are thought to be mediated by elevated levels of sex steroids. Progesterone decreases lower esophageal sphincter pressure and small bowel motility [2]. A decrease in progesterone has also been linked to a subjective increase in appetite [3]. Colonic emptying slows in pregnancy but the cause is not quite as clear. A decrease in lower esophageal sphincter pressure leads to heartburn, gastroesophageal reflux, and even stricture formation. Delayed gastric emptying can lead to increased gastric residual volume, and possibly to nausea and vomiting,

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reflux, and pulmonary aspiration with general anesthesia. The slow colonic transit time may lead to constipation and, subsequently, pain [4].

Pregnancy also affects the urologic system. The ureters become dilated as early as the first trimester and remain dilated into the postpartum period [5]. There are two plausible explanations for this. According to the first explanation, an increase in progesterone relaxes the smooth muscle of the ureter, slowing peristalsis, and thus leading to dilatation. According to the second explanation, the pregnant uterus may also compress the ureters, leading to dilatation; this effect is more pronounced on the right because the overlying colon protects the left ureter. This distension may lead to urinary stasis, increasing not only the risk of urolithiasis but also infection.

Other physiologic changes may affect clinical presentation of abdominal pain in pregnancy. Increased progesterone increases respiratory drive; total minute ventilation increases because of a larger tidal volume while respiratory rate is unchanged [6]. Chest films frequently show an increased cardiothoracic ratio largely due to the gravid uterus displacement of the diaphragm. This results in an overall decrease in functional residual capacity. These changes result in an increase in Po_2 and a decrease in Pco_2, resulting in a mild respiratory alkalosis. In the third trimester of pregnancy, normal Pco_2 is 27 to 32 mm Hg, and normal pH is greater than 7.4 [7].

Cardiac output in the pregnant state increases by 17% at high altitudes to as much as 40% at sea level [8]. The increase, which begins early in pregnancy and peaks in the second trimester, is mostly directed to the uterus [9]. This is accompanied by a decrease in systemic vascular resistance, which leads to an increase in the resting pulse of about 10 to 15 beats per minute above baseline. Pregnancy is also associated with a 25% increase in red cell volume and 40% increase in plasma volume [10], which peaks around 28 to 32 weeks. These changes lead to the so-called ''physiologic anemia of pregnancy.'' It is not uncommon to see a hemoglobin less than 11.0 with a normal mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC), although the increased demand for iron during pregnancy may manifest as an iron-deficiency anemia, with a low MCV and MCHC. Given the increase in total blood volume, if intraperitoneal hemorrhage is suspected, clinical signs of hypotension and tachycardia indicate massive intravascular losses of at least 25% of total blood volume.

Beyond 20 weeks' gestation, the compressive effects of the uterus on the inferior vena cava can lead to a decrease in venous return, subsequent decrease in preload, and ultimately to a decrease in cardiac output. The decrease in cardiac output can be as much as 25% to 30% [9]. This decrease is more often seen when the patient is in a supine position and may manifest as complaints of dizziness and syncope. Fortunately, this is easily corrected by lateral displacement of the gravid uterus.

Hemostatic changes also add to the challenge of evaluating and caring for pregnant women. Pregnancy produces a thrombogenic state, with two- to

threefold increases in fibrinogen levels. Other clotting factors, VII, VIII, IX, X, and XII, can increase by as much as 20% to 1000%, peaking at term [11]. Levels of von Willibrand factor increase by as much as 400% at term [12]. Prothrombin and factor V levels remain unchanged while levels of factors X and XIII decline, along with a decrease in protein S activity and subsequent increase in resistance to activated protein C [11]. Pregnancy is therefore associated with an increased tendency for thrombosis. Use of thrombo-embolism deterrent (TED) hose and sequential compression devices should be considered in all pregnant women undergoing nonobstetric surgery during pregnancy.

Infection may be more difficult to assess during pregnancy, as white blood cell counts increase to a normal range of 10,000 to 14,000 cells/mm^3 [13]. In labor, white blood cell counts may be as high as 20,000 to 30,000 cells/mm^3 [14]. By 1 week postpartum, the white blood cell count should return to normal.

Diagnostic procedures

"Don't penalize her for being pregnant!" Never is this phrase truer than when evaluating a pregnant woman who may require surgical intervention. Radiologists often approach the pregnant patient with trepidation, but radiologists are not alone. Among obstetricians, the use of radiologic procedures is viewed with undo fear. In a study by Ratnapalan [15], obstetricians' perception of potential fetal harm by CT scan and conventional radiograph was unrealistically high. Usually it is unnecessary delay in diagnosis that leads to untoward outcomes. Ultrasound and MRI are not associated with ionizing radiation, have not been shown to have any deleterious effects on pregnancy, and should be used when feasible. While ionizing radiation exposure can lead to cell death, carcinogenesis, and genetic effects or mutations in germ cells [16], no single diagnostic radiograph procedure results in radiation exposure to a degree that would threaten the well-being of the developing preembryo, embryo, or fetus, according to the American College of Radiology [17]. Exposure to less than 5 rad has not been associated with an increase in fetal anomalies or pregnancy loss [18,19].

Information gleaned from atomic bomb survivors shows the greatest risk to the fetus is exposure at 8 to 15 weeks' gestation [16], with radiation-induced mental retardation the highest specific potential danger. Risk increases linearly as exposure rises above 20 rad. Most of the procedures ordered in evaluation of the pregnant woman have much lower doses than 5 rad. When possible, always shield the abdomen during diagnostic procedures and counsel patients on the baseline risks of known adverse events, such as miscarriage, genetic disease, congenital anomalies, and growth restriction. Listed in Table 1 are common diagnostic radiologic procedures and the dose of ionizing radiation to the fetus [16].

Table 1
Estimated fetal exposure from some common radiologic procedures

Procedure	Fetal exposure
Chest radiograph (two views)	0.02–0.07 mrad
Abdominal film (single view)	100 mrad
Intravenous pyelography	>1 rad[a]
Hip film (single view)	200 mrad
Mammography	7–20 mrad
Barium enema or small bowel series	2–4 rad
CT scan of head or chest	<1 rad
CT scan of abdomen and lumbar spine	3.5 rad
CT pelvimetry	250 mrad

[a] Exposure depends on the number of films.

Data from American College of Obstetricians and Gynecologists. Guidelines for diagnostic imaging during pregnancy. ACOG Committee opinion No. 299. Obset Gynecol 2004;104:649.

Anesthesia during pregnancy

Elective, nonobstetric surgery should be avoided if possible during pregnancy. Surgery safely delayed from the first to the second trimester avoids the period of organogenesis and highest pregnancy loss [20]. When possible, regional analgesia is favored over general anesthesia as the maternal mortality is 16 times higher with general [21]. The effect of anesthesia on the fetus remains unclear without good evidence to suggest a clear relationship between outcome and type of anesthesia [22]. There is little evidence that any drug used during general anesthesia is a proven teratogen in humans, and this should be relayed to the patient to alleviate any anxiety she may have before surgery [23]. There is an increased chance of pulmonary aspiration and all pregnant women should be treated as though they have a full stomach. Premedication with citrate and histamine-2 receptor blockers is warranted.

The rate of preterm labor after nonobstetric surgery during pregnancy tends to increase with increasing gestational age and depends on the type and duration of the procedure. In a review of over 720,000 births during a 9-year period in Sweden, nonobstetric surgery complicated 0.75% of pregnancies [24]. The incidence of preterm delivery increased by 46% in those complicated by surgery compared with those not complicated by surgery. While some advocate prophylactic tocolytic therapy, others argue that there is no benefit [25,26] and no consensus exists; each case should be individualized. Tocolysis is not recommended in the presence of maternal infection.

Intraoperative fetal monitoring has also been suggested by some, but there are no comparative studies to suggest that this improves fetal outcome. According to the American College of Obstetricians and Gynecologists, this decision should be individualized and made by the surgeon and obstetrician

who is consulted [27]. The authors do not routinely recommend intraoperative fetal monitoring. Logically, fetal heart rate monitoring is an indirect reflection of uteroplacental blood flow, so careful attention to avoid hypotension during the surgery, with the goal of maintaining systolic blood pressure within 20% of baseline and a left or right uterine displacement of the uterus off the vena cava are recommended [28]. At the authors' institution, pre- and postoperative fetal heart rate is documented with careful attention to end tidal carbon dioxide and maternal blood pressure, heart rate, and oxygenation during the procedure.

Laparoscopic surgery

The safety and timing of laparoscopic surgery in pregnancy is another area where better studies are needed. Based on retrospective evaluation and survey data, laparoscopy is comparable to laparotomy in safety during pregnancy [24,29]. Laparoscopy is associated with decreased hospital stay, quicker return of bowel function, less postoperative pain, quicker time to ambulation, and smaller chance of wound infection and hernia [30]. Access to the peritoneal cavity must be based on the size of the uterus. Some investigators suggest the use of Hasson's trochar [31], although others feel comfortable with Veres needle insufflation [32]. A surgeon experienced in laparoscopic surgery is required. In general, when planning the procedure, an open laparoscopic procedure using Hasson's trochar and a more upward placement of the laparoscopic camera to a supraumbilical location appears logical, as there has been a report of Veres needle placement into the amniotic cavity with insufflation at 21 plus weeks with subsequent fetal loss [33]. Otherwise, insufflation and camera placement in the midclavicular line, 1 to 2 cm inferior to the costal margin may be considered. The goal is to avoid the gravid uterus and to limit pneumoperitoneal pressure to no more than 12 to 15 mm Hg in an attempt to decrease the likelihood of fetal acidosis. In studies of pregnant ewes, the carbon dioxide used for insufflation was absorbed across the peritoneum into the maternal blood stream and across the placenta, leading to fetal respiratory acidosis and ultimately hypercapnia [34]. This can be corrected with careful anesthetic attention to maternal ventilation. Some have proposed arterial blood gas determination of the mother over routine capnography [35]. Others suggest that reliance on maternal end tidal carbon dioxide should be sufficient, but that more invasive monitoring may be needed in those with a history of cardiovascular or pulmonary disease [36]. Keeping the intraperitoneal pressure at 12 to 15 mm Hg may preclude adequate visualization, especially in the obese patient or those with adhesive disease from prior surgery, and must be kept in mind when planning surgery. After insufflation is performed, the placement of other trocars depends on the procedure and the size of the gravid uterus. Besides the concern of carbon dioxide absorption, the pneumoperitoneum itself may decrease venous return, cardiac output, and ultimately uteroplacental blood

flow. As gestation progresses, the likelihood increases that the pneumoperitoneum will decrease venous return, cardiac output, and uteroplacental blood flow. The optimal gestational age at which to perform laparoscopic surgery is unclear, but an upper limit of 26 to 28 weeks has been suggested [37]. Recently, in a case series with 18 women undergoing laparoscopy in the third trimester, there was no fetal loss [38].

The most commonly reported indications for nonobstetric surgery in the pregnant patient are appendicitis, cholelithiasis, persistent ovarian cyst, and ovarian torsion [30].

Appendicitis

Appendicitis affects 1 in 1500 pregnancies and is the most common reason for nonobstetrical surgical intervention in pregnancy [39]. The incidence, cause, diagnosis, and management are similar to those affecting the nonpregnant patient, with some notable exceptions. The location of the appendix has traditionally been described as rising in the peritoneal cavity as the uterus enlarges, beginning around 12 weeks, and reaching the iliac crest by 24 weeks [40,41]. More recently this has been challenged in a prospective study comparing the location of the appendix in women undergoing cesarean at term, in pregnant women undergoing appendectomy, and in nonpregnant women undergoing appendectomy, with no difference in appendix location among the three groups [42]. The most common presenting complaint of the patient suspected of having appendicitis is right lower quadrant pain [39]. Anorexia, nausea, and vomiting with initial periumbilical pain are similar in the pregnant and nonpregnant state. Fever may also be present. As discussed earlier, the white blood cell count may increase during pregnancy and leukocytosis does not always indicate appendicitis, but an increased number of bands is more indicative of a pathologic process [1]. Careful physical examination is key to making the diagnosis. Gross peritoneal signs with rebound and guarding are not normal in pregnancy, although laxity of the anterior abdominal wall and an enlarged uterus may delay these signs. A high clinical suspicion is therefore needed when evaluating a pregnant patient for appendicitis. Delay in diagnosis remains the leading cause of morbidity in this disease process. An unruptured appendix is associated with a fetal loss rate of around 3% to 5% with little effect on maternal mortality, in contrast to a fetal loss rate of 20% to 25% and maternal mortality rate of 4% with ruptured appendicitis [43,44]. When history and physical examination are not conclusive, prompt imaging may be helpful; undue delay only increases fetal and maternal morbidity. Some studies support the use of ultrasound by an experienced sonographer in the diagnosis of appendicitis in pregnancy. In a blinded prospective study, Poortman and colleagues [45] found a similar sensitivity and specificity in diagnosing appendicitis in 199 patients with the use of graded compression sonography and unenhanced focused single-detector helical CT. Helical CT has the

advantage over traditional CT of less ionizing radiation to the fetus (reported as 300 mrad), however, only case series describing the use of helical CT in pregnancy have been reported. Sonography is technically more difficult, so the radiologist must be experienced. Given the dynamic nature of the test, the pictures cannot be reliably reevaluated with ultrasound, and a ruptured appendix is not as clearly visualized [45]. When using compression ultrasound, the diagnosis of appendicitis is made when there is a noncompressible, blind-ended tubular structure in the right lower quadrant greater than 6 mm in diameter. The use of ultrasound is limited to less than 35 weeks, as the graded compression technique is not able to visualize the appendix clearly and is less useful later in pregnancy [46]. If ultrasound is not available or not interpretable, CT of the abdomen with oral and intravenous contrast can be used. This is the best studied modality for diagnosing appendicitis, with the radiologist looking for right lower quadrant inflammation, an enlarged nonfilling tubular structure, and/or fecalith. On MRI, the radiologist looks for an enlarged fluid-filled appendix greater than 7 mm in diameter. Recently, retrospective studies have suggested that MRI of the appendix is useful in delineating the presence of appendicitis in pregnant women, but the small number of patients in these studies limits the inference that can be drawn [41,47]. The diagnosis is best made based on clinical suspicion by history and examination and a negative appendix at the time of surgery is justifiable, especially given the morbidity in pregnancy associated with delay in treatment. As discussed earlier, laparoscopy appears to be as safe as laparotomy for the treatment of this disease and has become the standard at some institutions [48]. Another benefit of diagnostic laparoscopy is that it can decrease the number of false-positive appendectomies performed [1].

Gallbladder disease

Biliary sludge and gallstone formation is common, occurring in up to 31% and 2% of pregnancies, respectively. While most patients remain asymptomatic, 28% manifest with pain [49]. It has been suggested that the increase in sex steroids during pregnancy delays gallbladder emptying, precipitating the development of stones. Despite this, the incidence of acute cholecystitis does not increase during pregnancy. Biliary colic presents with episodic postprandial right upper quadrant pain and abdominal ultrasound documents cholelithiasis. Acute cholecystitis presents with right upper quadrant pain, anorexia, nausea, vomiting, and fever. Physical examination usually reveals a tender right upper quadrant, and/or a positive Murphy's sign (pain in the right midclavicular line upon deep inspiration). Differential diagnosis includes appendicitis, hepatitis, pancreatitis, right-sided pneumonia, intraabdominal abscess, and, rarely, acute fatty liver of pregnancy. On laboratory analysis, an elevated white blood cell count with the presence of bandemia, and sometimes elevation of liver enzymes (particularly direct bilirubin) point toward the diagnosis. Abdominal ultrasound may reveal gallstones,

inflammation of the gallbladder, and dilatation of the common bile duct. Management begins with admission to the hospital, intravenous antibiotics, adequate hydration, and instructions to withhold liquids or solids by mouth. Conservative management of acute cholecystitis is championed in pregnancy unless evidence of pancreatitis, ascending cholangitis, or common bile duct obstruction is noted. Endoscopic retrograde cholangiopancreatography (ERCP) can be safely performed in pregnancy with little ionizing radiation exposure to the fetus if the patient has cholangitis or pancreatitis due to a common bile duct stone [50]. If the patient fails to respond to conservative management, has repeated bouts of biliary colic, or has gallstone pancreatitis or cholangitis that is not amenable to ERCP, surgical intervention should be considered. Laparoscopic cholecystectomy during pregnancy is the most common laparoscopic procedure performed in pregnancy, and ideally is performed in the second trimester. There are several reports in the literature of cases performed in the first trimester with few instances of fetal loss [48,51]. In a review of the literature, fetal loss is low, except in cases associated with acute pancreatitis, suggesting the underlying disease process and not the surgery itself increases mortality [30].

Other gastroenterologic conditions

Small bowel obstruction in pregnancy complicates 1 in 3000 pregnancies. The most common causes are adhesions, followed by volvuluses, intussusceptions, and hernias [1]. Presenting symptoms include nausea, vomiting, and abdominal distension. This clinical entity should not be confused with hyperemesis gravidarum, as delay in diagnosis and timely surgery can lead to increased fetal and maternal mortality. Nausea and vomiting, accompanied by peritoneal signs should never be considered normal in pregnancy.

In a report of the literature of 66 cases of bowel obstruction in pregnancy, there were 4 maternal deaths [52]. The fetal mortality rate in this review was 26%. Diagnosis of bowel obstruction is made with serial examinations and abdominal series. Initial management is conservative but with worsening clinical symptoms, surgery should not be delayed. Careful maintenance of fluid, electrolyte, and nutritional balance is essential. A midline vertical incision to expose the peritoneal cavity is suggested and there is no place for laparoscopy.

Pancreatitis in pregnancy complicates 1 in 3000 pregnancies, most commonly secondary to cholelithiasis [53]. The classic presentation includes upper abdominal pain, sometimes with radiation to the back and often relieved by leaning forward, accompanied by nausea, and vomiting. Most cases occur in the third trimester and are mild and self-limiting, but may progress to multisystem disease [54]. Diagnosis is made based on symptoms and elevations of pancreatic amylase and lipase. Imaging in the form of ultrasound to look for evidence of gallstone formation is prudent, and CT scan is rarely needed. Treatment is usually nonoperative and supportive, with bowel

rest, nasogastric suction, pain medicine, and repletion of electrolytes and fluids. In a review of 43 cases, Perdue and colleagues [52] noted that most patients did well with supportive treatment, with symptoms resolving in about 5 days, and without any maternal deaths. Surgical intervention should be strongly considered in all trimesters for gallstone pancreatitis. In a review of 30 patients presenting with acute pancreatitis in pregnancy, 70% of those with gallstone pancreatitis were noted to relapse without surgery [55]. The differential diagnosis is similar to that for acute cholecystitis in pregnancy.

Nephrolithiasis

Symptomatic nephrolithiasis complicating pregnancy is an infrequent occurrence, reported as 1 in 3300 deliveries in one retrospective review [56]. Symptoms include lower abdominal and flank pain, sometimes accompanied by nausea and vomiting. Fever is present if there is associated upper urinary tract infection. There may be a history of dysuria, frequency, and often gross hematuria. Twenty percent will have a history of renal colic. On physical examination, costovertebral angle tenderness may be elicited and urinalysis reveals hematuria in 75% to 95% of cases. It is postulated that the increase in blood volume and subsequent glomerular filtration rate increases excretion of calcium. This and the previously described urinary stasis appear to promote urinary calculi in pregnancy, although some reports indicate no increase in renal colic in pregnancy [57]. Perhaps this is explained by a propensity for stone formation but decreased symptomatology due to ureteric dilatation. Management is conservative with hydration, adequate analgesia, and straining the urine for calculi. Spontaneous passage occurs in 85% of cases [58]. In evaluating for the presence of a calculus, abdominal ultrasound is safe, but may not result in adequate visualization because the ureters are difficult to visualize in pregnancy. The use of the resistance index in some series has helped to increase the sensitivity in abdominal ultrasound, but is limited to the first 48 hours. Before the procedure, anti-inflammatories should be withheld [59]. If the renal arterial resistance index is not diagnostic, and symptoms do not abate, a one-shot intravenous pyelogram can be helpful in confirming the diagnosis. Radiation exposure to the fetus is a tenth that of CT of the renal system [59]. Rarely is further action needed, but if symptoms do not resolve, urologic consultation for ureteral stent placement may be necessary. Rarely should nephrostomy tubes be required. There is minimal effect on fetal or maternal morbidity.

Adnexal masses in pregnancy

While causes of an acute abdomen in pregnancy are frequently gastrointestinal, the ovary can be a source of pathology as well. Unlike gastrointestinal disorders, in which delay of treatment can lead not only to fetal

morbidity and mortality, but also to maternal morbidity and mortality, it is unclear whether the persistent adnexal mass poses such a risk. The incidence of torsion in case reports and series varies from less than 1% to 22% [60]. As the incidence of first-trimester ultrasound increases, so does the diagnosis of adnexal masses, ranging from 0.2% to 2.9% [61]. When followed, adnexal masses at or larger than 5 cm in diameter visualized in the first trimester spontaneously resolve about 70% to 85% of the time, which suggests a functional nature to the cyst [62]. Using pooled data of over 65,000 women screened for adnexal masses and followed, there were only 6 cases of torsion requiring surgical intervention (0.01%) [62]. This information seems to warrant conservative management of adnexal masses incidentally found on ultrasound. Also, surgery for benign adnexal masses in pregnancy is associated with a higher rate of preterm labor than that following expectant management [60].

Ovarian torsion in pregnancy can be confused with other intraperitoneal processes. It most often presents with lower abdominal pain that may be waxing and waning in nature. Symptoms may appear to be out of proportion to physical examination. There may be associated nausea, vomiting and fever. An adnexal mass may be difficult to palpate later in pregnancy because of the gravid uterus. A high index of suspicion is required to make the diagnosis. Frequently a leukocytosis is seen. The differential diagnosis includes ectopic pregnancy, ruptured hemorrhagic cyst, appendicitis, endometriomas, and degenerating fibroid. Ultrasound evaluation with Doppler examination may aide in providing more information by indicating an adnexal mass and sometimes free peritoneal fluid. The presence of Doppler flow does not exclude the diagnosis of torsion [63]. The diagnosis is usually made at the time of surgery by encountering an ovary and fallopian tube with a bluish, blackish appearance. Surgery may be performed laparoscopically or by open laparotomy [64]. Previously there was concern for the risk of ovarian vein thrombus formation at the time of torsion, especially in the pregnant patient, with the risk of subsequent pulmonary embolus. Manually examining the infundibulopelvic ligament at the time of surgery was recommended for the presence of cords. If present, salpingoophorectomy at the time of torsion was recommended to guard against pulmonary embolus. More recently, the use of salpingoophorectomy in such cases has been challenged. In a series of 102 patients with adnexal torsion, of whom 25% were pregnant, detorsion by untwisting the infundibulopelvic ligament was undertaken. Laparoscopy was used in two thirds of the cases, with only 5 requiring reoperation for subsequent torsion, and no documented cases of pulmonary emboli [65].

Uterine fibroids

Uterine fibroids are another cause of abdominal pain that may complicate pregnancy. Fibroids are present in 2.7% to 4% of pregnancies when

discovered on second-trimester ultrasound examination [66,67]. This might be an underestimation. As the number of first-trimester ultrasounds increase, it is likely that the reported incidence of fibroids in pregnancy also increase. It was once theorized that pregnancy, and the influence of increased sex steroids, namely estrogen, cause hypertrophy of uterine fibroids. Serial ultrasound shows that most fibroids remain the same size [68] or shrink [69] during gestation. Pain is theorized to be due to degeneration of the fibroid as it outgrows the blood supply [70] and may require hospitalization in 5% to 15% of women [71]. Patients typically present complaining of lower abdominal pain, and may have nausea, vomiting, and fever, thus mimicking other gastrointestinal disorders. Leukocytosis may be present, and on physical examination there is usually tenderness over the area of the fibroid, and sometimes frank peritoneal signs [72]. Treatment is usually conservative, including short-term (48-hour) administration of indomethacin [73]. Rarely is surgery required or recommended.

Summary

- Numerous physiologic changes in pregnancy may affect the presentation of abdominal pain in pregnancy. A high index of suspicion must be used when evaluating a pregnant patient with abdominal pain.
- General anesthesia is considered safe in pregnancy with little evidence to suggest teratogenic or harmful effects to the fetus. Intraoperative monitoring and tocolytics should be individualized with little evidence to support their usefulness.
- Laparoscopic surgery should be performed in the second trimester when possible and appears as safe as laparotomy, but more studies are needed to delineate the rates of fetal loss and preterm labor.
- If indicated, diagnostic imaging should not be withheld from the pregnant patient.
- Appendectomy and cholecystectomy, in the hands of experienced laparoscopists, appear to be safe in pregnancy.
- The reported incidence of adnexal masses and fibroids in pregnancy may increase with increasing use of first-trimester ultrasound. Conservative management, with surgical management postpartum, appears reasonable in most cases.

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Current Management of Ectopic Pregnancy

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Ectopic pregnancy, which is any pregnancy implanted outside the uterine cavity, remains the leading cause of pregnancy-related first-trimester death among women in the United States. Fertilization of the ovum occurs in the fallopian tube. As the zygote divides, it becomes first a morula and then a blastocyst, normally arriving in the uterine cavity and beginning implantation on day 6 after fertilization. Anything that delays or impedes tubal transport may allow implantation to begin while the blastocyst is still in the tube; approximately 97% of ectopic pregnancies are tubal in location.

Ectopic pregnancies represent approximately 2% of all pregnancies [1,2]. This estimate is conservative, as the analysis did not include patients whose condition was diagnosed and managed exclusively as outpatients. While the incidence of ectopic pregnancy has continued to increase, the case fatality rate has dropped from 69% in 1876 [3], to 0.35% in 1970, and to 0.05% in 1986. The death rate for African American and other minority women remains over double that for white women, and the highest death rate occurs in the 15- to 19-year-old age group [4].

With documented intrauterine pregnancy, the risk of coexisting ectopic (heterotopic pregnancy) is approximated at 1 case in 10,000 patients to 1 case in 30,000 [5,6]. This risk increases to approximately 1 case in 100 patients if the woman is being treated for infertility [7].

Risk factors

Risk factors for ectopic pregnancy are strongly associated with conditions that cause alterations to the normal mechanism of fallopian tubal

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transport. It is postulated that the more damage that occurs to the fallopian tube, the higher the risk for developing an ectopic pregnancy. This damage may result from a number of factors, such as infection, surgery, congenital anomalies, or tumors. Many potential risk factors have been reported in the literature, some with good evidence and others with less convincing data. There is good evidence to support the following as risk factors for developing an ectopic pregnancy: history of previous ectopic pregnancy, previous tubal surgery, tubal ligation, tubal pathology, in utero diethylstilbestrol exposure, and current use of an intrauterine device (IUD) [8].

In a 1996 meta-analysis, Ankum and colleagues [8] reported an odds ratio of 6.6 (95% CI, 5.2–8.4) with a history of a previous ectopic pregnancy. Barnhart and colleagues [9] in 2006 confirmed previous reports that a history of previous ectopic pregnancy was the strongest risk factor associated with ectopic pregnancy. A history of one previous ectopic pregnancy conferred an odds ratio of 2.98 (95% CI, 1.88–4.73) and a history of two ectopic pregnancies increased the risk to 16% overall (odds ratio 16.04; 95% CI, 5.39–47.72). Table 1 presents a comparison of the odds ratios evaluated in these two studies.

Reconstructive tubal surgery has also been shown to be a high risk factor for ectopic pregnancy with an odds ratio of 4.7 [8]. Reconstructive tubal surgery is closely linked to the underlying tubal damage caused by a previous ectopic pregnancy or pelvic inflammatory disease. The complexity of surgical restoration of the damaged tube correlates with subsequent risks of developing an ectopic pregnancy [10]. The underlying risk factors, and not the surgery itself, are the likely major contributing factors in these cases. Patients who have undergone tubal reanastomosis are also at risk for ectopic pregnancy. In one study, 6.6% of patients were diagnosed with an ectopic pregnancy after undergoing tubal reanastomosis. The same study also found that patients who had a history of tubal occlusion by cautery were at higher risk than those who had reversals after noncautery methods [11].

Tubal ligation failures also confer a high risk for ectopic pregnancy. The US Collaborative Review of Sterilization prospectively followed 10,863 women electing tubal sterilization. Thirty-three percent of post-sterilization pregnancies occurring in this population (47 out of 143 pregnancies) were ectopic; all but 1 were tubal. The risk was highest in patients who had a tubal ligation using bipolar cautery, and in women sterilized under the age of 30. The risk of ectopic pregnancy in these patients was 31.9 per 1000 procedures compared with 1.2 per 1000 procedures in patients who had a postpartum salpingectomy [12]. The increased risk with bipolar cautery is most likely associated with fistula formation of the fallopian tube leading to subsequent failure. There are currently no data on the risk of ectopic pregnancy after hysteroscopic sterilization.

The use of both hormonal and nonhormonal contraceptive methods confers protection against ectopic pregnancy [13]. This includes the use of both hormonal and nonhormonal IUDs. However, should a patient get pregnant

Table 1
Risk factors for ectopic pregnancy

Risk factor	Ankum (odds ratio; 95% CI)	Barnhart (odds ratio; 95% CI)
High risk factor		
Previous ectopic pregnancy	6.6; 5.2–8.4	2.9; 1.9–4.7 (if >2 ectopic pregnancies: 16.0; 5.4–47.7)
Previous tubal surgery	4.7; 2.4–9.5	Not reported
History of tubal ligation	9.3; 4.9–18.0	Not reported
In utero DES exposure	5.6; 2.4–13.0	Not reported
Current use of IUD	4.2–45.0	Not reported
Moderate risk factor		
History of PID	2.5; 2.1–3.0	1.5; 1.1–2.1
History of infertility	2.5–21.0	Not reported
Smoking	2.5; 1.8–3.4	Not reported
History of gonorrhea	2.9; 1.9–4.4	See below
History of chlamydia	2.8; 2.0–4.0	See below
Weak or no association		
Outpatient treatment chlamydia/gonorrhea	Not reported	1.22; 0.6–2.6
Sexual partners >1	2.1; 1.4–4.8	Not reported
Coitarche <18y	1.6; 1.1–2.5	Not reported
Past use of IUD	1.6; 1.4–1.8	1.1; 0.6–1.9
History of TAB	1.6; 1.0–1.6	0.99; 0.6–1.6
Nontubal surgery	1.5; 1.1–2.6	0.95; 0.67–1.4
Prior cesarean section	0.56; 0.3–1.1	Not reported

Abbreviations: DES, diethylstilbestrol; PID, pelvic inflammatory disease; TAB, threatened abortion;

Adapted from Ankum WM, Mol BW, Van der Veen F, et al. Risk factors for ectopic pregnancy: a meta-analysis. Fertil Steril 1996;65(6):1093–9; and Barnhart KT, Sammel MD, Gracia CR, et al. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril 2006;86(1):36–43.

while using an IUD, her risk of an ectopic pregnancy rises dramatically, with reported odds ratios of 4.2 to 45 [13,14]. Some studies have reported a potentially small increased risk of ectopic pregnancy in past users of an IUD, but more current, well-controlled research indicates there is no increased risk with previous IUD use [9,13].

Previous genital tract infection is the major cause of tubal damage and infertility. A history of previous cervical infection with *Neisseria gonorrhea* or *Chlamydia trachomatis* and pelvic inflammatory disease has been linked to increased risk for ectopic pregnancy [8,15]. A recent study found that a previous history of pelvic inflammatory disease had an odds ratio of 1.5 (95% CI, 1.11–2.05) for ectopic pregnancy [9]. This study specifically looked at patients treated for *N gonorrhea* or *C trachomatis* in the outpatient setting versus those requiring inpatient treatment for pelvic inflammatory disease. The investigators found that patients who received outpatient treatment

for *N gonorrhea* and/or *C trachomatis* did not have an increased risk for ectopic pregnancy (odds ratio 1.22; 95% CI, 0.6–2.6). These findings suggest that the insult to the normal tubal transport mechanism may be greater when patients present with symptoms or findings that require inpatient management. Hillis and colleagues [15] reported that repeated chlamydia infections increased the risk for ectopic pregnancy. The odds ratio after two infections was 2.1 and rose to 4.5 after three infections.

A history of nontubal pelvic surgery has been inconsistently reported to confer a potential increased risk for ectopic pregnancy [16–18]. Barnhart and colleagues [9] in 2006 found no strong association for nontubal surgery (including cesarean section) and ectopic pregnancy. In addition, there was also no association between a history of voluntary interruption of pregnancy (therapeutic abortion), regardless of number, and ectopic pregnancy. This study did not mention appendectomy as a risk factor, but in another study, a history of an appendectomy was more commonly reported in cases of ectopic pregnancy [19].

Diethylstilbestrol exposure in utero has been shown to confer a ninefold increased risk of ectopic pregnancy [20]. Other potential risk factors include smoking, young age at coitarche, multiple sexual partners, vaginal douching, and infertility [8,21]. Many of these risk factors likely act through a common pathway of tubal damage by infectious or environmental agents.

Location

The most common location for an ectopic pregnancy is in the fallopian tube. Other less common sites include the abdomen, ovary, cervix, and the interstitial portion of the fallopian tube. In one study, over 95% occurred in the fallopian tube in the following locations: ampulla (70%), isthmus (12%), fimbria (11.1%), and interstitium/cornua (2.4%). The remaining sites of ectopic pregnancies were ovarian (3.2%), abdominal (1.3%), and cervical (<1%) [22]. Identifying the location of an ectopic is important for therapy, but may be very challenging. Ultrasound remains the best method to diagnose location. The location of an ectopic pregnancy may alter the approach to treatment and subsequent follow-up. Depending on location, a combination of medical and surgical treatment may need to be employed. This review will focus on the management and treatment of tubal ectopic pregnancy.

Presentation

The classic triad of abdominal pain, amenorrhea, and vaginal bleeding should always alert the clinician to evaluate for an ectopic pregnancy. Unfortunately the diagnosis may be quite challenging because the presentation of an ectopic pregnancy can vary significantly. In one study, the percentage

of patients who presented with ectopic pregnancy with abdominal pain was 98.6%, amenorrhea 74.1%, and irregular vaginal bleeding 56.4%. Abdominal tenderness (97.3%) and adnexal tenderness (98%) were the most common physical findings [23]. Barnhart and colleagues [9] reported an increased odds ratio for ectopic pregnancy in patients presenting with first-trimester symptoms if moderate to severe bleeding (odds ratio 1.42; 95% CI, 1.04–1.93) and pain (odds ratio 1.42; 95% CI, 1.06–1.92) were present.

Although these signs and symptoms are common, the clinical presentation of ectopic pregnancy can vary significantly from the classic presentation. Physical examination findings may also reveal a change in vital signs, such as tachycardia or orthostatic changes; cervical motion tenderness; adnexal/uterine tenderness (from blood irritating the peritoneal surfaces); or a palpable mass. Physical examination findings may also be unremarkable or subtle. Ectopic pregnancy can also mimic other conditions, such as spontaneous abortion, early pregnancy failure, ruptured corpus luteal cyst, and infection. Thus, in the setting of a positive pregnancy test, ectopic pregnancy should always be high on the clinician's differential diagnosis. In clinical scenarios of patients with known high risk factors for ectopic pregnancy, some investigators have advocated early screening for ectopic pregnancy once they have a positive pregnancy test [24].

Diagnosis

Early diagnosis can reduce the mortality and morbidity associated with ectopic pregnancy. Following the history and physical examination, the two most important diagnostic tests in evaluating for an ectopic pregnancy are transvaginal ultrasound (TVUS) and a serum human chorionic gonodatrophin (hCG) level. The sensitivity and specificity of combining these tests has been reported to range from 95% to 100% [25–27].

The first step in the diagnosis of an ectopic pregnancy is to evaluate for an intrauterine pregnancy. Confirmation of an intrauterine pregnancy almost definitively rules out an ectopic pregnancy; the risk of a heterotopic pregnancy is one for every 10,000 to 30,000 spontaneous pregnancies [5,6]. However, in the setting of assisted reproductive technologies the risk can rise to 1% [7].

TVUS can identify intrauterine pregnancy at a gestation of 5.5 menstrual weeks at nearly 100% accuracy [28]. At 4.5 to 5 weeks, the first ultrasound marker of intrauterine pregnancy is a gestational sac with a ''double decidual sign'' (double echogenic rings around the sac) [29]. The yolk sac appears next at 5 to 6 weeks and remains until about 10 weeks. The embryo (fetal pole) and cardiac activity can be first detected at about 5.5 to 6 weeks. A potentially confounding ultrasound finding is a pseudosac. This is described as a collection of fluid within the endometrial cavity that is usually localized centrally within the uterus. This can be potentially mistaken for an intrauterine gestational sac. A pseudosac is the result of endometrial bleeding from decidualized endometrium in the setting of an extrauterine pregnancy

[30]. Unfortunately, identification of a pseudosac is not diagnostic of an ectopic pregnancy, has a high false-positive rate, and thus cannot be relied on to make the diagnosis of an ectopic pregnancy [31].

In the absence of a reliable last menstrual period, the hCG level is instrumental in the evaluation of ectopic pregnancy. The concept of a discriminatory zone should be used to help facilitate ultrasound findings. The discriminatory zone is defined as the level of hCG at which an intrauterine pregnancy should be visualized. With abdominal ultrasound, most radiologists use 6500 mIU/mL, but this has been further refined with the use of TVUS, reducing the discriminatory zone to 1500 to 2500 mIU/mL [30,32]. The exact cutoff to use depends on the success of the institution in diagnosing the discriminatory zone, the quality of the equipment, and the expertise of the sonographer.

When the hCG level has reached the discriminatory zone and an intrauterine pregnancy cannot be diagnosed, an extrauterine pregnancy should be highly suspected. An exception to this would be in cases of multiple gestations. Patients at risk for multiples, such as those using assisted reproductive technologies, can be carefully followed to a higher discriminatory zone [33]. The detection of an abnormally rising or declining hCG has also aided in the diagnosis of an ectopic pregnancy. Kadar and colleagues [34] first reported on the concept of a "doubling" hCG in normal pregnancies every 1.4 to 2.1 days, with a minimum 66% rise in 2 days. More recently the hCG curves have been redefined. The lower limit of a normal rise for a normal pregnancy has been reported to be 53% in 2 days. A rise lower than this is highly suggestive of an abnormal pregnancy [35]. While abnormally rising hCG levels are useful to distinguish an abnormal pregnancy, normally rising hCG levels do not rule out ectopic pregnancy. The same researchers recently reported hCG profiles for women diagnosed with an ectopic pregnancy. They reported that the number of women with ectopic pregnancy who experienced a rise in hCG (60%) was similar to those with a decrease in hCG (40%) and that there was no definitive way to characterize the pattern of hCG for women with an ectopic pregnancy [36].

In situations where there is no definitive ultrasound diagnosis of an intrauterine pregnancy and the hCG level is above the discriminatory zone, uterine evacuation is indicated to differentiate between an early pregnancy failure (miscarriage) and an ectopic pregnancy. In these cases, women have an equal chance of being diagnosed either with a miscarriage or ectopic pregnancy [37]. The same study reported that the presumed diagnosis of ectopic pregnancy was incorrect nearly 40% of the time. The addition of uterine evacuation to the treatment algorithm (Fig. 1) can help minimize the inadvertent administration of methotrexate to patients with early pregnancy failures without a significant difference in complication rates or cost [38]. Uterine evacuation is superior to Pipelle endometrial biopsy in the diagnosis of ectopic pregnancy and should be the method employed [39]. In the absence of chorionic villi, an ectopic pregnancy is likely and medical or surgical treatment is indicated.

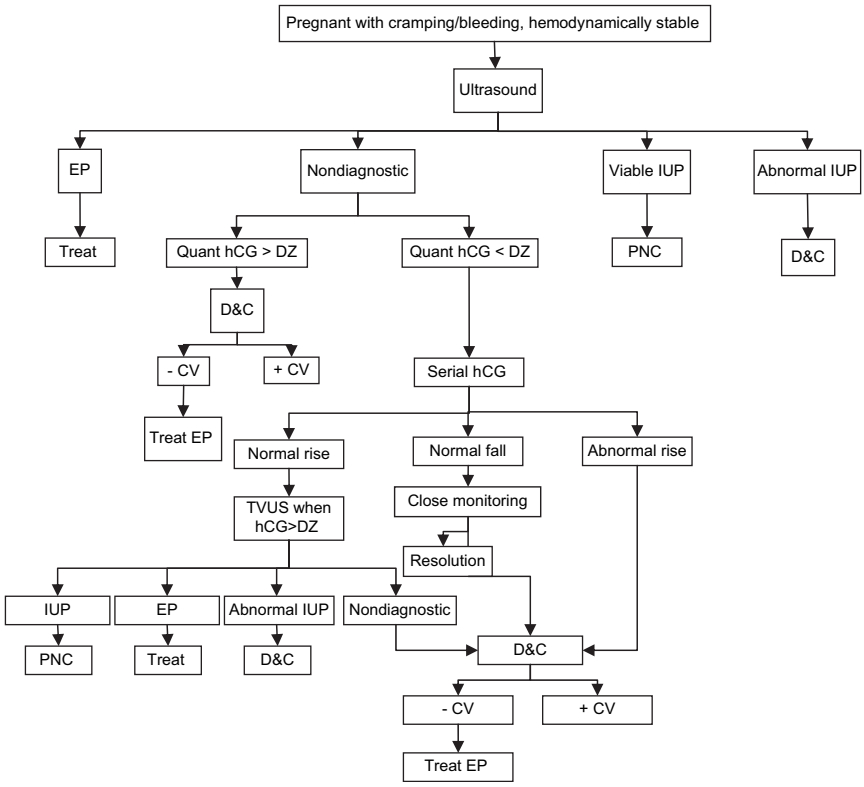

Fig. 1. Evaluation of the symptomatic first-trimester pregnancy. CV, chorionic villi; D&C, dilation and curettage; DZ, discriminatory zone; EP, ectopic pregnancy; IUP, intrauterine pregnancy; PNC, prenatal care.

The usefulness of a single progesterone level to diagnose ectopic pregnancy has been debatable. During the first 8 to 10 weeks, progesterone is produced by the corpus luteum and remains relatively stable. A progesterone level above 25 ng/mL is usually consistent with a normal pregnancy (97% sensitivity), while a progesterone level less than 5 ng/mL has been shown to be 99% specific in confirming an abnormal pregnancy. Unfortunately, the lower limit cannot differentiate between an early pregnancy failure and an ectopic pregnancy [40]. In 1998, a meta-analysis of 26 studies concluded that progesterone alone is not sufficient to diagnose ectopic pregnancy with good reliability [41].

Treatment

After the diagnosis is made, several factors influence the decision to treat an ectopic pregnancy medically or surgically. If the patient is unstable, then immediate surgical treatment via laparotomy or laparoscopy is necessary. In

the past, laparotomy with salpingectomy was considered the gold standard, but with the availability of minimally invasive technology and increasing physician skill, laparoscopy is now the treatment of choice [42]. Laparoscopy is associated with a faster recovery, shorter hospitalization, reduced overall costs, and less pain, bleeding, and adhesion formation. In a hemodynamically stable patient, surgery is still the preferred route for heterotopic pregnancy, tubal rupture, or imminent risk of rupture. Other indications for surgery include no desire for or an inability to comply with medical treatment, contraindication to methotrexate, and failure of medical treatment. Surgery should also be considered for patients with conditions that seem to predispose to failure of medical therapy, such as a tubal pregnancy greater than 5 cm or fetal cardiac activity seen on TVUS [43,44]. These factors are considered in more detail below.

Salpingectomy versus salpingostomy

Once the decision is made to proceed to the operating room, the surgeon must decide on the appropriate surgical technique. Often this decision must be made in the operative suite. Thus, appropriate preoperative counseling is important. Taking into consideration risk factors, patient desire for future fertility, and the condition of the patient also helps guide the intraoperative decision. Salpingectomy is the segmental or entire removal of the fallopian tube. The indications for removing the tube include recurrent ectopic pregnancy in the same tube, a severely damaged tube, uncontrolled bleeding (before or after salpingostomy), heterotopic pregnancy, and lack of desire to bear more children.

Salpingostomy is the method of choice in women of reproductive age who wish to preserve their fertility. Salpingostomy is typically performed by making an incision on the antemesenteric border of the fallopian tube at the point of maximal distension. The use of vasopressin before incision has been reported to reduce bleeding and operative time in some studies, but has also been found to not be significant in others [45,46]. Removing the product of conception by hydrodissection is recommended, along with avoiding excessive handling of the tube and excessive cautery to prevent potential further damage to the fallopian tube. The rate of intrauterine pregnancy is improved in patients having linear salpingostomy versus salpingectomy, although the recurrent ectopic pregnancy rate is also higher [47–49].

Persistent ectopic pregnancy

One of the potential hazards of conservative surgical management of ectopic pregnancy with salpingostomy is persistent ectopic pregnancy. The risk of persistent ectopic pregnancy after salpingostomy is reported to be

2% to 11% with laparotomy and 5% to 20% with laparoscopy [32,50]. The increased rate in patients treated by laparoscopy is thought to be associated with the learning curve of laparoscopy. Because of the potential risk of tubal rupture and hemorrhage, some investigators recommend following weekly hCG serum levels to ensure complete resolution [51]. If the hCG level plateaus, methotrexate is usually indicated as the first option, followed by salpingectomy if medical treatment fails. Some investigators have advocated the use of prophylactic methotrexate after salpingostomy to reduce the risk of persistent ectopic pregnancy [52,53]. Risk factors for salpingostomy failure, such as an ectopic pregnancy less than 2 cm, or rapidly rising preoperative hCG levels, may help guide the decision to administer prophylactic methotrexate after salpingostomy [54]. Small masses, by preventing complete evacuation of the ectopic pregnancy, may potentially place patients at higher risk for persistent ectopic pregnancy.

Medical management

Before the mid-1980s treatment for ectopic pregnancy was exclusively surgical. The first case report of methotrexate for the treatment of ectopic pregnancy appeared in 1982 [55]. Many other agents have been used with varying rates of success. Prostaglandins, dactinomycin, etoposide, hyperosmolar glucose, anti-hCG antibodies, potassium chloride, and mifepristone have all been described in the literature [56].

Methotrexate has been the most successful method of medical management for ectopic pregnancy and is currently the medical treatment of choice. Methotrexate for ectopic pregnancy was proposed after the observation that actively replicating trophoblasts in gestational trophoblastic disease were successfully treated with methotrexate [57]. Methotrexate is a folinic acid antagonist that binds to the catalytic site of dihydrofolate reductase inhibiting the synthesis of purines and pyrimidines, thus interfering with the synthesis of DNA and cell replication [58].

Hemodynamically stable patients are eligible for medical management with methotrexate. The inclusion and exclusion criteria for administration of methotrexate are listed in Boxes 1 and 2 [59]. The initial treatment regimens for ectopic pregnancy consisted of multiple doses of methotrexate with citrovorum rescue. Stovall and colleagues [60] in 1989 demonstrated a success rate of 96% with their multiple-dose regimen. Their protocol consisted of intramuscular methotrexate, 1 mg/kg of actual body weight alternating with citrovorum rescue factor 0.1 mg/kg. Methotrexate was continued only until there was a 15% decline in the level of hCG. These investigators then observed that most of their patients treated with the multidose regimen had declining levels of hCG before receiving the second and/or third dose of methotrexate [61]. This led to the publication of the development of the single-dose regimen without citrovorum rescue [62]. Table 2 describes the

Box 1. Criteria for receiving methotrexate

Absolute indications
- Hemodynamically stable without active bleeding or signs of hemoperitoneum
- Patient desires future fertility
- Nonlaparoscopic diagnosis
- Patient able to return for follow-up care
- General anesthesia poses risk
- Patient has no contraindications to methotrexate

Relative indications
- Unruptured mass ≤3.5 cm at greatest dimension
- No fetal cardiac activity
- β-hCG limit does not exceed a predetermined value (6–15 K)

Adapted from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:99; with permission.

single-dose methotrexate regimen. The single-dose protocol uses 50 mg/m^2 of patient body surface area, administered intramuscularly. Lipscomb [63] later reported the University of Tennessee's experience with their first 315 patients treated with single-dose methotrexate and reported an overall success rate of 91.1%.

Single-dose versus multidose protocol

There is currently no consensus as to which methotrexate protocol should be used [59]. The overall success rate reported in the literature for both protocols is approximately 90% [64]. In a recent randomized trial of 108 patients, the success rate with a single dose was 88.9% compared with 92.6% for multidose patients [65]. This was not considered statistically significant (odds ratio 0.64; 95% CI, 0.17–2.1) and no differences in side effect profiles were reported. In a systematic review, women treated with the single-dose regimen were reported to have a higher failure rate (odds ratio 4.74; 95% CI, 1.77–12.62) [66]. The data obtained for this review were from case series and not randomized controlled studies. In addition, it is difficult to ascertain whether there may have been selection bias between patients receiving single- versus multidose regimens. The review did confirm that success was inversely associated with hCG levels for both protocols. Given the current available data, the single-dose methotrexate protocol appears to have similar efficacy and side effect profile while making the least impact on resources of patients and providers.

Box 2. Contraindications to medical therapy

Absolute
- Breastfeeding
- Immunodeficiency
- Abnormal creatinine (>1.3 mg/dL), aspartate aminotransferase (twice the normal value)
- Alcoholism or liver disease
- Preexisting blood dyscrasias
- Peptic ulcer disease
- Active pulmonary disease
- Known sensitivity to methotrexate

Relative
- Gestational sac >3.5 cm
- Cardiac activity

Adapted from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:99; with permission.

Predictors of success

Various predictors of success with methotrexate have been reported in the literature. Limited and anecdotal evidence has attributed success partially or entirely to such factors as hCG levels, ectopic size, fetal cardiac activity, progesterone levels, and free peritoneal blood in the cul-de-sac. Lipscomb and colleagues [44] reviewed their experience and reported that high hCG and progesterone levels and, the presence of fetal cardiac activity, were associated with higher failure rates. They further concluded that the single best predictor for success with methotrexate was the initial hCG level. In counseling patients who receive a single-dose methotrexate regimen, it is important to consider the available data on failure rates (Table 3). Patients with an hCG below 5000 mIU/mL had the best success with methotrexate.

Table 2
Single-dose methotrexate protocol

Day	Therapy
0	hCG ± dilation and curettage
1	hCG, aspartate aminotransferase, serum urea nitrogen/creatinine, complete blood cell count, Rh, methotrexate (50 mg/m^2)
4	hCG
7	hCG

Data from Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol 1991;77(5):754–7.

Table 3
Success rates by hCG

Serum β-hCG	Success rate
<1000	98% (118/120)
1000–1999	93% (40/43)
2000–4999	92% (90/98)
5000–9999	87% (39/45)
10,000–14,999	82% (18/22)
>15,000	68% (15/22)

Data from Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999;341(26): 1974–8.

Patients with hCG levels between 5000 mIU/mL and 9999 mIU/mL had failure rates of 13%, increasing to 18% with an hCG between 10,000 mIU/mL and less than 14,999 mIU/mL. Above 15,000 mIU/mL, the failure rates rose to 32%. This study also concluded that a large ectopic and the presence of free peritoneal blood were not associated with higher failure rates. There is currently no set defined limit above which methotrexate should not be administered, but based on available data, the higher failure rates with hCG levels above 5000 mIU/mL need to be taken into consideration.

Surveillance

Once the decision is made to proceed with medical management, it is important to counsel patients about potential side effects (Box 3) and the need for close follow-up. The day of methotrexate administration is considered day 1 (see Table 2). Patients receiving the single-dose protocol then need to follow up on day 4 and 7 for additional laboratory draws and reevaluation. The day-4 hCG level can plateau or rise before a decrease begins. It is not uncommon to see a rise in the day-4 hCG level because of the continued production of hCG from syncytiotrophoblasts, despite cessation of hormone in the cytotrophoblast [67]. A study looking at the predictability of day-4 hCG on success of methotrexate found no association with success of treatment or the need for potential surgical intervention [68].

Many patients (33%–60%) also experience abdominal pain (''separation pain'') 3 to 7 days after administration of methotrexate [48,69,70]. Separation pain is thought to be secondary to tubal abortion or an expanding hematoma within the fallopian tube [71]. This is usually self-limited and most patients can be managed conservatively with nonsteroidal anti-inflammatory agents. Patients who report no relief with supportive measures should be immediately evaluated to rule out tubal rupture. The majority of methotrexate-treated ectopic pregnancies can be associated with an increase in size by TVUS, likely representing hematoma formation within the tube. This finding does not reliably predict treatment failure unless other signs of rupture are present [72,73].

Box 3. Side effects associated with methotrexate

Drug related
- Nausea
- Vomiting stomatitis
- Gastric distress
- Dizziness
- Reversible alopecia (rare)
- Severe neutropenia (rare)
- Pneumonitis
- Vaginal bleeding
- Increase in abdominal pain
- Increase in hCG levels from day 1 to day 4

Data from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:97–103.

Signs of treatment failure include significantly worsening abdominal pain (despite change in hCG levels), signs of hemodynamic instability, less than a 15% decline between day-4 and day-7 hCG levels, and increasing or plateauing hCG levels after the first week of treatment [59]. In a study of ruptured ectopic pregnancies, tubal rupture was encountered more frequently in women with no previous history of ectopic pregnancies [74], suggesting that surveillance of patients at presumed lower risk should be just as diligent as for patients with known risk factors. The same study also reported a rupture rate of greater than 11% in patients with hCG levels less than 100 mIU/mL.

If no signs of treatment failure are present by day 7 and there is a decline of 15% between day 4 and day 7, weekly hCG levels are recommended until complete resolution (hCG <15 mIU/mL) is seen [61,63]. If on day 7 the drop in hCG is not greater than 15% from day 4, and if the patient is clinically stable, a second dose of methotrexate with weekly follow-up is suggested. In general, a second dose is needed in 15% to 20% of patients, with less than 1% requiring more than two doses [63,66]. The average time to resolution (hCG <15 mIU/mL) for patients successfully treated with single-dose methotrexate was 33.6 days [63].

Expectant management

Expectant management of ectopic pregnancy has been employed with rates of reported in the range of 48% to 100%. That large gap in rates is in part due to the differences in inclusion criteria [48,75]. In one study, expectant management was most successful (32 of 33) in women with hCG

levels less than 175 mIU/mL [76]. In subjects with hCG greater than 175 mIU/mL, only 41 out of 74 were managed successfully. In a situation of a clinically stable patient with hCG less than 175 mIU/mL, indeterminate TVUS, and declining hCG levels, it may be reasonable to employ expectant management. On the other hand, given the low complication rate of methotrexate, many clinicians opt for medical treatment over expectant management.

Summary

While mortality from ectopic pregnancy has dropped precipitously because of improved diagnostic and management techniques, it remains a significant gynecologic emergency, and delay in diagnosis or treatment can be catastrophic. Diagnosis rests on maintaining a high index of suspicion for women with symptomatic complaints in the first trimester, or women without complaints but with risk factors, such as a prior ectopic pregnancy, an IUD in situ, or pregnancy following assisted reproductive technology. Algorithms, such as that shown in Fig. 1, identify how combined use of hCG measurement, TVUS, and examination of uterine contents after confirming nonviability may be used to efficiently prevent under- or over-treatment. Choice of the best management technique, ranging from expectant, to outpatient medication, to conservative versus radical surgery, is based on the patient's clinical condition; factors related to the ectopic, such as size, evidence of rupture, or rate of hCG rise; and the patient's wishes.

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Postpartum Hemorrhage

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"She died in childbirth." These haunting words have echoed throughout the ages. Hemorrhage probably has killed more women than any other complication of pregnancy in the history of mankind. Annually, an estimated 150,000 maternal deaths worldwide result from obstetric hemorrhage [1,2]. The majority of these are from postpartum hemorrhage (PPH). In countries with less developed medical facilities and limited access to blood transfusion services, obstetric hemorrhage continues to take a tremendous toll on women's lives. In fact, in both Africa and Asia, PPH is the leading cause of pregnancy-related mortality [1]. During the past century, in the developed world, maternal deaths resulting from obstetric hemorrhage have dropped precipitously, mainly because of the advent of blood transfusions, fluid management, coagulation factor replacement, and improved surgical techniques. A significant proportion of deaths from PPH are potentially preventable. At least one study has indicated that 90% of deaths from PPH were preventable. Thus, those caring for pregnant women must be aware of the risk factors for PPH and be prepared to deal aggressively with this complication when it does occur. This article focuses on the etiology, prediction, prevention, and management of PPH.

Definition

PPH traditionally has been defined as blood loss in excess of 500 mL after a vaginal delivery and 1000 mL after a cesarean delivery. Such traditional definitions are not that helpful, however, because studies have demonstrated

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that the average blood loss is about 500 mL at a vaginal delivery and 1000 mL at cesarean delivery [3]. Furthermore, there is consistent evidence that obstetricians frequently underestimate blood loss at delivery. Using the traditional definitions, at least one half of deliveries would be categorized as having PPH. Perhaps a more useful definition of PPH would include blood loss sufficient to cause symptoms of hypovolemia, a 10% drop in the hematocrit after delivery or to require transfusion of blood products [4]. Such loss occurs in approximately 4% of vaginal deliveries and 6% of cesarean deliveries [5]. The majority of PPH occurs within the first 24 hours after delivery and is called ''primary PPH.'' Secondary PPH occurs between 24 hours and 6 weeks after delivery.

Clinical implications

PPH is associated with significant morbidity and mortality. In fact, it is the leading cause of death in pregnancy worldwide and is second only to thromboembolic events in Europe and North America. Hypovolemic shock, blood transfusion and its attendant complications, surgical injury, fever, renal and hepatic failure, acute respiratory distress syndrome, disseminated intravascular coagulopathy, loss of fertility, and Sheehan's syndrome are among the consequences of PPH.

Relevant physiology

To understand the causes and management of PPH, it is important first to understand the mechanisms by which excessive blood loss is prevented during normal pregnancy. Blood flow to the gravid uterus at term is 800 to 1000 mL/min, and large amounts of blood can be lost rapidly. Without mechanisms to minimize blood loss, maternal exsanguination could occur rapidly. After delivery of the placenta, the uterus contracts. Because the myometrial fibers run in different directions, contraction of these fibers occludes blood vessels, preventing blood loss. This contraction, rather than formation of clot or aggregation of platelets, is the major mechanism for hemostasis after delivery. Thus, if the uterus is well contracted immediately after delivery, and hemorrhage develops, the bleeding is most likely the consequence of a genital tract laceration or injury. Strategies to treat primary PPH first must ensure uterine contraction and then identify and repair any genital tract injuries.

Maternal adaptation during pregnancy

Maternal blood volume expands by 40% to 50% during pregnancy, the result of a rise in both plasma volume and red blood cell mass. This increased blood volume to some extent protects the mother from the consequences of

hemorrhage during and following delivery. Thus, following delivery, a woman may lose up to 20% of her blood volume before clinical signs become apparent. In volume-contracted conditions such as pre-eclampsia, women may be more vulnerable to the effects of blood loss at delivery and may decompensate more quickly.

Risk factors and etiology

Risk factors for PPH are listed in Box 1. A history of PPH in a prior pregnancy, abnormal placentation, and operative delivery rank among the most important risk factors [6]. More direct causes of PPH are listed in Box 2. Essentially, they may be categorized into two groups: those in which the uterus is not contracted, and those in which it is. By far the most common cause of early PPH, contributing to approximately 80% of cases, is uterine atony. If the uterus is contracted, the leading causes of primary PPH are genital tract trauma and pathologic placentation. Secondary PPH is caused most frequently by retained products, subinvolution of the uterus, and uterine infection. Coagulopathy is a relatively uncommon cause of primary PPH; it typically occurs when one of the other causes already has produced significant blood loss. The retained dead fetus syndrome, described in most obstetrics texts, clinically manifests about 6 weeks after fetal death and is rarely seen in modern obstetrics. Congenital coagulation

Box 1. Risk factors for postpartum hemorrhage

Prior postpartum hemorrhage
Advanced maternal age
Multifetal gestations
Prolonged labor
Polyhydramnios
Instrumental delivery
Fetal demise
Placental abruption
Anticoagulation therapy
Multiparity
Fibroids
Prolonged use of oxytocin
Macrosomia
Cesarean delivery
Placenta previa and accreta
Chorioamnionitis
General anesthesia

Box 2. Causes of postpartum hemorrhage

Primary causes
Uterine atony
Genital tract lacerations
Retained products
Abnormal placentation
Coagulopathies and anticoagulation
Uterine inversion
Amniotic fluid embolism

Secondary causes
Retained products
Uterine infection
Subinvolution
Anticoagulation

disorders such as Von Willebrand's disease or specific factor deficiencies (factors II, VII, VIII, IX, X, and XI) are uncommon individually but as a class of disorders may be present more frequently than commonly thought.

Uterine atony

Uterine atony may result from overdistension of the uterus, as occurs with polyhydramnios, multifetal gestations, and fetal macrosomia. Other causes of uterine atony include the myometrial laxity that is associated with multiparity, prolonged labor, use of large quantities of oxytocin, tocolytic therapy, and general anesthesia.

Genital tract trauma

Upper genital tract trauma most often is the result of uterine rupture, which may result from separation of a prior cesarean or myomectomy scar. There also may be bleeding from direct uterine injury at the time of cesarean birth or through injury of associated vascular structures such as the uterine artery or broad ligament varicosities. Lower genital tract trauma includes perineal, cervical, or vaginal lacerations, which may occur spontaneously or result from episiotomy, obstetric maneuvers, or operative instrumented deliveries.

Prediction and prevention of postpartum hemorrhage

Perhaps the most important aspect of the management of PPH is its prediction and prevention. In all pregnant women, early in pregnancy,

a detailed history should be taken to determine whether or not the patient has risk factors for PPH (see Box 1). In addition, the patient should be questioned regarding any religious beliefs that may lead to the patient's declining blood transfusions. Any history of heavy menses or bleeding abnormalities should be noted carefully. In all women, especially those who have identified risk factors, anemia should be corrected before delivery.

Women identified as being at risk should be delivered at a center with facilities for blood transfusion and with properly trained obstetric and anesthesiology personnel. Prolonged labor should be avoided if at all possible. Any anticoagulation agents used during pregnancy should be stopped before the onset of labor. Large-bore (at least 18-gauge) intravenous catheters should be inserted when labor is established. Patients having protracted, difficult labors and those who have intrapartum intraamniotic infection also should be considered at risk of PPH. Immediately following delivery of the placenta, uterotonic agents should be given and uterine massage performed to minimize the chance of bleeding from uterine atony. The active management of the third stage has been shown to reduce the risk of PPH. Fluid replacement should be timely and adequate. The Joint Commission on Accreditation of Health care Organizations recommends that regular clinical drills be conducted to enhance the management of PPH [7]. In addition, there is evidence that training of health care personnel on estimating blood loss improves the accuracy of blood loss estimation [8].

Personnel in management of postpartum hemorrhage

The basic principles of PPH management involve relieving the causative factors (especially surgically correctable injuries) and prompt replacement of intravascular volume, blood, and coagulation factors as needed. Perhaps the most important aspect in the management of PPH is the attitude of the attendant in charge. It is critical to maintain equanimity in what can be a chaotic and stressful environment. Confusion and paralysis of assistants may result if too many orders are given at once and are not directed to specific individuals. Assistants should be designated with specific tasks; instructions should be clear, distinct, and brief. Only support staff with a crucial role should be in the room. An excessive number of well-meaning individuals increases the ambient noise, adds to confusion, and opens the door to communication errors. The newborn infant should be removed from the room by nursery personnel, and it usually is appropriate to have any family members who are present accompany the infant. In massive PPH, it is important to inform and mobilize all necessary staff. These personnel include the most experienced obstetrician and anesthesiologist available, the operating room staff, nursing staff, the hematologist/blood bank staff, critical care/intensive care staff, and, where available, interventional radiology personnel. Finally, having a readily available obstetric hemorrhage procedure tray that contains all the instruments that could be needed for

the management of PPH along with personnel familiar with the instruments may help improve outcomes [9].

Initial therapy

Prompt recognition of excessive bleeding after delivery is crucial. A healthy woman may lose 10% to 15% of her blood volume without a drop in blood pressure [4]. The initial finding is a very modest increase in pulse rate. By the time her blood pressure drops appreciably, the woman frequently has lost at least 30% of her blood volume. Thus, depending on vital signs alone to make a diagnosis of PPH, or to determine its severity, may be misleading. Initial therapy should be aimed at simultaneous aggressive fluid and blood replacement to maintain adequate circulating volume and direct treatment of the cause of the hemorrhage. Several wide-bore intravenous catheters should be inserted, and aggressive volume replacement should be commenced.

The first interventions should be directed toward ensuring that the uterus is contracted. Often uterine contraction can be achieved initially by bimanual compression. Manual exploration of the uterus should be performed to ensure that there are no retained secundines. The bladder should be emptied, and uterotonic agents should be administered. If the uterus is well contracted, the lower genital tract (cervix and vagina) should be examined carefully to determine whether there are any lacerations. This examination requires good exposure, adequate lighting, good pain relief, and a competent assistant. This often is best done in an operating room. If genital tract trauma is identified, and the uterus is well contracted, these lacerations should be repaired promptly. It is important to keep up with volume replacement.

Medical treatment of postpartum hemorrhage

Medical treatment of PPH comprises two main categories: (1) medications that cause uterine contraction, and (2) medications that promote coagulation or correct abnormalities of coagulation. This discussion focuses, for the most part, on uterotonic medications that promote uterine contraction.

Medical therapies that cause uterine contraction

Oxytocin

Oxytocin is the most common medications used to achieve uterine contraction and thus is the first-line agent for prevention and treatment of PPH [4]. It may be administered intramuscularly or intravenously. The parenteral dose is 10 mg. Oxytocin generally is well tolerated and has few side effects, but rapid intravenous push may, rarely, contribute to hypotension. Oxytocin also is commonly administered by an intravenous infusion of 10

to 20 units in 1000 mL of lactated Ringer's solution, with the infusion rate titrated to achieve adequate uterine contraction. Oxytocin, a nonapeptide produced in the neurohypophysis, has biologic similarity to antidiuretic hormone; therefore large doses administered with large volumes of fluid may result in water toxicity.

Ergot alkaloids

Ergot alkaloids such as methylergonovine rapidly induce strong tetanic uterine contractions. They also have been used widely as first-line agents in the prevention and treatment of PPH [4]. They may be given orally or parenterally. In cases of PPH, the intramuscular route is the route of choice with dosages of up to 0.2 mg. These medications may cause significant rapid elevation of the blood pressure and thus are contraindicated in patients who have hypertension or pre-eclampsia. Except in very unusual circumstances, intravenous use should be avoided.

Prostaglandins

The 15-methylated prostaglandin F2α analog carboprost is a potent uterotonic agent that has a long duration of action. It may be administered in a 250-μg dose intravenously, intramuscularly, or injected directly into the myometrium. The dose may be repeated every 15 to 20 minutes up to a total of 2 mg, although a single dose is effective in most patients. Increased doses up to 500 μg can be used if the initial 250-μg doses are ineffective. This prostaglandin agent may cause bronchoconstriction and elevation in blood pressure and therefore is contraindicated in asthmatics and patients who have hypertension. It also has significant gastrointestinal side effects and may cause diarrhea, nausea, and vomiting as well as fever.

Misoprostol, an inexpensive, relatively new prostaglandin E1 analog, is used in obstetrics primarily for cervical ripening and induction of labor. It is a potent uterotonic and has been used for both the prevention and treatment of PPH. Meta-analyses have found that misoprostol is less effective than ergot alkaloids and oxytocin in the prevention of PPH and that misoprostol has more side effects [10–12]. Studies, however, have found that misoprostol is highly effective in the treatment of PPH caused by uterine atony [13–16]. Misoprostol may be administered by the oral, vaginal, or rectal route [17]. The typical dosage for the treatment of PPH is 400 to 1000 μg [14,17]. Side effects include diarrhea and fever.

Surgical therapy

Surgical therapies may be divided into four groups: (1) those that decrease blood supply to the uterus, (2) those that remove the uterus, (3) those aimed at causing uterine contraction or compression, and (4) those that tamponade the uterine cavity.

Surgical techniques the reduce uterine blood flow

Uterine artery ligation

Uterine artery ligation is one of the easiest and most effective surgical measures for controlling PPH refractory to initial attempts to control the bleeding. This technique is particularly useful when excessive bleeding occurs during cesarean section. A large curved needle with an absorbable #1 suture is directed anterior to posterior through the myometrium, approximately 1 to 2 cm medial to the broad ligament. The suture then is directed posterior to anterior through a cleared avascular space in the broad ligament close to the lateral border of the uterus and tied. The suture may be passed from posterior to anterior if doing so facilitates an easier approach. The suture usually is placed at the level of the internal cervical os (which lies at the junction of the corpus and the lower uterine segment) but, depending on ease and safety, may be placed higher or lower. The technique is a mass ligature, and the uterine artery does not have to be dissected or mobilized. Personal experience supported by the literature has proven efficacy in 75% of cases of severe PPH [18–20]. Successful pregnancy following uterine artery ligation can be expected [21].

A few case reports have described a vaginal approach to uterine artery ligation [22,23]. In this technique, an anterior colpotomy is created, the bladder is reflected cephalad, and caudad traction is placed on the cervix with sponge forceps. Traction on the cervix is maintained in a direction contralateral to the side on which the uterine artery ligation is to be performed. The uterine artery then is ligated at the insertion into the uterus [22,23]. Ureteral injury, bleeding, and hematoma formation are potential complications that have raised concerns about the safety of the operation [24]. The abdominal approach is performed under direct visualization, has a documented low complication rate, a high success rate, and a large amount of literature supporting its validity, making it the approach of choice.

Ovarian artery ligation

The anastomosis of the ovarian vessels with the uterine vessels can be ligated near the insertion of the utero-ovarian ligament. Alternatively the ovarian artery can be ligated directly between the medial margin of the ovary and the lateral aspect of the fundus in the area of the utero-ovarian ligament. A stepwise combination of unilateral and then bilateral ligatures starting with the uterine artery and working to the ovarian vessels can be an orderly and effective strategy [25].

Hypogastric artery ligation

Ligation of the internal iliac (hypogastric) artery should be performed only by an experienced surgeon who is familiar with pelvic anatomy and, most importantly, with the retroperitoneal course of the ureters. In the United States this procedure is performed less often than in the past [4],

perhaps because the procedure is more complicated and requires more time than uterine artery ligation, has potential serious complications, and, if not successful, may delay recourse to hysterectomy [26]. This procedure, however, is effective in perhaps two thirds of cases in which a woman wishes to maintain her fertility [27,28]. If this procedure fails, it is important to proceed quickly to more definitive therapy (ie, hysterectomy) [29].

Several approaches can be taken to access the retroperitoneal space to locate the anterior division of the internal iliac artery. The round ligament can be divided, the area between the infundibulopelvic ligament and the round ligament can be incised, direct incision into the posterior peritoneum can be performed, with care taken to avoid the ureters, and a primary retroperitoneal approach can be employed. The ureter is reflected medially, the areolar tissue in the retroperitoneal space is dissected away carefully, and the branching of the common iliac artery into its external and internal branches is identified. The internal iliac artery should be grasped with a Babcock clamp and gently elevated. Then a large silk suture is passed beneath the artery about 2 to 3 cm distal to the bifurcation where the anterior division of the hypogastric artery is located. Only a blunt-tipped instrument such as a Mixter clamp should be used to avoid a disastrous puncture of the vessels, especially the internal iliac vein. The tip of the clamp should be passed in a medial-to-lateral direction to reduce further the likelihood of vessel injury. The suture is tied, but the artery is not divided. It is preferable to ligate the anterior division because ligation may decrease the amount of collateral flow that can ensue to the area of distribution; however, this vessel is not always readily obvious.

Surgical techniques that remove the uterus

Hysterectomy

Hysterectomy is required in the management of PPH in approximately 1 in 1000 deliveries [30,31]. The procedure should be reserved for cases in which other measures have failed, and the American College of Obstetricians and Gynecologists recommends that if hysterectomy is performed for uterine atony, there should be documentation of first attempting other therapies [4]. In most cases of suspected placenta accreta, however, hysterectomy should be the primary management, especially when the woman does not desire future fertility [32]. Seventy percent of peripartum hysterectomies follow cesarean delivery, with the remaining 30% performed after vaginal delivery. In the past most hysterectomies were performed for uterine atony. Now, however, the increasing frequency of placenta accreta associated with the dramatic rise in the rate of cesarean sections has made morbid placental adherence the most common indication for peripartum hysterectomy [31–35]. Even in the modern era, maternal mortality associated with emergency peripartum hysterectomy can be as high as 5% [35,36].

The technique of peripartum hysterectomy is similar to that performed in gynecology, but the vascular changes of pregnancy demand a significantly

modified technique. The blood flow to the uterus is tremendous, and minor errors acceptable in gynecologic surgery may lead to a life-threatening situation in an obstetric hysterectomy. There is considerable potential for injury to adjacent structures, particularly the ureters and bladder. The precise technique used depends on whether the surgery is performed with a stable patient or in one who is rapidly losing massive quantities of blood. In the first situation, it is good practice to keep pedicles small and ensure that they are carefully and doubly ligated. The engorged and edematous tissues that exist following delivery can cause vessels tied within large pedicles to slip and retract, which may lead to massive bleeding. In the latter, more emergent situation, rapid control of blood loss calls for quick clamping and cutting until the bleeding is controlled or the uterus is removed. Only when hemostasis is secured are the pedicles tied off. The risk of injury to adjacent structures is greater when hysterectomy is performed rapidly in a blood-filled field. Urinary tract injuries complicate 5% to 22% of peripartum hysterectomies, with the bladder being the most frequently involved structure [37,38]. Tissue malacia can develop, particularly in cases of placenta accreta, rendering a wet-cardboard consistency to the uterus and parametria. In cases of suspected placenta accreta, placenta previa with prior cesarean sections, or other cases in which there is a high probability of hemorrhage, preoperative placement of a three-way Foley catheter connected to a bladder-irrigation infusion can be useful in identifying injuries to the bladder. The drainage port can be clamped, and an infusion into the catheter of sterile saline containing indigo carmine or sterile milk at room temperature is commenced. A temperature difference will be noticed between the bladder and adjacent structures. Injury may be detected by observing fluid or dye leaking into the operative field. Distending the bladder also helps define tissue planes between the uterus, bladder, paravesical, and parametrial areas. The authors have found large, noncrushing angulated Glassman intestinal clamps invaluable because they prevent the tearing into pedicles that often occurs with crushing clamps. These clamps can be placed along almost the entire length of the lateral margin of the uterus, providing uterine traction, compressing the uterine vessels, and providing a stopgap measure while bleeding is assessed and hemostasis is being achieved. If a ureter is grasped in this clamp inadvertently, a crush injury is much less likely to ensue than when crushing clamps are used [39].

Because the cervix frequently is involved with a complete placenta previa, total hysterectomy generally is the operation of choice; however, supracervical hysterectomy may be preferable, especially when the bleeding is caused by uterine atony, when removal of the cervix is not essential for hemostasis, or when there is difficulty maintaining the patient in stable condition. The cervico-vaginal junction can be identified either by placing a finger through the uterine incision and hooking the finger between the cervical rim and the vaginal wall or by palpating the upper vagina, pinching to palpate the cervix.

Surgical techniques that cause uterine compression

The B-Lynch stitch and other uterine compression sutures

In 1997 Christopher B-Lynch and colleagues first reported an innovative approach to the surgical management of PPH in a series of five patients [40]. This surgical technique is based on the principle that a contracted uterus does not bleed. The suture is sometimes referred to as the "brace suture" because of its resemblance to trouser suspenders. The B-Lynch suture aims at compressing the uterus in women in whom bimanual compression, administration of uterotonic agents, and other early interventions have failed. Following their initial report of the technique, B-Lynch and associates, and others, have published several reports documenting wide success in stopping uterine hemorrhage and preventing hysterectomy [41–45]. This technique is performed most easily at the time of cesarean section. It requires that the uterine incision be reopened. Following vaginal delivery, a laparotomy must be performed, and the lower uterine segment must be opened through a transverse incision. The technique begins using a rapidly absorbable suture on a large, curved needle, taking a bite approximately 3 cm medially from the lateral margin of the uterus and 3 cm below the inferior edge of the uterine incision [46]. The needle then exits about 4 cm from the lateral margin of the uterus and 3 cm above the superior edge of the uterine incision. The suture is drawn over the serosal surface of the fundus and then down the posterior aspect of the uterus to the level of the uterine incision on the opposite anterior wall. A horizontal bite is taken, entering and exiting 3 to 4 cm from the lateral margins of the uterus. Next the suture is drawn back over the serosal surface of the fundus, down the anterior wall, and a bite is taken 3 cm from the superior edge of the uterine incision and 4 cm from the lateral margin. The needle exits 3 cm below the inferior edge, approximately 3 cm from the lateral margin. The suture is tied firmly, compressing the uterus directly. Initial reports suggested that the procedure was safe and associated with no significant morbidity. Subsequently, however, there have been reports of severe uterine necrosis, infections, and other complications following this technique [47–49]. Erosion of the suture through the uterine wall into the cervical canal also has been described [50]. The B-Lynch suture is best used for PPH resulting from uterine atony; the successful use of this technique in controlling PPH associated with placenta previa accreta also has been described [51]. Successful term pregnancies following the B-Lynch technique have been reported [52,53].

Similar compression techniques have been described by Ouahba and colleagues [54], Cho and colleagues [55], Ghezzi and colleagues [56], and Hayman and colleagues [57]. The hemostatic suturing technique of Cho and colleagues [55] often is referred to as "box" suturing [55]. In this procedure the anterior and posterior uterine walls are sutured together so that the space in the uterine cavity is eliminated. At an arbitrary point in an area of heavy bleeding, a straight needle with an absorbable suture is passed

through the anterior wall of the uterus, exiting on the serosal surface of the posterior wall. The needle is reinserted several centimeters lateral to the exit in the posterior wall and is drawn right through the uterus to the serosal surface of the anterior uterine wall. The needle then is redirected 2 to 3 cm above the second exit point, from anterior to posterior as described previously. The suturing is completed by passing the needle 2 to 3 cm to the side of the previous exit point through the uterine walls and tied securely, forming a box. Several of these sutures can be placed from the fundus to the lower uterine segment, as needed. Cho and colleagues [55] reported success with this technique, avoiding hysterectomy in 23 women who had not responded to other conservative methods. These authors and others also noted a return to normal fertility in women treated by this technique [55,58]. A case report has described the formation of uterine synechiae following this procedure [59].

Hayman [57] reported a technique that combined modifications of both B-Lynch and Cho techniques and employed compression by suturing the anterior and posterior walls of the uterus. In this method, which has the advantage of not requiring that the uterus be opened after vaginal delivery, the needle is passed from the anterior wall through the posterior wall about 2 cm medial to the lateral margin of the uterus. The suture then is tied over the fundus. Four such sutures are placed, two on each lateral border of the uterus. In addition, isthmic-cervical compression sutures can be placed below the bladder reflection by driving a #2 absorbable suture on a straight needle anterior to posterior and then reinserting the needle 2 cm medially posterior to anterior and tying the suture. An instrument such as a clamp can be placed between the areas to be sutured to ensure patency of the cervical canal [57].

Techniques for uterine tamponade

A variety of techniques have been used to tamponade the uterine cavity. These techniques include uterine packing [60], the umbrella pack, the Sengstaken-Blakemore balloon, and a variety of other adapted balloons and packs. Some obstetricians have used a large, inflated Foley catheter [61]. Condous and Arulkumaran [62] described the use of the tamponade test to determine whether an intrauterine balloon would be effective in the management of PPH and to select patients who required further surgery. The Sengstaken-Blakemore tube, with the stomach end cut off, was inserted into the uterine cavity and then inflated with 75 to 150 mL of saline. If bleeding stopped after inflation of the balloon, the woman was considered not to require further surgery. Seror and colleagues [63] used an intrauterine Sengstaken-Blakemore tube inflated with 250 mL of saline in 17 women who had PPH that had not responded to conventional conservative therapy. Hemorrhage was controlled in 71% of cases, and further surgery was avoided in 88% of cases [63]. A similar technique using a Rusch urological

hydrostatic catheter, which can be inflated with 500 mL of saline, has been used successfully to manage PPH refractory to conventional therapies [64,65]. In a variation of this technique, Bakri and colleagues [66] developed a commercially available balloon for use in the management of PPH. These authors claim that the balloon may be used successfully in the management of hemorrhage caused by placenta previa.

Uterine packing also has been used successfully in controlling PPH in the past but is used infrequently in more modern obstetrics [60,67–70]. Nonetheless, the technique may be very effective in stopping postpartum bleeding and avoiding hysterectomy. The packs generally are removed 24 to 48 hours after delivery.

Pelvic pressure packing

In 1926, Logothetopulos described a pelvic pressure pack also known as a mushroom, umbrella, or parachute pack for the control of PPH [71]. This pack is filled with gauze swabs and is inserted in the pelvis with the stalk passing out into the vagina. Gravity traction is applied to the end of this stalk, thereby pressing the pack against the pelvic vessels. This technique is rarely used today but may have a role in massive hemorrhage that has not to responded to other therapies [71,72]. Occasionally, when all else has failed, packing the pelvic cavity with swabs in bags at laparotomy with enough pressure to tamponade bleeding vessels and closing the abdominal incision is effective in stopping hemorrhage. The patient may be reoperated on in 24 to 48 hours to remove the sponges. This procedure carries significant risks including infection and bowel ischemia/infarction.

Uterine artery and internal iliac artery embolization

Embolization in obstetrics was described first for the control of intractable PPH [73]. The procedure, performed by an interventional radiologist, now is used widely in obstetrics and gynecology. Numerous reports have documented the efficacy of this technique in controlling life-threatening PPH [74–81]. In the most common approach, the femoral artery is catheterized, and the catheter is passed under fluoroscopic guidance into the anterior branch of the internal iliac artery or into the uterine artery. These catheters may contain balloons at their tips, which may be inflated to occlude blood flow to the uterus. An occlusive material then is injected under fluoroscopy until arterial flow to the uterus ceases. Typical embolic agents include absorbable gelatin sponge and clear acrylic microspheres. Side effects and adverse reactions include inadvertent embolization of collateral structures leading to necrosis and gangrene, allergic reactions, and renal impairment. Embolization requires a skilled interventional radiologist and some degree of stability in the patient. The catheters may be placed prophylactically in the radiology suite in patients at risk of severe hemorrhage such as those who have placenta accreta. In general, it is considered best to wait to

embolize vessels until after the fetus is delivered. Embolization also may be performed as an emergent procedure in the operating room, using a C-arm. There have been numerous reports of successful subsequent pregnancies after uterine or internal iliac artery embolization, although these patients may be at risk of intrauterine growth restriction or recurrence of hemorrhage [79,82].

Special situations

Magnesium sulfate

Women who have received prolonged therapy with magnesium sulfate for seizure prophylaxis in pre-eclampsia or for tocolysis may be at increased risk for PPH caused by uterine atony. This type of PPH may not respond well to usual pharmacologic therapies. Should hemorrhage occur in these situations, any remaining magnesium sulfate infusions should be stopped, and calcium carbonate can be administered, which may help the myometrium contract. Seizure prophylaxis can be resumed later if the mother has been stabilized and there is no further bleeding.

Uterine inversion

Uterine inversion occurs in approximately 1 in 2000 deliveries and generally is the result of overenthusiastic attempts to deliver the placenta by cord traction or fundal pressure before complete placental separation. Inversion of the uterus may lead to massive postpartum hemorrhagic shock. The condition is treated by aggressive fluid/blood replacement and uterine replacement. A variety of techniques have been used to replace the uterine fundus. These include manual replacement and the use of hydrostatic pressure. Uterine replacement may require general anesthesia and uterine relaxant agents.

Morbid adherence of the placenta

Morbid adherence of the placenta (placenta accreta/increta/percreta) is an increasingly common cause of severe PPH and has become the leading cause for peripartum hysterectomy [33]. Typically the placenta does not separate following the delivery, and attempts to separate it are accompanied by torrential hemorrhage. A multidisciplinary team approach has the potential to reduce morbidity and mortality [32]. The key to a good outcome lies in prenatal diagnosis and planned delivery in a center with good blood transfusion services [32]. Placenta accreta should be suspected in any patient who has had a prior cesarean and who has a low-lying placenta or placenta previa. The diagnosis can be made sonographically based on the following findings: (1) prominent echolucent vascular spaces in the placenta giving it a ''Swiss-cheese'' appearance; (2) thinning of the placenta-myometrial

border; (3) protrusion of the placenta into the bladder; and (4) abnormal turbulent Doppler flow in the vascular spaces and on the surface of the bladder [83]. It is recommended that no attempts be made to separate the placenta [32]. The uterus should be opened through a fundal incision and hysterectomy performed with the placenta in situ. Embolization of the uterine or internal iliac vessels after delivery of the baby and before the hysterectomy may reduce blood loss greatly [32].

Transfusion therapy

The first documented successful transfusion of human blood was performed by James Blundell in 1825 for a woman dying from PPH [84]. His interest in blood transfusion had been stimulated when he attended a woman who died from PPH 7 years before [84]. Since that first experience, transfusion of blood has been a critical component of life-saving resuscitation in PPH.

Recommendations for transfusion based on laboratory values and changes in vital signs alone are reasonable in a nonpregnant bleeding patient, but the obstetric patient experiencing rapid heavy blood loss that cannot be stemmed is subject to sudden decompensation and exsanguination. Hypovolemic shock, defined as poor tissue perfusion associated with hypoxia, first must be treated with replacement of vascular volume. Crystalloid solutions such as Ringer's lactate are readily available, inexpensive, and easily administered. Crystalloids should be administered as a volume three times the estimated blood loss, because they have a lower oncotic pressure than plasma and rapidly leave the vascular tree to the extravascular space. Although colloids have a higher oncotic pressure and can be administered in less volume, there is little difference in clinical response, and postresuscitation diuresis is better with crystalloids. Life can be sustained, temporizing, by keeping the circulating volume replete and the cardiac pump primed.

Whole blood is rarely used for transfusion, but it has several advantages. It contains all the coagulation factors. In urgent situations, uncrossed O-negative blood may be administered. Type-specific blood is preferable. Packed red blood cells (PRBCs) are the primary transfusion product used to increase the oxygen-carrying capacity. A typical volume of about 300 mL is mixed with normal saline before infusion. Diluting PRBCs with Ringer's lactate can cause calcium to precipitate with the citrate used as a preservative in stored blood. A single unit of PRBCs can be expected to raise the hemoglobin and hematocrit by 1 g and by 3%, respectively, in a nonbleeding patient.

Fresh-frozen plasma is a secondary transfusion product indicated mainly in states of coagulopathy or with massive transfusion. It comes in 250-mL units and contains all the coagulation factors, especially fibrinogen. One unit will raise the fibrinogen level by 10 mg/% in a nonbleeding patient. It is reasonable to consider transfusing 1 unit of fresh-frozen plasma to

every 4 units of PRBCs in an actively bleeding patient, but the clinical circumstances guided by fibrinogen level, prothrombin time, and activated partial thromboplastin time should dictate the amount transfused.

Cryoprecipitate is a tertiary transfusion product that contains as much fibrinogen as a unit of fresh-frozen plasma but in a volume of only about 15 mL. It also contains factor VIII, factor XIII, and von Willebrand's factor. It also will raise the fibrinogen level about 10 mg/% per unit. Its main indication for transfusion is in a hemorrhaging patient who is volume replete but has low fibrinogen levels. A large amount of fibrinogen can be administered in a small volume using cryoprecipitate.

Platelets also are a tertiary transfusion product and are administered to heavily bleeding patients who have thrombocytopenia. Platelets are stored at room temperature on an oscillator in the blood bank and have a short shelf life of 3 to 5 days. Blood banks preferably issue single-donor platelets with a volume of about 300 mL. A unit of single-donor platelets raises the platelet count by 30,000 to 60,000 in a nonbleeding patient. Platelet packs, which usually consist of 6 units, are less preferred because of the increased risk of developing platelet antibodies and blood-borne infection, but the volume and increase in platelet count are similar. The goal of platelet therapy is to stimulate coagulation and maintain a platelet count of 50,000 to 100,000.

Developments in the field of transfusion medicine have led to new products that hold promise now and in the future. Human recombinant activated factor VII (rfVII) has been approved by the Food and Drug Administration (FDA) for treatment of bleeding associated with hemophilia A and B and congenital factor VII deficiency. Case reports are accumulating describing successful use of rfVII in the control of life-threatening hemorrhage after other standard measures have failed [85–87]. It has been successful in stopping hemorrhage in cases of amniotic fluid embolus, disseminated intravascular coagulopathy, placenta previa, placenta accreta, uterine atony, and hemolysis, elevated liver enzymes, and low platelets syndrome. The dose of rfVII has varied from 16.7 to 120 μg/kg. A review of the literature suggests that a dose of 70 to 90 μg/kg could be sufficient to stop 75% of cases of refractory PPH [88]. Factor VII interacts with tissue factor at a site of vascular injury; this interaction activates factors X and IX, leading to a burst of thrombin that in turn leads to a functioning fibrin clot. Platelet-dependant clotting mechanisms also are stimulated by rfVII [85,89]. It must be remembered that although rfVII seems to be very promising for treatment of PPH, it is an off-label use, complications have been reported, and the actual incidence of complications in the setting of obstetric hemorrhage is unknown. Documented complications include thrombosis, disseminated intravascular coagulation, and myocardial infarction [90]. The pharmacy costs of rfVII may be as high as several thousand dollars for a dose of 70 μg/kg.

Blood substitutes have been in development for more than a decade, and some have been approved for use overseas and in veterinary medicine.

Hemoglobin-based oxygen carriers have been prepared from various sources; at present the most promising are derivatives of either bovine hemoglobin or outdated human packed red blood cells. Hemopure, produced by Biopure Corporation of Cambridge, Massachusetts, polymerizes hemoglobin obtained from a specially managed herd of cattle into long chains that resist filtration in the kidney. It has been approved for use in South Africa for use in general surgery. Its complementary veterinary product, Oxyglobin, has been approved by the FDA and is in current use in the United States for canine transfusion. Polyheme, developed by Northfield Laboratories, Evanston, Illinois, another erythrocyte-free hemoglobin under trials, is the product of cross-linked polymers of human hemoglobin. The potential advantages of these products are a shelf life of about 1 year, lack of need for cross matching, and decreased risk for the development of antibodies to red blood cell surface membrane antigens. Potential risks include vascular reactivity resulting in increased systemic and pulmonary artery pressure and neurotoxicity. The newer generation of polymerized hemoglobins has not caused the nephrotoxicity associated with earlier preparations.

An alternative approach to deliver oxygen to the tissues without red blood cells involves perfluorocarbon emulsions. Oxygent is one such product developed by Alliance Pharmaceutical subsidy San Diego, California. The perfluorocarbon is mixed with lecithin and buffer salts and then is homogenized. When a high concentration of oxygen (70%–100%) is inspired, the oxygen is dissolved in the infused perfluorocarbon emulsion. The oxygen is not carried as with hemoglobin derivatives, but the dissolved oxygen is able to diffuse into tissues. As with hemoglobin-based oxygen carriers, this product does not require cross matching, does not carry risk of antibodies developing against antigens in the red cell membrane, can be stored at room temperature on the floor, and has a longer shelf life than banked blood. There has been concern about cerebral vascular events with this product. It is retained in the reticuloendothelial system and can result in reticuloendothelial suppression. Lowering of the platelet count also has been noted. Another potential disadvantage is its short half-life of about 12 to 24 hours [91].

These innovative products may have a role in the future, but at present none are approved for clinical use in humans in the United States. It may take several years before any of these products is perfected and gains FDA approval.

Summary

The incidence of PPH can be reduced drastically by anticipation and preventive measures. When PPH does occur, the resulting morbidity and mortality can be prevented in most cases by early recognition and aggressive and appropriate management.

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Blood Component Therapy in Obstetrics

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Hemorrhage is the leading cause of intensive care unit admission and one of the leading causes of death in the obstetric population [1]. This emphasizes the importance of a working knowledge of the indications for and complications associated with blood product replacement in obstetric practice. This article provides current information regarding preparation for and administration of blood products, discusses alternatives to banked blood in the obstetric population, and introduces pharmacological strategies for treatment of hemorrhage.

Preparing for transfusion

Preparing for an obstetric hemorrhage requires the drawing of a blood sample from the patient to obtain crossmatched blood. The first step in the process of preparing blood is determining ABO type and the presence or absence of Rh factor. To determine ABO type, the blood is mixed with commercially available antibodies that react with A or B antigens on the patient's erythrocytes, causing agglutination [2]. The Rh factor status is also classified by this method. Then the blood type is confirmed by mixing the patient's blood with cells that contain A or B antigens. Because most people have antibodies to antigens that they lack (ie, type-AB patients do not have antibodies and type-O patients have anti-A and anti-B antibodies), agglutination will occur when antigen–antibody complexes are present.

Following typing, blood is screened for common antibodies. Screening involves mixing the recipient's blood with commercially available antigens. If red blood cell agglutination or hemolysis occurs, antibodies are present and must be characterized. This initial "type and screen" takes approximately 45 minutes and is best for patients at low risk for requiring blood transfusion

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[2]. The most recent American Society of Anesthesiologists Practice Guidelines for Obstetric Anesthesia [3] state that a routine blood crossmatch is not necessary for healthy and uncomplicated parturients for vaginal or operative delivery. The decision whether to order or require a blood type and screen, or crossmatch, should be based on maternal history, anticipated hemorrhagic complications (eg, placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies.

Patients should undergo blood crossmatching when blood transfusion is imminent or likely. To crossmatch blood, the recipient's blood is mixed with the donor's to mimic the transfusion (serologic crossmatch) [2]. This process detects antibodies in the Kell, Duffy, Kidd, and MN groups as well as antibodies that are present in low titers and that do not agglutinate easily [4]. Blood crossmatching typically takes an additional 15–45 minutes after the blood has been typed and screened [2].

In an emergency where the patient requires transfusion before type-specific or crossmatched blood can be obtained, type-O blood can be administered. In obstetric patients, it is especially important to administer type-O, Rh-negative blood because of the risk of Rh sensitization. Crossmatched blood should be administered as soon as it is available because the estimated risk of a hemolytic transfusion reaction with this emergency blood has been reported to be as high as 5%, although publications with trauma patients report much lower complication rates [2,5].

The American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the American College of Obstetricians and Gynecologists [6] recommend that all facilities providing obstetric care be prepared to manage hemorrhagic emergencies [3]. Immediate availability of such equipment as hand-inflated pressure bags, an automatic rapid infusion system, a fluid warmer, and a forced-air warming device is recommended. Knowledge of blood bank capability is paramount and resources vary depending on the hospital. Therefore, it is essential to know the time required for obtaining type-O, type-specific, and crossmatched blood as well as platelet and clotting factor availability. Response to massive hemorrhage takes a coordinated effort between clinicians and the blood bank; it is helpful to have a massive hemorrhage protocol outlined before an emergency occurs [7]. Facilities should also consider writing and posting such a protocol in addition to running clinical drills on obstetric hemorrhage scenarios [6,8].

For patients who are at risk for bleeding or who are actively hemorrhaging, the importance of adequate intravenous access cannot be emphasized enough. Flow through an intravenous cannula is directly proportional to the fourth power of the radius and inversely proportional to the length. For these reasons, one or more short, large-bore peripheral intravenous catheters are often preferable to central venous access with a longer catheter (such as a double- or triple-lumen catheter). An arterial line can be extremely helpful during a hemorrhagic emergency, both for beat-to-beat monitoring of blood pressure and for obtaining frequent laboratory tests.

Determining when to transfuse

Determining the point at which a patient requires blood transfusion can be difficult. Many factors, including vital signs, ongoing blood loss, and coexisting disease should be considered. Estimating blood loss during and after delivery can also be difficult and is often underestimated because the blood is not always contained in one space and because amniotic fluid is present. As a result, postpartum hemorrhage is not clearly defined. However, an estimated blood loss greater than 500 mL for a vaginal delivery and 1000 mL for a cesarean delivery are typical definitions used to describe postpartum hemorrhage [6].

The American College of Surgeons separates the severity of hemorrhagic shock into classes based on vital signs and mental status [9]. Signs and symptoms of inadequate perfusion due to hypovolemia are presented in Table 1 and include tachycardia, decreased pulse pressure, tachypnea, decreased urine output, and an altered mental status ranging from anxious to lethargic [9,10]. While the physiologic changes of pregnancy (eg, increased blood

Table 1
Signs and symptoms in patients with obstetric hemorrhage

Severity of shock	ACS class	Signs and symptoms	Blood loss (mL)	% Blood volume lost	Notes
None	Class I	None	Up to 750	10–15	
Mild	Class II	Tachycardia (<100 bpm); mild hypotension; normal or ↑ pulse pressure (peripheral vasoconstriction)	750–1500	15–25	Volume replacement with crystalloid and/or colloid
Moderate	Class III	Tachycardia (100–120 bpm); hypotension (systolic blood pressure 80–100 mm Hg); ↓ pulse pressure; anxiety, confusion; oliguria	1500–2000	25–40	Transfusion probable
Severe	Class IV	Tachycardia (>120–140 bpm; hypotension (systolic blood pressure <80 mm Hg); ↓ pulse pressure; confusion, lethargy; anuria	>2000	>40	Transfusion probable; massive transfusion possible

Abbreviations: ACS, American College of Surgeons; bpm, beats per minute.
Data from Refs. [7,9,10].

volume) can limit the utility of this table, classes III and IV hemorrhage indicate significant hypoperfusion and almost always require transfusion [9].

Historically, patients were transfused to keep the hemoglobin concentration greater than 10 mg/dL [11]. This practice has been challenged by a recent study demonstrating decreased mortality in critically ill patients who were transfused at lower hemoglobin thresholds (ie, transfusions administered with hemoglobin concentrations less than 7 g/dL) [12]. On the other end of the spectrum, Karpati and colleagues [13] found an approximately 50% incidence of myocardial ischemia in intensive care patients admitted with postpartum hemorrhage and hypovolemic shock. Risk factors for myocardial ischemia in this population were a hemoglobin of 6.0 g/dL or lower, systolic blood pressure of 88 mm Hg or lower, diastolic blood pressure of 50 mm Hg or lower, and a heart rate greater than 115 beats per minute [13].

The purpose of packed red blood cell (PRBC) administration is to increase the oxygen-carrying capacity of blood. According to the American Society of Anesthesiologists Task Force on blood product replacement, PRBC transfusion is rarely indicated with a hemoglobin level greater than 10 g/dL and is almost always indicated with a hemoglobin level less than 6 g/dL [14]. Table 2 outlines the indications for PRBC and other blood products.

A recent survey of anesthesiologists and obstetrician/gynecologists found that the transfusion threshold for most providers is 7 to 8 g/dL, with the anesthesiologists transfusing at 7.5 g/dL and obstetricians at 8 g/dL [15]. While the clinical situation should dictate when to transfuse red blood cells, a threshold in the range of 6.5 to 8.5 g/dL appears prudent given current data.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) occurs when an inciting event initiates the biodegradation of fibrinogen and clotting factors, resulting in hemorrhage and microvascular thrombosis. Obstetric disorders associated with DIC include amniotic fluid embolism, placental abruption, retained products of conception, eclampsia, and abortion [16]. Disseminated intravascular coagulation is commonly associated with obstetric hemorrhage and causes profuse bleeding due to inadequate blood clot formation. Therefore, obstetric care providers must consider the need for platelet and/or clotting factor administration in a hemorrhaging patient, especially when a condition associated with DIC is present.

Platelets

Platelets are usually available in six- to nine-unit equivalents from apheresis or whole blood. One unit of platelets increases the platelet count by 5000 to 10,000 cells/μL in the absence of platelet destruction [7]. Platelet transfusion

Table 2
Blood product information

Product	Contents	Indications for administration	Notes
Packed red blood cells	Red blood cells	• Improve oxygen-carrying capacity • Almost always for hemoglobin <6 g/dL • Rarely for hemoglobin >10 g/dL	Type-specific and crossmatched blood preferred
Platelets	Platelets	• Microvascular bleeding with platelet counts $<50{,}000$ cells/μL	Blood product most often associated with bacterial contamination
Fresh frozen plasma	All plasma proteins and clotting factors	• Microvascular bleeding due to clotting factor deficiency • International normalized ratio $>2\times$ normal • Activated partial thromboplastin time $>1.5\times$ normal	Must be thawed before administration (20–30 min)
Cryoprecipitate	Factor VIII and fibrinogen	• Microvascular bleeding due to fibrinogen deficiency • Fibrinogen <80–100 mg/dL	Can also be used to treat congenital fibrinogen deficiencies or von Willebrand's disease when clotting factors are unavilable

is rarely indicated when the platelet count is greater than 100,000 cells/μL, but should be considered when there is excessive bleeding with platelet counts less than 50,000 cells/μL [14]. While it is possible to transfuse ABO-incompatible platelets, these cells may have a shorter life span [2]. Rh compatibility should be considered in the obstetric population and Rh immune globulin should be administered if Rh-positive platelets are administered to an Rh-negative individual [17].

Clotting factors

Fresh frozen plasma (FFP) is collected from whole blood or plasma apheresis after platelets and cells are removed. It contains all plasma proteins and clotting factors. FFP is stored at -18°C to -30°C and must be thawed before administration. Thawing takes 20 to 30 minutes. In the

obstetric setting, common indications for FFP are treatment of microvascular bleeding due to coagulopathy and/or factor deficiency following massive transfusion. Additional indications include reversal of warfarin, correction of isolated factor deficiencies when specific factor concentrates are unavailable, and antithrombin III deficiency in patients receiving heparin [14]. Recommendations for FFP administration include measurement of the activated partial thromboplastin time (aPTT) and prothrombin time before administration and when the prothrombin time and international normalized ratio are greater than two times normal and/or the aPTT is greater than 1.5 times normal [14]. Because anti-ABO antibodies are present in plasma, ABO compatibility should be considered when transfusing FFP [2]. For example, a patient with type-AB blood should not receive type-O plasma because of the presence of anti-A and anti-B antibodies [2].

Cryoprecipitate is extracted from slowly thawing FFP. It is rich in factor VIII and fibrinogen and is used to treat microvascular bleeding in the presence of fibrinogen deficiency, which most commonly occurs because of DIC or massive transfusion. Ideally, a fibrinogen level should be obtained before administration of cryoprecipitate. Fibrinogen concentrations greater than 150 mg/dL usually do not require cryoprecipitate, but fibrinogen concentrations less than 80 to 100 mg/dL indicate need for transfusion [14]. Cryoprecipitate can also be administered for treatment of congenital fibrinogen deficiencies or bleeding in patients with von Willebrand's disease when factor concentrates are unavailable [14]. Because cryoprecipitate has only a small amount of plasma, ABO compatibility is unnecessary [2].

Autologous blood donation

Because of concern about cost-effectiveness, routine autologous blood donation is not recommended for routine obstetric deliveries [11]. However, autologous blood transfusion is a viable option for patients at risk for peripartum hemorrhage, especially those with rare antibodies who will be difficult to transfuse with compatible homologous blood. Autologous blood donation during pregnancy has been shown to have minimal maternal hemodynamic effects with maintenance of fetal umbilical artery systolic/diastolic ratio [18].

Yamada and colleagues [19] published an analysis of 82 patients with placenta previa after implementation of an autologous blood donation protocol. They found that women who did not donate blood prepartum had a four times greater rate (12% versus 3.1%) of peripartum homologous blood transfusion. They recommended beginning the blood donation at 32 weeks' gestation with removal of 400 mL per week to achieve a total stored volume of 1200 to 1500 mL [19]. In the study, patients who donated autologous blood had a higher overall rate of blood transfusion, with 71% receiving blood peripartum compared with 12% of patients who received homologous blood. While autologous blood has a slightly smaller incidence

of bacterial contamination, the risk of ABO mismatching is similar for both autologous and homologous blood [20,21]. Thus, administration of autologous blood should not be viewed as innocuous and should be administered for the same indications as banked blood.

Acute normovolemic hemodilution

Acute normovolemic hemodilution is a technique involving collection of autologous blood immediately before surgery or delivery. Normovolemia is maintained by intravenous fluid administration with colloid or crystalloid. The volume of colloid administered should be equal to the volume of blood withdrawn. When crystalloid is administered, the volume should be three times the volume of blood removed [22,23]. When blood is subsequently lost, it has less red blood cell mass and the blood removed can be returned to the patient as needed.

Because the blood is collected and stored at the bedside for immediate reinfusion, the risks of bacterial contamination and administrative error associated with autologous blood storage are significantly reduced. This technique has been successfully reported in patients at risk for blood loss during cesarean delivery, with an average of 1000 mL of blood collected just before the surgery [22]. In this study, no patients experienced symptoms of nausea, vomiting, dizziness, or lightheadedness and there were no abnormalities in vital signs or fetal heart rate [22].

Intraoperative cell salvage

Another alternative to allogenic banked blood is the use of an intraoperative cell salvage device, or cell saver. This technique involves suctioning of blood from the operative field followed by cell washing, suspension in saline, and reinfusion to the patient [24]. Concerns about its possible association with amniotic fluid embolism (AFE) have made this technique controversial [25–27].

The cause of the coagulopathy and cardiovascular collapse associated with AFE is unclear [28]. Tissue factor is present in amniotic fluid and plays a role in the initiation of coagulation, prompting speculation that tissue factor is responsible for the DIC associated with AFE. The effectiveness of a commonly available cell saver system to remove functionally active tissue factor from blood contaminated with amniotic fluid has been demonstrated [29]. Fetal squamous cells, meconium, and other particulates have also been implicated in the development of AFE [30]. Waters and colleagues [26] demonstrated that when cells are washed and a leukocyte depletion filter is used, the resulting blood has a concentration of fetal squamous cells similar to a preoperative maternal blood sample [26].

In a multicenter historical cohort study, 139 patients received autologous blood transfusion during cesarean delivery via intraoperative cell salvage

technique with no patients experiencing AFE or adult respiratory distress syndrome [31]. While the investigators concluded that their study had enough power to detect a clinically significant increase in AFE, it is still possible that this rare event can be associated with this technology. In fact, one case report exists of a patient who developed hypoxia, cardiovascular collapse, and death minutes after infusion of cell saver blood following cesarean delivery. The patient had coexisting diseases, including hemolysis–elevated-liver-enzymes–low-platelets (HELLP) syndrome, so the exact cause of death was unclear. However, a clinical diagnosis of AFE was made [32].

Fetal hemoglobin is present in the processed cell saver blood, raising concerns about maternal alloimmunization and the potential for problems with subsequent pregnancies [26,27]. Rh mismatch is particularly important and anti-D immune globulin should be administered to Rh-negative mothers who receive salvaged blood [24]. Because the exact volume of fetal blood administered to the mother via the cell saver is highly variable, a Kleihauer-Betke test should be considered to allow for dose adjustment of Rh immune globulin [33].

Critics caution that because the inciting factors in AFE are unknown and the incidence is so low, the safety of salvaged blood cannot be proven [25,27,32]. Furthermore, because obstetric hemorrhage can be unpredictable, availability of equipment and skilled personnel is a significant drawback to intraoperative cell salvage [25,27]. However, this technique has been used safely in many patients and should be considered in patients at high risk for hemorrhage who would be difficult to crossmatch or object to blood transfusion (eg, a Jehovah's Witness with a known placenta accreta) [6,24,34].

Massive transfusion

Massive transfusion is defined as administration of greater than 10 units of packed red blood cells [35]. Because large amounts of blood products will be needed, it is important to notify the blood bank when massive hemorrhage occurs in an obstetric patient. A massive hemorrhage protocol can be extremely helpful, especially one that outlines how blood products will be transported to the obstetric suite and how clotting factors will be prepared in a timely way [36]. Clear communication between personnel, especially the obstetrician, anesthesiologist, and nursing staff regarding ongoing blood loss and the continued need for blood products is important.

The massively bleeding patient must be reassessed frequently to determine the efficacy of treatment as well as to identify correctable complications. Massive transfusion is associated with the "bloody vicious cycle," which was originally used to describe coagulopathy following trauma [35]. Active hemorrhage is worsened by coagulopathy, which is caused by metabolic acidosis and core hypothermia. The treatment of the hemorrhage with

red cell transfusion can worsen the coagulopathy by diluting platelets and clotting factors as well as contributing to hypothermia and acidosis [35]. In a prospective analysis of trauma patients receiving greater than 10 units of PRBC, approximately 50% developed coagulopathy [35]. Patients who also had a core temperature of less than 34°C and persistent metabolic acidosis had an even higher incidence of life-threatening coagulopathy [35]. In obstetrics, the exact incidence of coagulopathy with massive transfusion is unknown, but may be even higher given the high incidence of DIC in the obstetric population. For these reasons, platelets and coagulation factors must be administered to the massively bleeding patient. Core temperature must be measured and every effort made to warm both the patient and blood products being administered. Other complications associated with massive transfusion are discussed later in this article and include hypocalcemia and hyperkalemia.

Errors and transfusion

While patients are often highly concerned about the infectious risks associated with blood transfusion, patients are actually at more risk for complications resulting from ABO incompatibility errors and similar mixups unrelated to infections [20,21,37]. A survey of transfusion errors in New York state over a 10-year period found the incidence of erroneous administration to be one for every 19,000 red blood cell units administered with blood being administered to the wrong recipient representing 38% of the errors [20]. The incidence of ABO incompatibility errors ranges from one for every 38,000 units administered to one in every 138,000 units administered [20,21,37]. Overall, the incidence of a fatal reaction due to erroneous administration is approximately one in every 1,500,000 units of blood administered [37]. In many cases, multiple errors are involved and can include phlebotomy errors, patient misidentification, sample mislabeling, and laboratory errors [20,37]. Clearly, vigilance is required of all personnel involved in blood product administration and is paramount to keeping these risks at an absolute minimum.

Hemolytic reactions

The most serious complication arising from erroneous blood product administration is an acute hemolytic reaction. This occurs as a result of the recipient's circulating antibodies destroying the donor's red blood cells. An acute hemolytic reaction is characterized by fever, urticaria, nausea, chest and flank pain, hyperkalemia, hypotension, DIC, hemoglobinemia, and acute renal failure [4,7]. If an acute hemolytic reaction is suspected, the transfusion should be stopped immediately with initiation of supportive care, including blood pressure support, aggressive intravenous fluid

replacement, diuresis, and alkalinization of the urine [4,7]. Laboratory studies, including urine and plasma hemoglobin, an antibody screen, coagulation parameters, and blood counts should be obtained [4,7]. The blood being infused should be sent to the blood bank with a sample of the patient's blood to confirm incompatibility.

A delayed hemolytic reaction is due to extravascular hemolysis of donor erythrocytes. It results from the presence of antibodies from previous transfusions or pregnancy in recipient serum that were at levels too low to be detected during the crossmatch [4]. Clinical manifestations occur approximately 1 week after a seemingly compatible transfusion and are characterized by anemia, mild fever, increased unconjugated bilirubin, jaundice, hemoglobinuria, decreased haptoglobin, and spherocytosis on the blood smear [4,7]. Because the hemolysis is extravascular, the reaction is much less severe than an immediate hemolytic reaction and the symptoms are self-limited [4].

Transfusion-transmitted infectious disease

The incidence of transfusion-transmitted infectious diseases has decreased dramatically over the last 20 years, mainly because of improved donor screening and technological advances in blood bank testing. Of particular importance has been the development of nucleic acid testing for viral pathogens, such as HIV, hepatitis C, and hepatitis B. Historically, transfusion-transmitted viral infections posed a large risk to recipients. The incidence of such infections is now so low that mathematical models must be used to estimate the incidence of pathogen transmission. The current incidence of various infectious diseases associated with blood transfusion is summarized in Table 3. The estimated risk of HIV is one infection for every 2,135,000 units of blood administered and that of hepatitis C is

Table 3
Estimated incidence of transfusion-associated disease

Transfusion-associated disease	Incidence (incidence of disease/units of blood administered)
HIV	1:2,135,000 [38]
Hepatitis C virus	1:1,935,000 [38]
Hepatitis B virus	1:200,000[a] [38]
West Nile virus	Incidence varies seasonally and geographically; approximately 1:1,000,000 [39]
Chagas' disease	Rare
Malaria	Rare
Variant Creutzfeldt-Jakob disease	Rare
Bacterial contamination	1:12,000 for platelets; 1:500,000 for red blood cells [11]

[a] Estimate made before introduction of nucleic acid testing.

one for every 1,935,000 units administered [38]. The genetic diversity of HIV is increasing and constant surveillance of the blood supply is required to optimize detection of this virus and keep transfusion-associated transmission at its current rate [39].

Other potentially infectious agents are continually surfacing. Transfusion-associated transmission of West Nile virus was first reported in 2002 and prompted the development of nucleic acid testing, especially in locales with high West Nile virus activity [39]. Variant Creutzfeldt-Jakob disease is an emerging concern, with one probable case of transfusion-associated transmission prompting exclusion of blood donors who have spent more than 6 months in the United Kingdom from 1980 to 1996 [39]. In parts of the world where variant Creutzfeldt-Jakob disease transmission is a significant concern, plasma treated with a solvent-detergent can be imported from the United States to minimize the risk [40].

Trypanosoma cruzi, the pathogen responsible for trypanosomiasis (ie, Chagas' disease), can also be transmitted via blood transfusion. This disease is a growing concern in the United States because the parasite can survive the cold storage and cryopreservation of blood products. While the incidence of transmission remains low, screening tests are being improved with potential universal screening of blood donations in the future [39]. Transfusion-associated transmission of malaria, another parasitic illness, remains a potential threat, with approximately three cases per year in the United States [39]. Currently, because laboratory screening tests lack accuracy, the risk is reduced by excluding donors who have recently traveled to endemic areas [39].

Bacterial contamination of blood products is the most common cause of acute transfusion-associated mortality from an infectious agent [39]. Bacterial contamination occurs most often with platelets, with an estimated incidence of one for every 12,000 units of blood administered [11]. This is due to the fact that platelets must be stored at room temperature and therefore have a higher potential for supporting bacterial growth than do other blood products. The most frequent contaminating organism is *Yersinia entercolitica* for red blood cells and *Staphylococcus aureus* for platelets [11]. The clinical presentation ranges from mild fever to acute sepsis leading to death. Bacterial contamination should be suspected and antibiotic therapy considered in patients who develop a fever within 6 hours after platelet transfusion [11].

Transfusion-associated acute lung injury

Transfusion-associated acute lung injury (TRALI) is an acute respiratory distress syndrome occurring within 2 to 6 hours after transfusion [41–43]. It is characterized by noncardiogenic pulmonary edema manifesting as hypoxia with bilateral infiltrates on chest radiograph [41–44]. The true incidence

of TRALI is unknown because it is difficult to distinguish from other forms of acute lung injury and it often occurs in patients with multiple coexisting illnesses [43]. However, it is not a rare entity, and is estimated to occur once in every 2000 to 5000 transfusions of blood or blood products [43]. According to the Food and Drug Administration, TRALI is the leading cause of death from transfusions in the United States [43].

The leading hypothesis for the pathogenesis of TRALI is antibody-mediated [45]. A donor HLA or granulocyte-specific antibody is transfused into a recipient who possesses the corresponding leukocyte antigens [45]. This antibody–antigen interaction then initiates a cascade of cellular activity in the lung, resulting in endothelial damage and capillary leakage into alveoli [45]. Women who have had multiple pregnancies and patients with a history of prior transfusions are the most likely donors to be implicated in cases of TRALI [46]. Of particular interest in the obstetric setting is the association of TRALI in children whose mothers act as directed blood donors. In such cases, TRALI presumably stems from the development of antibodies toward paternally derived antigens present in the offspring [47]. An alternate hypothesis for the pathogenesis of TRALI involves two events, the first being a preexisting clinical condition in the patient that causes activation of the pulmonary endothelium [45]. The second event is the transfusion of biologically active substances that cause neutrophil activation and lead to pulmonary endothelial damage and alveolar edema [45].

Treatment for TRALI is supportive, with mechanical ventilation required for most patients. Small tidal volumes are recommended. Hypotension is generally responsive to intravenous fluid but diuretic administration can worsen the patient's condition [42].

Miscellaneous complications

Other complications associated with blood transfusion are associated with the citrate phosphate dextrose (CPD) used as an anticoagulant preservative in PRBC. In massive transfusion, citrate can bind plasma calcium and lead to hypocalcemia, causing hypotension, tetany, and cardiac arrhythmias [4]. Plasma calcium levels should be measured during massive transfusion and hypocalcemia treated with intravenous calcium chloride [4].

Another potential complication associated with the CPD preservative is acidosis. The pH of stored blood is approximately 7.0 because of the preservative and can decrease to 6.9 during storage because of the metabolism of glucose to lactate [4]. It is unclear whether the acidity of banked blood contributes to acidosis in the patient. When massive transfusion is required, therapy should be guided by frequent blood gas analysis [4,35].

Hyperkalemia can occur with PRBC administration because of passive diffusion of potassium out of the red blood cells during storage. In patients with normal renal function, the excess potassium is usually transported back into the cells or excreted in the urine. However, potassium levels should also

be measured in patients requiring transfusion. If EKG changes, such as peaked T waves and wide PR and QRS intervals, are observed, the patient must be treated for hyperkalemia [4].

Because blood is stored at 1°C to 6°C, hypothermia can result from blood transfusions, especially during massive transfusion. Extreme hypothermia can result in impaired coagulation, decreased tissue perfusion, arrhythmias, and decreased drug activity [7,48–50]. Because of this, temperature monitoring, active warming, and use of a blood warmer are imperative when massive transfusion is required [3,14].

Activated recombinant factor VII

A promising new alternative to blood component therapy is recombinant activated factor VII (rFVIIa). This drug is identical in structure and function to human factor VIIa and was originally developed to prevent or control bleeding in patients with hemophilia A or B with inhibitors to factors VIII or IX. However, the drug has been used in other situations with uncontrolled bleeding, including life-threatening obstetric hemorrhage [49,51,52]. Several case reports and reviews have described decreased blood product requirements in surgical and trauma patients with uncontrolled bleeding with the administration of rFVIIa [53,54]. The mechanism of action of rFVIIa is to augment the intrinsic clotting pathway by binding with tissue factor and directly activating factors IX and X [49,54]. The use of rFVIIa for postpartum hemorrhage is off-label and therefore the dose is based on case reports. The most commonly reported effective dose is 50 to 100 μg/kg intravenously every 2 hours until hemostasis is achieved, with the vast majority of patients requiring only one dose [6,49].

It is important to ensure adequate levels of platelets and clotting factors (by administration of blood products if necessary) because rFVIIa increases clotting by acting on these substrates [49,52,55]. While the optimal timing of rFVIIa administration is not known, reports suggest improved outcome when rFVIIa is administered relatively early in a hemorrhagic emergency [49,52,55]. Furthermore, the activity of rFVIIa is reduced during hypothermia and acidosis, highlighting the importance of its use before the patient develops some of the consequences of massive transfusion [49].

Because rFVIIa is derived from recombinant technology and not from human proteins, there is no risk of viral transmission from the drug [49]. The most commonly reported adverse events associated with factor VIIa administration are thrombosis, including cerebrovascular accidents, myocardial infarction, pulmonary embolism, and clotting of indwelling devices [56]. Most occur within 3 hours of administration of the last drug dose [56]. More information regarding the off-label use of this new product for obstetric hemorrhage is needed and will surely become available as its use increases. For now, rFVIIa should be considered, if available, in a hemorrhagic emergency.

Summary

Hemorrhagic emergencies are common in obstetrics. Blood component therapy should be administered to treat specific conditions, such as inadequate oxygen delivery, microvascular bleeding, and coagulation factor deficiency. Alternatives to banked blood include autologous blood donation, normovolemic hemodilution, and intraoperative cell salvage. These should be considered in patients who are difficult to crossmatch and/or who refuse banked blood. Recombinant factor VIIa is a new adjunct for treatment of massive hemorrhage and should be considered, if available.

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Early Goal Directed Therapy for Sepsis During Pregnancy

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Sepsis is the leading cause of death in critically ill patients in the United States and is among the 10 leading causes of death overall [1–6]. The costs associated with sepsis are staggering, approaching $17 billion dollars annually as sepsis accounts for 2% to 11% of all hospital admissions [2,3,7]. The annual rate of sepsis is estimated at 240 to 300 cases per 100,000 population, and this rate has increased over the past decade [3,5–7]. This increase is attributed in part to an aging population, greater antimicrobial resistance, and the increased use of invasive procedures, immunosuppressive drugs, chemotherapy, and transplantation. Annually, over 750,000 cases are thought to occur, and estimates for the year 2010 are projected at 934,000 cases per year [3,8].

Historically, imprecise definitions of the terms bacteremia, septicemia, sepsis, and septic shock hindered the ability to establish an early diagnosis in the evolving process of sepsis [9]. These terms were often used interchangeably in both the general and obstetric literature. This imprecision makes study comparisons difficult. Furthermore, the lack of clear definitions has hampered the ability to understand the pathophysiology of sepsis and the development of successful therapy [3]. In 1992, the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) published a consensus report based on a panel convened to standardize the definitions for the classification of sepsis [10]. Despite the specific diagnostic criteria, considerable overlap remained. Thus, in 2001, an international group of critical care specialists met to provide some resolution to the case definition dilemma [11]. The results were standardized definitions published in 2003 and shown in Table 1 [12]. Widespread use of these definitions has helped clarify the epidemiology and outcomes of persons with sepsis.

Studies looking at sepsis during pregnancy are particularly difficult to analyze because of the retrospective nature of the data, small numbers,

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Table 1
Definitions of sepsis

Condition	Definition
Infection	A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Bacteremia	Presence of viable bacteria in the blood; may be transient and of no clinical significance; presence alone not sufficient to diagnose sepsis
Sepsis	Systemic inflammatory response to infection
Systemic inflammatory response syndrome	Widespread inflammatory response defined by two or more of the following: Temperature $>38^{\circ}C$ or $<36^{\circ}C$ Pulse >90 beats/min Respiratory rate >20/min or $PaCO_2 <32$ mm Hg White blood cell count $>12{,}000$ mm^3 or <4000 mm^3 or $>10\%$ immature (band) forms
Severe sepsis	Sepsis with associated organ failure
Septic shock	Sepsis with hypotension refractory to fluid resuscitation

Data from Levy MM, Fink MP, Marshall JC, et al, for the International Sepsis Definitions Conference. The 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6; and American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.

and different methodologies. The varying definitions of bacteremia, sepsis, septic shock, and the systemic inflammatory response syndrome over time make data comparison difficult. Furthermore, mortality estimates from sepsis during pregnancy may be underestimated partly because, in many studies, sepsis is neither defined nor classified as an infectious cause of mortality [13].

A recent review of the global burden of maternal sepsis conducted by the World Health Organization (WHO) highlighted the problem of imprecise nonuniform terminology [14]. WHO collected published data and examined regional office databases from around the world. Reporting was not uniform. As expected, rates of obstetrical sepsis differed dramatically in developing and developed countries. The incidence of ''sepsis'' varied from a low of 0.96 to a high of 7.04 per 1000 women age 15 to 49 years. Similarly, estimated mortality rates ranged from 0.01 to 28.46 per 100,000 women age 15 to 49 years. Despite the obvious limitations of combining data from varied sources, common themes were noted. These are delineated in Box 1. Lack of access to prenatal care is strongly associated with higher sepsis rates. In developing countries, malaria, HIV, and community-acquired pneumonia are common ''nonobstetric'' causes of sepsis during pregnancy [15]. Obstetrical sepsis is primarily the result of pelvic infections due to choriomanionitis, endometritis, wound infections, septic abortion, or urinary tract infections [9,16–19].

Box 1. Bacterial infections associated with septic shock in the obstetric patient

Obstetric
Chorioamnionitis
Postpartum endometritis (more common after cesarean section)
Septic abortion
Septic pelvic thrombophlebitis
Cesarean wound infection
Episiotomy infections

Nonobstetric
Appendicitis
Cholecystitis
Urinary tract infections
Pyelonephritis (perinephric abscess, renal calculi)
Pneumonia
HIV
Malaria

Invasive procedures
Necrotizing fasciitis
Infected cerclage
Postchorionic villus sampling/amniocentesis (septic abortion)

Miscellaneous
Toxic shock syndrome

Chorioamnionitis rates are strongly associated with preterm delivery and number of vaginal examinations [15]. Endometritis and wound infections are common complications of cesarean delivery and are probably underreported in most series because the diagnosis is frequently made as an outpatient following discharge [14,20]. The most common risk factor for maternal sepsis is cesarean delivery [14]. The cesarean rate appears to be increasing worldwide. It is estimated that the increasing rates of cesarean will result in increased numbers of women diagnosed with infection and sepsis.

Septic abortion is also common throughout the world. Access to birth control and ''legalized'' abortion significantly influence the rates of septic abortion and maternal sepsis [15]. Septic abortion is not only associated with maternal morbidity and mortality short term, but is associated with secondary infertility and chronic pain in survivors [14]. Asymptomatic bacteriuria, urinary tract infections, and pyelonephritis rates all increase during pregnancy [18,19,21,22]. When any of these are left untreated, sepsis can occur.

Pregnant patients who present with sepsis, regardless of the cause, are at high risk for delivery during their admission [23]. Outcomes for the baby

depend upon the gestational age at the time of delivery and the presence of neonatal infection. The prognosis for the mother's recovery from septic shock is favorable, particularly when compared with prognoses for nonobstetric patients [1,3,5,24,25]. For the gravid patient, the factors contributing to a decreased rate of septic shock as well as a favorable prognosis in the face of septic shock include a younger patient profile with fewer comorbidities and organisms that are usually responsive to common broad-spectrum antimicrobials [16,26]. In addition, a common site of infection in the pregnant patient is the pelvis, a location amenable to medical and surgical intervention. These characteristics also lead to a lower mortality rate [16,26–28].

The following is a review of the microbiology, pathophysiology, and management guidelines to reduce morbidity and mortality from obstetrical sepsis.

Microbiology and risk factors

Most obstetric patients who develop bacteremia do not develop sepsis. In multiple studies, the prevalence of bacteremia in the obstetric population is estimated to be 7.5 per 1,000 admissions, of which 8% to 10% develop sepsis [29–35]. Although gram-negative bacteria are commonly identified in patients with sepsis, gram-positive species have emerged as a predominant pathogen over the last decade [5]. Still, in the obstetric patient with sepsis, many studies have shown aerobic gram-negative rods to be the principal etiologic agents followed by gram-positive bacteria and mixed or fungal infections [16,17,25]. Ledger and colleagues [31] identified gram-negative bacteremia in approximately 3 out of 1000 obstetric admissions. The most frequently recovered organisms were *Escherichia coli*, *Enterococci*, and *Beta-hemolytic streptococci*. The most commonly isolated anaerobes were *Peptostreptococci, Peptococci*, and *Bacteroides*. Blanco and colleagues [29] noted that in 176 bacteremic obstetric patients, *E coli* accounted for 57% of cases with group B streptococci noted in 28%. Endotoxin, a complex lipopolysaccharide present in the cell wall of gram-negative bacteria, is released when the bacteria are lysed, thereby initiating the inflammatory cascade. Gram-positive species cause a similar response by release of exotoxin. In the nonpregnant population, 15% to 20% of severe sepsis cases are polymicrobial in nature [2,7]. Less is known about the obstetric population. However, multiple organisms are commonly implicated in pelvic infection. Box 2 lists the organisms that have been identified in obstetric septic shock.

Pathophysiology

In general, the pathophysiology of sepsis is complex and not completely understood. The severity of the condition is determined not only by the

Box 2. Pathogens implicated in obstetric septic shock

Gram-positive cocci
Pneumococcus
Streptococcus, groups A, B, and D
Staphylococcus aureus

Gram-negative rods
Escherichia coli
Hemophilus influenzae
Klebsiella species
Enterobacter species
Proteus species
Pseudomonas species
Serratia species

Gram-positive rods
Listeria monocytogenes

Anaerobes
Bacteroides species
Clostridium perfringens
Fusobacterium species
Peptococcus
Peptostreptococcus

Fungal species

virulence of the offending organism, but also by a number of host factors, including age, genetic factors, site of infection, and the presence of comorbid conditions. Our understanding primarily comes from critically ill general medical or surgical patients. Specific information relating to pregnant patients is limited as these women are typically not included in most studies because the condition in pregnancy is rare, because of concern for the developing fetus, and because of confounding by the significant physiologic changes associated with pregnancy.

The goal of the host inflammatory response is to localize and eliminate any invading organisms. With microbial infection a complex cascade of events occurs. Macrophages and neutrophils are activated, which in turn directly release inflammatory mediators and activate CD4 T cells. These cells then release proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which have a variety of physiologic functions aimed at containing and eliminating the infection. Cytokines further recruit other macrophages and neutrophils. The cytokines also lead to the generation of oxygen free radicals, production of proteases, induction

of nitric oxide synthase, release of vasoactive hormones, increase in endothelial permeability, activation of the coagulation cascade, and inhibition of the fibrinolytic system. Although these various physiologic responses are important in containing an infection, they can lead to host tissue damage. To minimize this, CD4 T cells are also stimulated to release anti-inflammatory cytokines, which attempt to keep the system in check. It is the failure to control the inflammatory response as well as over-expression of the anti-inflammatory response that leads to the pathologic events associated with sepsis [1,6,36].

Although the inflammatory cascade exerts its effects throughout the body simultaneously, the hemodynamic responses are prominent early in the clinical course. Vasodilation and a decrease in systemic vascular resistance (SVR) occur at least in part because of increased nitric oxide production. The "relative" hypovolemia stimulates the baroreceptors, which in turn activate the sympathetic nervous system, resulting in tachycardia. The tachycardia combined with the decreased SVR results in increased cardiac output. In response to this, vasoconstrictive hormones, such as vasopressin and endothelin, are released. The renin-angiotensin system is also activated. These responses attempt to maintain vascular tone along with increasing the intravascular volume by increased sodium and water reabsorption in the kidneys [36].

The proinflammatory cytokines TNF-α and IL-1 also have procoagulant effects. The coagulation cascade is activated by TNF-α–induced release of tissue factor from endothelial cells. This ultimately results in thrombin production. Thrombin along with thrombomodulin activates protein C, which acts to inhibit coagulation. By down-regulating thrombomodulin, TNF-α inhibits this anticoagulation balance in the system. Fibrinolysis is also decreased by a TNF-α– and IL-1–stimulated increase in PAI-1, an inhibitor of fibrinolysis [1].

Complex physiologic adaptations happen during pregnancy and they must be understood when managing the pregnant patient with sepsis. In the cardiovascular system, the heart rate increases, peripheral vasodilation occurs, leading to a decrease in blood pressure and an increase in cardiac output [37]. These changes may not only mask the initial presentation of sepsis, but can further aggravate decreased organ perfusion seen in the septic patient [1,36]. Myocardial depression seen in advanced sepsis further complicates the situation [6].

Red cell mass and plasma volume both increase in pregnancy with a greater increase in the latter resulting in red blood cell dilution and thus anemia. Albumin and protein concentrations also decrease, likely because of the same mechanism. The decrease in albumin and protein concentrations results in a lower colloid osmotic pressure, leading to increased interstitial fluid [37]. These physiologic alterations are generally protective in pregnancy. However, in certain pathologic states, pregnant patients are more susceptible to develop pulmonary edema [1,38].

Changes in the respiratory system include increased tidal volume associated with a decrease in residual volume and functional reserve capacity. There is also a slight decrease in total lung capacity. The respiratory rate may increase slightly. The vital capacity is unaffected. Minute ventilation increases, leading to a decrease in $PaCO_2$ and a compensatory decrease in serum bicarbonate to maintain a normal pH. The net result is a compensated respiratory alkalosis. These physiologic adaptations are beneficial in a normal pregnancy. However, in the setting of sepsis and/or respiratory failure, these changes predispose the patient to rapid declines in oxygenation and decreased ability to compensate or buffer a metabolic acidosis [38].

In the kidneys, the renal plasma flow and the glomerular filtration rate (GFR) increase, resulting in decreased serum levels of blood urea nitrogen and creatinine. Normal nonpregnant serum levels of these metabolites may suggest mild renal compromise in the pregnant patient. The renal collecting system dilates because of smooth muscle relaxation. The growing uterus may add to the dilation by mechanical obstruction of the ureter. This leads to urinary stasis and an increased incidence of asymptomatic bacturia, which in turn is associated with an increased risk of pyelonephritis if left untreated [37,38].

Throughout the gastrointestinal tract, smooth muscle tone is decreased, leading to increased esophageal reflux, decreased gastric emptying, and delayed intestinal transit. Pregnant patients are thus more susceptible to aspiration pneumonia [38]. Transaminases and bilirubin values are slightly decreased in pregnancy, while alkaline phosphatase levels are increased due to placental production. Lactate dehydrogenase levels are unchanged. Understanding these biochemical changes is important when trying to interpret laboratory values in the septic obstetrical patient [37].

White blood cell counts increase throughout pregnancy while platelet counts decrease. A number of changes occur in the clotting cascade as well. Factors VII, VIII, IX, X, and XII; von Willebrand's factor; and fibrinogen all increase, while protein S decreases. Protein C and antithrombin III remain unchanged. There is also a decrease in the activity of the fibrinolytic system mediated by an increase in the plasminogen activator inhibitors 1 and 2 (PAI-1 and -2). As a result of the increased clotting factors along with the decreased anticoagulant activity and decreased fibrinolysis, pregnancy is associated with an increased risk of thrombosis [39,40]. The net effect is a procoagulant state leading to an increase in the risk of thrombosis and the potential exacerbation of disseminated intravascular coagulation (DIC) [1].

Many of these changes are further accentuated during labor and delivery. Heart rate and respiratory rates may increase with the exertion and stress of labor. Intravenous fluids are typically given. White blood cell counts are even more increased. Epidural use is common and prolonged use is associated with a rise in maternal temperature [41]. Large fluid shifts and significant blood loss can be seen with delivery. Cesarean delivery is

common today and is a factor associated with a greater risk of hemorrhage, infection, and thrombosis [20,42]. Diagnosis and management during labor and delivery can thus be particularly challenging.

Acute respiratory distress syndrome (ARDS) is a severe and life-threatening complication seen in sepsis. Although ARDS has multiple causes, not all of which are infection-related, the most common cause is reported to be sepsis. Pneumonia has been reported to be the most common infection associated with ARDS. The condition has also been associated with pyelonephritis and chorioamnionitis/endomyometritis [27,38,43]. ARDS-complicating sepsis is associated with maternal mortality rates ranging from 10% to 50% [27,43,44]. Some of this wide variation is due to the small number of patients in the reported case series. Generally, the mortality rate associated with ARDS appears to be lower in pregnant patients than in the nonpregnant population [38].

Although hemodynamic compromise is a hallmark of severe sepsis and the physiologic changes occurring during pregnancy can theoretically aggravate the condition, significant hemodynamic instability is not as common as respiratory failure [27]. Reports describing sepsis complicated by renal failure in pregnancy are limited and difficult to separate from reports about renal failure complicating other conditions. The mortality rate in these patients tends to be lower than would be expected by the severity of the patient's condition [27]. This is in contrast to the nonpregnant population where the combination of sepsis and renal failure is associated with a mortality rate as high as 70% [36].

Because of the procoagulant state associated with sepsis, DIC is not uncommon in severe sepsis and frequently complicates patients with multiorgan failure. It can lead to microthrombi in the glomerulii, resulting in renal failure. These two complications together–DIC and renal failure–are associated with a mortality rate of 75% among nonpregnant patients. In the pregnant patient, the combination of DIC and respiratory failure in sepsis is associated with increased maternal mortality [44]. Microthrombi can also occur in the liver, leading to failure. This failure can decrease protein production, further decreasing colloid oncotic pressure and aggravating DIC because of decreased production of clotting factors [15]. In the gastrointestinal tract, tissue hypoxia can lead to bleeding and pancreatitis [27].

Multiorgan failure in nonpregnant patients with sepsis is associated with mortality rates in excess of 70%. The highest rates have been associated with involvement of three or more organ systems [5,28]. Other factors influencing survival in patients with multiorgan failure in this population are age, associated comorbid medical conditions, and duration of the organ failure [28]. There appears to be an increased risk of mortality in the pregnant population as well. However, it is not of the same magnitude [27,44]. Acute Physiology and Chronic Health Evaluation (APACHE II) scores are used to estimate risk of mortality in intensive care unit patients. The scores are not reliable for septic pregnant patients and tend to overestimate their

risk of mortality [15]. Therefore, counseling regarding prognosis and decisions regarding therapy should be based on the presence of multiorgan failure, the presence of comorbid conditions, and the potential to identify and treat the source of infection [15].

Management

Early recognition and prompt, aggressive therapy is crucial to reduce maternal and fetal morbidity and mortality in women with suspected sepsis. To help standardize effective resuscitation strategies for persons with suspected sepsis, the Surviving Sepsis Campaign was initiated in October 2002. Subsequently, the working group has expanded and revised its recommendations [45,46]. Therapeutic bundles have been developed for early resuscitation (0–6 hours) and management (6–24 hours). The bundles were developed using evidence-based medicine principals. Table 2 reviews the strength of the evidence and the basis of the recommendations. Fig. 1 is an overview of early goal directed therapy (EGDT). Implementation of EGDT improves survival and is cost-effective in a variety of settings [47]. The following is a summary of the recommendations of the Surviving Sepsis Campaign with some caveats as they apply to the obstetrical population.

Diagnosis

A thorough history and physical examination is required to evaluate potential sources of infection. Ideally, cultures should be obtained before instituting antibiotic therapy to identify suspected pathogens, to monitor effectiveness of therapy, and to guide appropriate use of antibiotics [45].

Table 2
Evidence-based medicine guidelines rating systems

Grade	Basis of Grade
Recommendations	
A	Supported by at least two level I investigations
B	Supported by at least one level I investigation
C	Supported by level II investigations only
D	Supported by at least one level III investigation
E	Supported by level IV or V evidence
Evidence	
I	Large randomized control trial with clear-cut results
II	Small, randomized trials with uncertain results
III	Nonrandomized, contemporaneous controls
IV	Nonrandomized, historical controls, and expert opinion
V	Case series, uncontrolled studies, and expert opinion

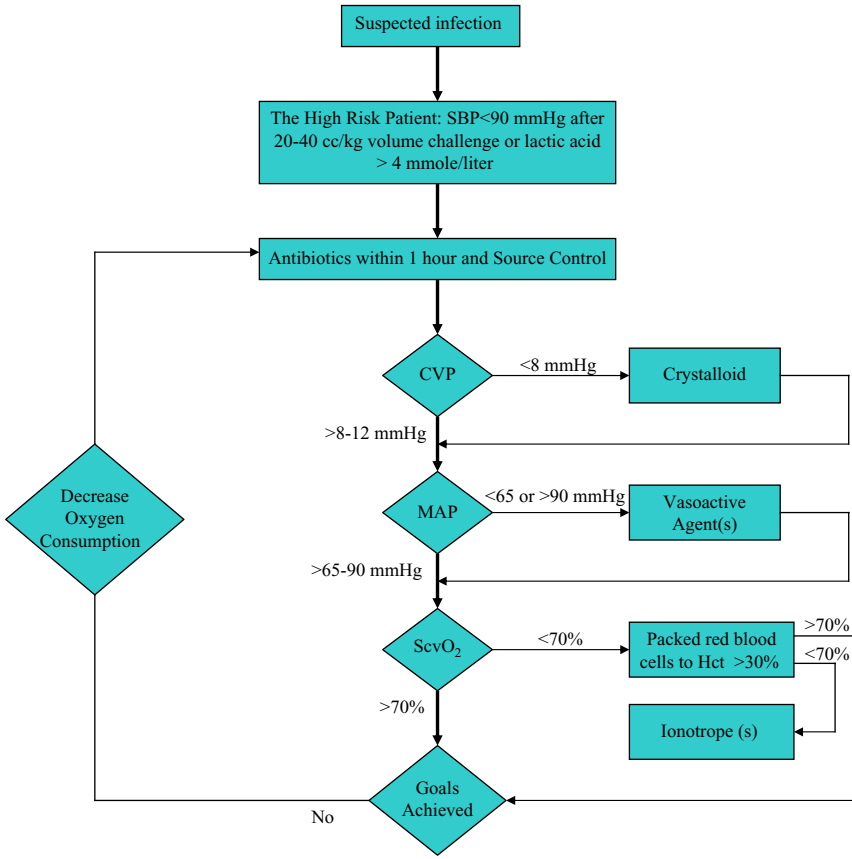

Fig. 1. Overview of early goal directed therapy. CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation; SBP, systolic blood pressure. (*From* Otero RM, Nguyen HB, Huang DT, et al. Early goal-directed therapy in severe sepsis and septic shock revisited concepts, controversies, and contemporary findings. Chest 2006;130(5): 1579–95; with permission.)

A grade D recommendation supports the practice of obtaining two blood cultures be obtained with at least one drawn peripherally and one drawn through a central access device if available. If the clinical situation warrants it, cultures of additional sites, including those from urine, wounds, respiratory secretions, and cerebrospinal fluid, should be performed. In the gravid woman with preterm labor, ruptured membranes or suspected chorioamnionitis, amniocentesis should be performed. In addition to culture, the amniotic fluid can be sent for Gram stain, white count, and glucose levels [48]. The results of these markers are available within hours, whereas culture results usually take days. In selected hospitals, evaluation of the proinflammatory cytokines (TNF-α, IL-1 beat, and IL-6) may be available [49,50].

Cervical cultures and/or placental cultures may also be useful. In postpartum women, transcervical endometrial sampling has been well described [51]. In the authors' experience, endometrial cultures obtained transcervically are frequently contaminated by normal vaginal flora, particularly anaerobes, and are not particularly helpful.

Initial resuscitation

Once severe sepsis is suspected, EGDT has been shown to improve survival, according to grade B evidence. Grade B evidence also suggests that during the first 6 hours of resuscitation (early therapy), the goals should include all of the following: central venous pressure (CVP) of 8 to 12 mm Hg, mean arterial pressure of greater than or equal to 65 mm Hg, urine output greater than 0.5 mL/kg/h, and central venous (superior vena cava) or mixed venous oxygen saturation of greater than or equal to 70% (Table 3) [45,52]. These goals were established in nonpregnant patients. Either crystalloids or colloids can be used for volume expansion, according to grade C evidence. Crystalloids have a larger volume of distribution and may result in more edema than colloids [45]. Large amounts of fluid (6–10 L) may be required initially [47]. Blood pressure, pulse rate, urine output, oxygen saturation, and fetal status can be used to judge clinical response to fluid challenges.

CVP and pulmonary artery wedge pressure measure cardiac filling pressures. Their use in general is limited because of errors in routine measurement and confounding from use of mechanical ventilation and increased abdominal pressure [45,53]. Their use in pregnancy has been widely described in obstetrical patients [54–57]. In gravid women, the CVP and pulmonary artery wedge pressures are not reliably related [54,57,58]. CVP levels may be normal in gravidas with left ventricular dysfunction or pulmonary edema. In contrast, the CVP may be elevated in women with no evidence of pulmonary edema [54,57,59]. No studies specifically evaluate

Table 3
EGDT goals and normal values in pregnancy

Measures	Resuscitation Goals	Normal third-trimester physiologic values[a]
Central venous pressure	8–12 mm Hg	4–10 mm Hg
Mean arterial pressure	≥65 mm Hg	84–96 mm Hg
Urine output	>0.5 mL/kg/h	Minimum 0.5 mL/kg/h
Mixed venous oxygen saturation	>70%	>80%[b]
Heart rate	Decreasing in response to treatment	83 (±10) beats/min

[a] Normal values in pregnancy. *Data from* Norwitz ER, Robinson JN, Malone FD. Pregnancy-induced physiologic alterations. In: Dildy GA III, Belfort MA, Saade G, et al, editors. Critical care obstetrics. 4th edition. Malden (MA): Blackwell Science; 2004. p. 19–42.

[b] Dependent upon cardiac output, fraction of inspired oxygen, and oxygen consumption.

Data from Refs. [45,52,47] for EGDT goals and [37] for normal values in pregnancy.

the use of CVP in obstetrical patients with sepsis. Nonetheless, the authors believe it is reasonable in the setting of suspected sepsis to use CVP measurements to guide initial fluid resuscitation in women with low CVP and evidence of hypoperfusion. Consideration may be given to using a pulmonary artery catheter in gravid, septic women with preeclampsia and/or cardiomyopathies where volume expansion may increase the risk of pulmonary edema and/or ARDS [54,57,59,60].

Patients receiving mechanical ventilation may benefit from a higher targeted CVP pressure of 12 to 15 mm Hg [45]. This may also be required in patients with increased abdominal pressure, which has increasing relevance with advancing gestation. Displacement of the uterus using lateral tilt or use of a hip roll minimizes aorto-caval compression and improves venous return to the heart.

Grade B evidence suggests that, if patients do not respond to volume expansion and if a central venous oxygen saturation or mixed venous oxygen saturation of greater than or equal to 70% is not achieved within 6 hours of diagnosis, transfusion with packed red blood cells to achieve a hematocrit of greater than or equal to 30% and/or administration of a dobutamine infusion (maximum of 20 μg/kg/min) is indicated. If time allows, type-specific, CMV-safe (leukoreduced) transfusions are preferred. There is no contraindication to using inotropes and/or vasopressors in gravid patients. Inotropes and vasopressors are administered by standardized protocols. The infusions are titrated upward to achieve the desired increase in blood pressure and/or cardiac output. Dobutamine, the first choice inotrope for patients with sepsis who have evidence of low cardiac output despite adequate filling pressures [45,53,61–64], is a potent inotrope with modest vasodilatory properties. Dobutamine increases cardiac contractility and improves cardiac output without a significant increase in heart rate. In patients with severe shock, vasopressors may be required to correct hypotension. The most commonly used vasopressors are dopamine, norepinephrine, epinephrine, and phenylephrine. The two agents specifically recommended in the Surviving Sepsis Guidelines for sepsis with refractory hypotension are dopamine and norepinephrine [45]. Dopamine increases mean arterial pressure and cardiac output because of an increase in stroke volume and heart rate. Norepinephrine improves mean arterial pressure by its vasoconstrictive properties. Dopamine and norepinephrine can reduce blood flow to the periphery, the gut, and the uterus. Thus, close monitoring is required. Vasopressin may be considered in patients with refractory shock. In the setting of shock, vasopressin is administered at a rate of 0.01 to 0.04 U/min [45,63].

Antibiotic therapy

Grade D evidence supports the initiation of antibiotic therapy as soon as possible. The initial selection of empiric antibiotics is based on the patient's

history, known drug allergies, physical examination, underlying disease, and clinical condition. It is essential that physicians are knowledgeable regarding community and hospital-specific antibiotic resistance patterns when initiating empiric therapy. Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism or organisms are identified and their susceptibilities defined [45]. Once a suspected source or pathogen is identified, restricting the number of antibiotics is appropriate. However, most patients with sepsis or septic shock have negative blood cultures [45]. This may be more common in pregnancy where antibiotic use is high [21,23,65]. If a positive blood culture is identified in the setting of suspected obstetrical sepsis, caution should be used in narrowing antibiotic coverage before recovery. The majority of obstetrical infections are polymicrobial [7,24,29,34,66]. One investigator hypothesized that in an obstetrical population, ''the microbe found in blood culture represent only the tip of an iceberg of pathogens at the original site of infection'' [18,66]. Using clinical findings and other culture results, the clinician ultimately needs to decide whether to continue broad-spectrum therapy, narrow therapy, or stop therapy. Consultation with microbiology and infectious disease specialists is recommended.

The task of selecting the appropriate antibiotic regimen in pregnancy is further complicated by several factors. Pharmacokinetic studies of antibiotic dosing in pregnancy are limited. All of the physiologic adaptations to normal pregnancy can have an impact drug availability, concentration, and effectiveness [21,67–69]. In particular, the increased volume of distribution and changes in absorption and distribution can affect drug levels. In general, antibiotics that are primarily eliminated by renal excretion result in lower serum levels during pregnancy as compared with those for the nonpregnant patient. The half-life of certain antibiotics is shorter. Transplacental passage occurs to some degree for all antibiotics according to the physicochemical properties of the drug. When choosing antibiotic regimens, attempts should be made to maximize effectiveness and minimize fetal harm. However, there may be specific cases where the ''best'' drug for the mother may not be ''safe'' for the fetus. In these rare situations, consultation with maternal–fetal medicine specialists is strongly recommended. Most antibiotics are safe to use in pregnancy. A comprehensive review of specific antibiotics in pregnancy is beyond the scope of this article. In general, the classes of antibiotics to avoid if a suitable alternative exists are tetracyclines, fluoroquinolones, and erythromycin estolate.

In septic pregnant women with obstetrical infections, most infections are the result of mixed flora, including gram positives, gram negatives, and anaerobes. Therefore, the approach to antibiotics is generally to administer broad-spectrum antibiotics using two to three agents. The most commonly cited combination is ampicillin, gentamicin, and clindamycin or metroniadazole [23,68]. There is limited data on efficacy and safety of once-daily dosing of gentamicin during pregnancy. Once-daily or

twice-daily dosing options are preferred postpartum [67]. Given the increased volume of distribution and clearance, drug levels are indicated in critically ill patients.

Source control

Once resuscitative measures are initiated, evaluation for a specific focus of infection that may be amenable to source control measures is essential. Transporting unstable patients to radiology may not be safe. Ultrasound at the bedside can be an invaluable tool. It is recognized, based on grade E evidence, that emergent intervention for necrotizing soft tissue infection or intestinal ischemia is essential to reduce morbidity and mortality [45]. Most obstetrical infections are amenable to source control measures. In women with chorioamnionitis, delivery should be accomplished as soon as possible, regardless of the gestational age. Obstetricians must use clinical judgment in determining route of delivery. Vaginal delivery is preferred in the patient who has a favorable cervix and/or is laboring spontaneously. If a long induction of labor is anticipated, cesarean may be a better choice in the hemodynamically stable patient. General anesthesia is necessary in cases where urgent delivery is required because of fetal distress that is not responsive to maternal resuscitation or in cases where cesarean is indicated and the mother is hemodynamically unstable [41]. Intubation of the gravid patient can be particularly difficult because of airway edema and anatomical challenges. Intubation of the gravid patient is also associated with an increased risk of gastric aspiration [70]. Skilled anesthesiologists familiar with the particular challenges of pregnancy should be present for intubation and surgery. Preoxygenation and rapid-sequence induction with cricoid pressure are essential to control the airway and to reduce the risk of aspiration [70]. Patients who develop respiratory failure and sepsis following a seizure or intubation should receive antibiotic coverage for potential aspiration pneumonia.

Adjunctive measures

The use of corticosteroids in sepsis is controversial. The Surviving Sepsis Campaign endorsed the use of intravenous corticosteroids (hydrocortisone 200–300 mg/d for 7 days in three to four divided doses or by continuous infusion) in patients with septic shock who require vasopressors. This recommendation is supported by grade A evidence. [45]. Hydrocortisone is not contraindicated in pregnancy. Other investigators recommend a corticotropin stimulation test to identify patients who would benefit from corticosteroids [71]. Cortisol levels and response to corticotropin may be influenced by pregnancy. Therefore, the authors recommend empiric therapy with corticosteroids in the septic gravid patient. In cases where preterm delivery of a viable fetus is likely, antenatal corticosteroid administration with betamethasone (12 mg intramuscularly every 24 hours times

two) or dexamethasone (6 mg intramuscularly every 12 hours times four) is also recommended [72].

The use of recombinant human activated protein C is also controversial. Patients at high risk for death (multiorgan failure, septic shock, or sepsis-induced ARDS) are potential candidates, according to grade B evidence [45]. Recombinant human activated protein C increases the risk of bleeding and is contraindicated in patients with active bleeding or recent surgery (within 30 days) [45,73,74]. Its use in obstetrical patients is limited to case reports [75,76]. Pregnancy should not be an absolute contraindication to its use. However, most septic gravid women are not candidates because of threatened labor or recent cesarean [23]. The implications for the fetus and newborn are largely unknown.

Thresholds for transfusion following initial resuscitation have not been established in pregnant patients. In general, a transfusion threshold of 7.0 to 9.0 g/dL is reasonable, according to grade B evidence. This may not be sufficient for the antepartum patient with high oxygen consumption and real potential for blood loss due to delivery. In an individual patient, the decision to transfuse should be based on maternal and fetal status. The fetal heart rate tracing and/or biophysical profile may be used as an indirect measure of maternal oxygen delivery and uterine blood flow. If there is evidence of non-reassuring fetal heart rate and the patient has not responded to fluid resuscitation, mothers should be transfused liberally. The benefit to correcting clotting abnormalities in patients with no evidence of bleeding is also unclear [45]. A patient with platelet levels of less than $5000/mm^3$ should be transfused regardless of apparent bleeding [45]. In patients who are candidates for surgery or invasive procedures, coagulation defects should be corrected and platelets transfused to a level greater than $50{,}000/mm^3$ preoperatively [45].

Patients with sepsis are at high risk for sepsis-induced acute lung injury and ARDS. Initiation of lung-protective ventilation is important. According to recommendations based on grade B evidence, ''low'' tidal volumes should be used (6 mL/kg of predicted body weight) while maintaining end-inspiratory plateau pressures less than 30 cm H_2O (grade B) [45]. To accomplish these goals, permissive hypercapnia (allowing $Paco_2$ ''above normal'') may be necessary. These goals were established in nonpregnant patients. If introduced slowly, increases in carbon dioxide are well tolerated in the absence of raised intracranial pressure or a severe metabolic acidosis [23,70,77–79]. In pregnancy, a normal $Paco_2$ is 26 to 32 mm Hg and serum bicarbonate is 18 to 21 mEq/L [37]. The respiratory alkalosis associated with pregnancy is essential for diffusion of carbon dioxide to occur from the fetus to the mother. Over time, the fetus gains the capacity to increase bicarbonate production in the kidneys and adapt to ''respiratory acidosis.'' Mechanical ventilation with low tidal volumes is probably well tolerated in most cases. However, permissive hypercapnia for prolonged periods may result in fetal acidosis. If hypoxia is also present, the potential for fetal

myocardial dysfunction and death exists. Fetal acidosis can be identified by the presence of late decelerations on fetal heart monitoring, depressed biophysical profile score, or abnormal Doppler studies. Ultimately, the only way to improve fetal status short of delivery is to improve maternal status. Attempts to minimize respiratory complications are essential to improve fetal and neonatal outcome. A comprehensive review of respiratory strategies to manage ARDS and weaning from mechanical ventilation is beyond the scope of this article. Several important references are included for review [23,70,77–79]. Unfortunately, to the authors' knowledge, all of the randomized trials evaluating respiratory therapies excluded pregnant women. Therefore, definitive recommendations are limited.

Patients who require mechanical ventilation require anxiolytics, analgesics, sedatives, and/or neuromuscular blockade [23,45,77–79]. These classes of drugs can all cross the placenta and may result in decreased fetal heart rate variability and depressed fetal movements [80,81]. Fetal assessment may be difficult. Attempts to minimize sedation and/or paralysis are recommended to avoid complications and to assess neurologic status [45].

Hyperglycemia is a common complication of sepsis. Insulin infusions should be used to maintain blood glucose less than 150 mg/dL , according to grade D evidence [45]. In surgical patients, maintaining glucose values between 80 and 110 mg/dL improved survival rates [74]. These target values are appropriate for pregnant women. Frequent monitoring to avoid hypoglycemia and ketosis is important.

Septic patients are at risk for thrombosis. This risk is magnified in pregnancy and in the postpartum period [40]. All pregnant women should wear external compression stockings or intermittent compression devices. Limited data exist regarding the optimal mechanical device in pregnancy. Recommendations based on grade A evidence suggest that patients without evidence of coagulopathy should receive prophylaxis with unfractionated heparin, if delivery is likely to occur within 12 hours of administration, or low molecular weight heparin, if delivery is not anticipated that soon [40,41]. Stress ulcer prophylaxis with H2 receptor inhibitors should be prescribed, according to grade A evidence [45]. These agents are not contraindicated in pregnancy. Nutritional therapy should be administered enterally, if possible [82]. In patients with contraindication to tube feeding, hyperalimentation can be administered peripherally or centrally. Increased caloric and nutritional demands in pregnancy must be met. Consultation with nutritionists helps develop an individualized plan of care.

Fetal monitoring and obstetrical interventions

In general, women with obstetrical sepsis are young and healthy. Aggressive intensive care should be employed with the goal of optimizing maternal and fetal health. Interventions that improve maternal hemodynamic stability and oxygen delivery to the fetus should result in improved maternal and

fetal outcomes. Decisions regarding timing of delivery and interventions to prolong pregnancy using tocolytics are complex. For pregnancies presenting before viability, optimizing maternal health is paramount. Pregnancies near term can be delivered once the maternal status is stable. For pregnancies between 24 and 32 weeks' gestation, decisions should be made based on maternal prognosis and family desires. Operative intervention on behalf of the fetus in an unstable mother increases maternal morbidity and mortality. Perimortem cesarean is an option. However, the neonatal outcomes depend on several important factors, including timing from arrest to delivery, fetal reserves, and the presence of fetal infection [80].

Summary

Sepsis is a leading cause of death in pregnancy, particularly in the developing world, and results in significant perinatal mortality. These deaths occur despite the younger age of pregnant patients, the low rate of comorbid conditions, and the potential for effective interventions that should result in rapid resolution of illness. To date, no "evidence-based" recommendations are specific to the pregnant patient who is critically ill or septic. Until pregnant women are included in therapeutic trials in the intensive care unit, particularly in the setting of sepsis, therapy will remain empiric and anecdotal with the potential for excess morbidity and mortality. Optimal care for the septic patient requires a multidisciplinary team with expertise in obstetrics, maternal–fetal medicine, critical care, infectious disease, anesthesia, and pharmacy. Coordination of care and good communication amongst team members is essential. Incorporation of EGDT for suspected sepsis into obstetric practice would seem to be essential to optimize maternal and neonatal outcomes.

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Thromboembolism in Pregnancy

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Of the potential clinical emergencies an obstetrician/gynecologist will confront, venous thromboembolism, which includes deep venous thrombosis and pulmonary embolus, has been associated with the highest risk for maternal and fetal morbidity and mortality. In the most recent Centers for Disease Control and Prevention data available, thromboembolism was shown to be responsible for 19.6% of pregnancy-related deaths in the United States as compared with 17.2% for hemorrhage [1]. Venous thromboembolism is estimated to complicate between 0.5 and 1 in 1000 pregnancies per year in the United States [2–10]. More recent evidence suggests that the risk is evenly divided among each of the trimesters [3,11], with an even higher risk in the postpartum period [12,13]. In addition, cesarean delivery confers a five- to ninefold higher risk over vaginal delivery [13,14].

Essentially, every pregnant patient is at risk for a venous thromboembolic event and the risk is estimated to be five- to 10-fold higher than for the nonpregnant patient. From a teleological perspective, the adaptation of the maternal hemostatic system to pregnancy (to prevent hemorrhage at the time of delivery) predisposes women to an increased risk of thromboembolism. Particular women seem to be at yet an even higher risk for venous thromboembolism in pregnancy. These women include multiparous patients, obese gravidas, women who have postpartum endometritis, and those with a history of venous thromboembolism or underlying thrombophilia. It is estimated that the recurrence risk in pregnancy is between 5% and 16% for women with a history of a venous thromboembolism [11,15] and may be related to the presence or absence of underlying maternal thrombophilia [16]. Others have demonstrated a 7.5% recurrence risk in pregnancy if the first venous thromboembolism was unprovoked, related to pregnancy, or related to use of oral contraceptives [17]. In contrast, there

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was no recurrence if the first venous thromboembolism was related to other transient risk factors [17]. Therefore, one must consider routine thromboprophylaxis in selected obstetrical patients [15,17–19].

However, despite prophylaxis, venous thromboembolism can occur in pregnancy and clinicians must have a heightened surveillance for this potential emergency. Diagnostic tests must be readily available and there should be no delay in initiating treatment when appropriate [20]. Treatment goals should include preclusion of further thrombus propagation and pulmonary embolism and prevention of recurrent venous thromboembolism and long-term complications, including venous insufficiency, pulmonary hypertension, right-sided heart failure, and "post-thrombotic syndrome" [21].

This article focuses on the clinical emergency posed by deep venous thrombosis and pulmonary embolism in pregnancy. The article begins with a brief review of the physiologic changes that predispose pregnant women to a thrombotic event. The article then reviews the signs and symptoms that should alert the clinician to the possibility of a thromboembolic event, and then presents an algorithm outlining specific diagnostic tests that guide the clinician to the correct diagnosis. The article then reviews recommended treatment regimens while attempting to resolve some of the controversies regarding optimal anticoagulation therapy in pregnancy. The article ends with a brief look at future directions, including innovative diagnostic tests that may be safer and easier to perform than current ones.

Physiology and pathophysiology of hemostasis in pregnancy

The adaptation of the maternal hemostatic system to pregnancy predisposes women to an increased risk of venous thromboembolism. Pregnancy produces the components of Virchow's triad, including an increase in vascular stasis, changes in the coagulation system, and vascular injury. Other risk factors for thrombosis involve inherited thrombophilias, including mutations in the factor V Leiden and prothrombin genes; deficiencies in protein C, protein S, and antithrombin III; and acquired maternal thrombophilias, such as the condition known as antiphospholipid antibody syndrome [12,22,23]. It is estimated that an underlying thrombophilia is present in at least 50% of those who develop a deep venous thrombosis or pulmonary embolism in pregnancy [23]. Therefore, a thorough understanding of the coagulation and fibrinolytic systems and their inhibitors with specific relation to pregnancy is essential.

Physiology

Platelet aggregation and vasoconstriction are the initial responses to hemorrhage following vascular disruption and endothelial damage. By limiting the size of the requisite plug required to obstruct blood flow through the vascular defect, vasoconstriction limits blood flow to promote platelet

plug formation. Integrins bound to platelet membranes adhere to subendothelial laminin, fibronectin, and vitronectin, and circulating von Willebrand's factor mediates platelet attachment by binding to both platelet GPIb/IX/V receptors and subendothelial collagen in damaged vessels [24]. Platelet adhesion then triggers calcium-dependent protein kinase C activation, which induces thromboxane A2 (TXA2) synthesis and platelet granule release. The α-granules contain von Willebrand's factor and various clotting factors while dense-granules contain adenosine diphosphate and serotonin, which together with thromboxane A2 (TXA2), exacerbate vasoconstriction and platelet activation. The latter process activates platelet GPIIB/IIIa receptors to promote aggregation by forming inter-platelet fibrinogen, fibronectin, and vitronectin bridges [25]. Epinephrine, arachidonic acid, and platelet activating factor can also activate platelets.

Tissue factor, a glycoprotein bound to cell membranes, is the primary initiator of hemostasis and the coagulation cascade. Tissue factor is expressed constitutively by epithelial, stromal, and perivascular cells throughout the body. Tissue factor is also expressed, particularly in pregnancy, in endometrial stromal cells and uterine decidua [26,27]. Clotting is initiated by the binding of tissue factor to factor VII after vascular injury and can be externally activated by thrombin, factor IXa, factor Xa, or factor XIIa [26,27]. The coagulation cascade is initiated and, ultimately, thrombin cleaves fibrinogen to fibrin monomers, which self-polymerize and are cross-linked via thrombin-activated factor XIIIa.

The counterpoise of the hemostatic system is the anticoagulant system. The tissue factor pathway inhibitor is the first agent in this system and acts on the factor-Xa–tissue factor–factor-VIIa complex to inhibit tissue-factor–mediated clotting [28]. However, factor XIa can bypass this block and sustain clotting for some time. As a result, additional endogenous anticoagulant molecules are required to avoid thrombosis, including activated protein C, protein S, and protein Z.

Fibrinolysis is initiated by tissue-type plasminogen activator (tPA), which cleaves plasminogen to generate plasmin. Plasmin, in turn, cleaves fibrin into fibrin degradation products (FDPs). These FDPs can also inhibit thrombin action, a favorable result when limited, but when generated in excess can contribute to disseminated intravascular coagulation. Inhibitors of fibrinolysis include α-2-plasmin inhibitor and type-1 and -2 plasminogen activator inhibitors (PAI-1 and -2), which inactivate tPA. The endothelium and uterine decidua are primary sources of PAI-1, while the placenta produces PAI-2 [29]. The thrombin-activatable fibrinolysis inhibitor modifies fibrin to render it resistant to inactivation by plasmin [30].

Pathophysiology

Changes in decidual and systemic hemostatic systems occur in pregnancy, likely to meet the hemorrhagic challenges poised by implantation,

placentation, and the third stage of labor. Decidual tissue factor and PAI-1 expression increase in response to progesterone, providing a potent local system of hemostasis to prevent hemorrhage. In addition, levels of placental PAI-2, circulating levels of fibrinogen, and levels of factors VII, VIII, IX, X, and XII and of von Willebrand's factor increase considerably in gestation [29–32]. While these mechanisms serve to generally prevent puerperal hemorrhage following significant uterine vascular trauma at the time of delivery, they predispose to thrombosis, a tendency aggravated by maternal thrombophilias.

Inherited thrombophilias refer to a genetic tendency to venous thromboembolism. Disorders include the factor V Leiden and prothrombin gene G20210A mutations, antithrombin deficiency, and protein C and S deficiencies. Acquired thrombophilias include the antiphospholipid antibody syndrome, which is characterized by the presence of antibodies directed against plasma proteins bound to anionic phospholipids.

The antiphospholipid antibody syndrome is responsible for 14% of venous thromboembolism in pregnancy [33,34]. The lifetime prevalence of arterial or venous thrombosis is approximately 30%, with an event rate of 1% per year [35]. The risks of venous thromboembolism are highly dependent upon the presence of other predisposing factors, including pregnancy, estrogen exposure, surgery, and infection. There is a 5% risk of a thrombotic event in pregnancy even with prophylaxis [36].

The inherited thrombophilias are a heterogeneous group of genetic disorders often associated with a personal or family history of venous thromboembolism. Such a history is an important modifier of projected risk. Thrombophilias are divided into high-risk thrombophilias and low-risk thrombophilias based on the overall risk of venous thromboembolism. Because of the association between thrombophilias and recurrent venous thromboembolism in pregnancy, the authors routinely obtain a comprehensive thrombophilia evaluation on patients diagnosed with venous thromboembolism in pregnancy. However, because functional levels of protein C, protein S, and antithrombin are altered in pregnancy, abnormally low levels should be confirmed 6 weeks postpartum before a diagnosis of a deficiency is made.

Diagnosis of deep vein thrombosis

Clinicians must have a high baseline index for suspicion of deep venous thrombosis in pregnancy because many of the common clinical signs and symptoms, such as lower extremity edema, are also common findings in normal pregnancy. A timely diagnosis of deep venous thrombosis is crucial because up to 24% of patients with untreated deep venous thrombosis will develop a pulmonary embolism [37]. A life-threatening pulmonary embolism usually originates from a clot in the deep veins of the pelvis and legs, including the internal iliac, femoral, and popliteal veins [7].

Common clinical features of deep venous thrombosis include lower extremity edema, pain, difficulty with ambulation, warmth, and erythema. However, the diagnostic sensitivity of these clinical signs and symptoms is at best 50% and the diagnosis of deep venous thrombosis is confirmed in less than a third of patients with these complaints [38,39]. Therefore, patients who present with any of these complaints warrant a full diagnostic workup. Diagnostic tests for evaluation of suspected deep venous thrombosis include D-dimer assays, venous color Doppler ultrasound, magnetic resonance venography, CT, and, less commonly, contrast venography [40,41].

D-dimer assays

D-dimer assay testing may be used as a screening test and/or in combination with venous ultrasound to facilitate diagnosis and prediction of a thromboembolic event. D-dimer is a product of the degradation of fibrin by plasmin. Therefore, elevated levels indicate increased thrombin activity and increased fibrinolysis following fibrin formation [42]. The assay employs monoclonal antibodies to detect D-dimer fragments. Commercial assays available include at least three accurate and reliable products: two rapid enzyme lined immunosorbent assays and a rapid whole-blood assay.

Though quite reliable in the exclusion of deep venous thrombosis in the nonpregnant patient [43,44], the value of D-dimer testing in pregnancy is somewhat controversial because D-dimer levels increase with gestational age and, in the postpartum period, even in the absence of venous thromboembolism [45–48]. This makes it difficult to assign a ''normal'' cutoff. Most studies report a sensitivity ranging from 85% to 97% but a specificity of only 35% to 45% [21,49]. In addition, there appears to be a wide variation in D-dimer assay results depending on the specific test used. These factors have led some investigators to conclude that the literature does not support the general use of D-dimer assays as a stand-alone test for the diagnosis of deep venous thrombosis in pregnancy [50]. However, others argue that D-dimer testing is likely to have a higher negative predictive value in pregnancy and therefore it has a role in the initial triage of patients with suspected deep venous thrombosis. In patients with a negative D-dimer assay and a low clinical probability of deep venous thrombosis, further testing may be unnecessary (Fig. 1). Several elaborate scoring systems (not validated in pregnancy) have been proposed to help classify patients as either low or high risk for deep venous thrombosis [51,52]. Another approach is to categorize patients as low risk if there is another reasonable clinical explanation for their symptoms and there are no major risk factors, such as recent major abdominal surgery, late pregnancy and postpartum, varicose veins, malignancy, and reduced mobility [53]. In addition, there may be a role for D-dimer testing to identify women at high risk for recurrent venous thrombosis [42].

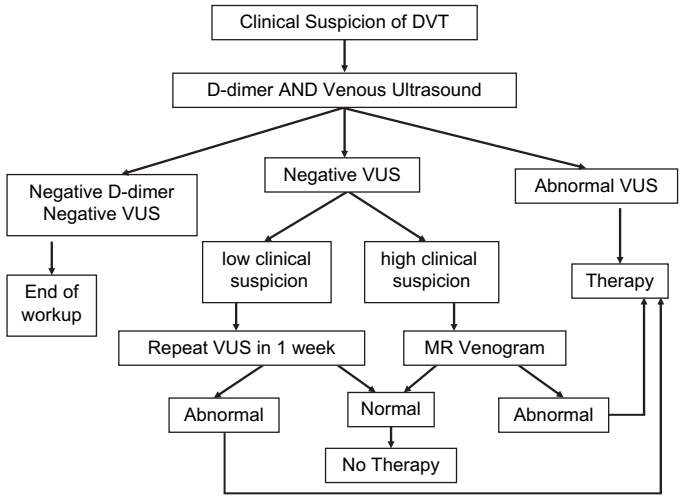

Fig. 1. Diagnostic algorithm for deep venous thrombosis. DVT, deep venous thrombosis; MR, magnetic resonance; VUS, venous ultrasound.

Venous ultrasound

Compression ultrasound aided by color flow Doppler imaging involves the use of firm pressure applied to the ultrasound transducer to detect an intraluminal filling defect of the major venous systems of the legs, including the common femoral, superficial femoral, greater saphenous, and popliteal veins. Noncompressibility of the venous lumen is the most accurate ultrasound criteria for thrombosis [38]. Venous ultrasound to detect deep venous thrombosis has been well studied in pregnancy [54]. It is noninvasive, easy to perform, and can be repeated if necessary without any restrictions. Sensitivity and specificity of venous ultrasound in the detection of proximal deep venous thrombosis is estimated at 95% and 96%, respectively [41,55]. There is a slightly lower sensitivity (75%–90%) in detecting more distal thrombosis in the leg [41,56].

Other modalities

It is estimated that in up to 3% of patients, venous ultrasound is not technically possible [57], and in some patients, despite negative ultrasound results, clinical suspicion remains high. Magnetic resonance venography and CT of the pelvis and lower extremities may be a viable alternative in these patients. Magnetic resonance direct thrombus imaging was shown in a blinded study of nonpregnant patients to have a sensitivity of 94% to 96% and specificity of 90% to 92% for the detection of deep venous thrombosis with similar results for calf deep venous thrombosis. MRI was well tolerated and interpretation was highly reproducible [58–60]. The reported

experience with MRI as a diagnostic modality for pregnant patients with deep venous thrombosis is extremely limited [61] and there is only limited safety data [62]. Thus, while magnetic resonance venography is promising, additional studies are needed before it can be routinely recommended. In the nonpregnant patient, CT of the pelvis and lower extremities to diagnose deep venous thrombosis is a useful modality with a reported sensitivity and specificity similar to ultrasound [63–65]. However, there is no reported experience with this modality in pregnancy and the natural preference during gestation is to test with ultrasound, which does not involve a risk of radiation exposure to the fetus.

Contrast venography involves the injection of radio-opaque dye into the vein below the site of the suspected thrombus. Imaging is then used to identify a filling defect [66]. However, the relative ease and noninvasive nature of compression ultrasound has made this more invasive test somewhat obsolete [21].

Workup of patients with suspected deep venous thrombosis

A diagnostic algorithm is presented in Fig. 1 to guide the clinician in the workup of a pregnant patient with a suspected deep venous thrombosis.

Diagnosis of pulmonary embolus

Timely diagnosis of pulmonary embolus in pregnancy is critical because of the potential for a catastrophic maternal and fetal outcome if overlooked. If the clinical suspicion is high, consideration should be given to empiric anticoagulation until the workup is completed [7]. Likewise, a precise diagnosis is vital to prevent unnecessary treatment of pulmonary embolism because treatment is associated with side effects for both the mother and fetus. Accurate imaging is essential, but fetal radiation exposure during diagnostic procedures often provokes unfounded anxiety for the clinicians involved [67].

An array of clinical, biochemical, and radiological tests is available to aid in the investigation of pulmonary embolism in pregnancy. Because, according to estimates, 70% of patients with proven pulmonary embolism have a proximal deep venous thrombosis, the basic workup begins with compression venous ultrasound if there are any signs or symptoms of thrombosis of the lower extremities. If a deep venous thrombosis is confirmed, then pulmonary embolism can be assumed, and treatment can be initiated without further workup [7,68]. If venous ultrasound is nondiagnostic or not performed, traditional teaching (based on older research) focused on the ventilation–perfusion (VQ) scan as the primary modality to diagnose pulmonary embolism in pregnancy. However, more recent studies support CT pulmonary angiography (CTPA) as the favored diagnostic tool. In fact, the most recent guidelines from the British Thoracic Society recommend CTPA as the initial

lung imaging modality in pregnancy for nonmassive pulonary embolism [53].

Clinical signs and symptoms

Traditional clinical hallmarks of pulmonary embolism, including dyspnea, tachycardia, tachypnea, pleuritic chest pain, and syncope or near-syncope are present in up to 90% of patients found to have a pulmonary embolus. However, these clinical signs and symptoms lack specificity and generate a broad differential diagnosis [69,70]. Other more objective measures, such as low oxygen saturation on pulse oximetry, abnormal arterial blood gas (ABG), abnormal chest radiograph, abnormal EKG, and abnormal echocardiogram, have also been proposed.

Low oxygen saturation on pulse oximetry or ABG has a limited role in the assessment of pregnant patients with suspected pulmonary embolism. These tests are useful in elderly populations, but lack diagnostic accuracy in younger patients, including pregnant patients [71]. Studies have shown that up to 20% of patients with a documented pulmonary embolism, had PO_2 measurements on ABG greater than 85 mm Hg [70]. The alveolar-arterial gradient may be a more sensitive indicator of pulmonary embolism in nonpregnant patients with 86% of patients with documented pulmonary embolism having an alveolar-arterial gradient greater than 20 [70]. However, 58% of pregnant women with documented pulmonary embolism had a normal alveolar-arterial gradient [72].

Abnormalities on EKG, including the classic S1-Q3-T3 changes, may be present in 70% to 90% of patients with pulmonary embolism but are considered nonspecific findings [73,74]. Other EKG findings, such as new-onset atrial fibrillation and right bundle branch block or right axis deviation, are typically later findings after pulmonary embolism and are more suggestive of significant cardiopulmonary compromise. Absence of abnormal EKG findings should not reassure a clinician who has a reasonable suspicion of pulmonary embolism [75].

Initial imaging modalities

The chest radiograph may be abnormal in up to 85% of affected patients. Common findings include effusions, infiltrates, and atelectasis. The ''classic'' wedge-shaped infiltrate (Hampton's hump) or decreased vascularity (Westermark's sign) are, in fact, rare findings [70,76]. Chest radiograph may be helpful in excluding other competing diagnoses, including pneumonia, pulmonary edema, pleural effusions, and pneumothorax.

Echocardiographic abnormalities of right ventricular size and function are present in a significant number of patients with acute large pulmonary embolism. Typical findings include a dilated and hypokinetic right ventricle and tricuspid regurgitation. Transesophageal imaging may enhance diagnostic accuracy [77–79]. A recent observation is that the release of cardiac

troponins can detect acute right heart strain from right ventricular muscle damage in major pulmonary embolism. However, the role of cardiac troponins in decision-making is limited and they are of no diagnostic value in nonmassive pulmonary embolism [80–83].

D-dimer

As with the evaluation of patients with suspected deep venous thrombosis, D-dimer is a sensitive, but not specific test for pulmonary embolism. In nonpregnant patients, a negative D-dimer has a negative predictive value of 95%, but only a 25% specificity [76]. However, as mentioned previously in the discussion regarding the diagnosis of deep venous thrombosis, abnormal cutoffs are difficult to assign in pregnancy because D-dimer levels increase with gestational age, and in the postpartum period, even in the absence of venous thromboembolism [45–48]. A negative D-dimer probably has a role in the exclusion of pulmonary embolism in patients with a low clinical suspicion (see description of risk assessment above), but the assay should not be performed in those with high clinical probability of pulmonary embolism [53].

Pulmonary angiogram

For many years the ''gold standard'' in diagnosing an acute pulmonary embolism was pulmonary arteriography. Sensitivity approaches 100%, though the ability to detect segmental and subsegmental lesions is considered diminished. The procedure involves catheterization of the pulmonary artery via a femoral or internal jugular approach and noting a filling defect via radiograph or fluoroscopy. This procedure carries significant risk, including 0.5% mortality risk and 3% complication rate, primarily due to the risks of contrast injection and catheter placement. Complications include groin hematoma, cardiac perforation, renal failure, and respiratory failure [69,84–86]. This apparent potential for morbidity led to an intensive effort over the past several years to identify a diagnostic modality that would be safer and easier to perform without sacrificing sensitivity.

Ventilation–perfusion scan

VQ imaging is a well-established diagnostic modality in the workup of a suspected pulmonary embolus in pregnancy and for many years it was the most frequently employed test in this subgroup of patients [67]. The test involves comparative imaging of the pulmonary vascular beds and airspaces using radiolabeled markers injected intravenously and as inhaled gases. Patients are then categorized into different diagnostic probability categories, including low, intermediate, high, normal, and indeterminate [38]. Any outcome other than high probability or normal requires further testing. Radiation dose can be minimized in pregnancy by using a half-dose perfusion scan and only using ventilation imaging if the perfusion scan is

abnormal [87]. Unfortunately, VQ scans are time-consuming and the sensitivity varies widely depending on the degree of clinical suspicion [7].

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study looked at the diagnostic accuracy of VQ scans in nearly 1000 nonpregnant patients with suspected pulmonary embolism. High-probability VQ scans correlated with pulmonary embolism in 87.2% of cases. However, only 41% of patients with pulmonary embolism had high-probability scans, yielding a sensitivity of 41% and a specificity of 97% [74]. In addition, it is estimated that over 10% of patients with a low-probability scan were found to have a pulmonary embolus on subsequent imaging. In the largest published study of VQ scans in pregnancy [68], fewer than 5% of pregnant patients had high-probability scans, almost 25% had indeterminate scans that required further evaluation, and more than 70% had normal scans. This is quite different than in the nonpregnant population where 40% to 70% of scans are nondiagnostic [67].

CT pulmonary angiography

CTPA employs intravenous contrast injection to highlight the pulmonary vasculature while using the latest generation of fast multislice scanners [53,76]. Much of the reluctance to use CTPA in pregnancy revolves around potential radiation exposure to the fetus. In fact, the authors' radiology colleagues often cite unfounded concerns regarding radiation exposure as a reason to refuse to perform CT scan and to promote VQ as the primary imaging modality.

In a recent study, Winer-Muram and colleagues [88] calculated the mean fetal radiation dose from helical chest CT by using maternal–fetal geometries obtained from healthy pregnant women and comparing the calculated CT doses with the doses reported with VQ scan. They found that the average fetal radiation dose is higher with VQ scan than with CT scan in all trimesters of pregnancy. As a corollary, in a survey of health professionals to determine their knowledge of dositometry in the workup of pulmonary embolism, only 58% appreciated correctly that a VQ scan delivers a higher fetal dose of radiation than that delivered by CT pulmonary angiography [89]. Interestingly, the survey population included medical trainees, radiologists, nuclear physicians, medical physicists, and pulmonologists. Lastly, in a survey of the PIOPED II investigators, only 31% recommended CT as the primary imaging test [90], but 75% of respondents in a conflicting study use CT angiography in pregnant patients [91].

CTPA is a well-validated diagnostic modality with a sensitivity and specificity between 94% and 100%. In a systematic review of available studies, the negative likelihood ratio of pulmonary embolism (pulmonary embolism confirmed by additional imaging) after a negative or inconclusive CT was 0.07; and the negative predictive value was 99.1%. The investigators conclude that the clinical validity of CTPA to diagnose pulmonary embolism

is similar to the clinical validity of pulmonary angiography [92], and missed diagnoses are rare [93]. Others have suggested that in patients with a low clinical suspicion of pulmonary embolism, CTPA has a greater discriminatory power than VQ scanning, but in patients with a high clinical suspicion, CTPA and VQ scan perform similarly [94].

CT is not only safe during pregnancy but also accurate for the diagnosis of pulmonary embolism in main, lobar, and segmental pulmonary arteries [88]. The latest CT technology and techniques are more accurate than VQ technology in identifying peripheral thrombus [53]. CT was also found to be the most cost-effective modality in diagnosing pulmonary embolism in pregnancy with a cost of $17,208 per life saved, compared with $35,906 per life saved for a VQ scan [95].

Given the safety data presented above and the relative ease in obtaining a CT versus a VQ scan, the authors prefer CTPA as the initial diagnostic approach to suspected pulmonary embolism in pregnancy. CTPA is easier to perform, is readily available even in off hours, and rarely requires any follow-up imaging. In fact, many radiology departments have sufficient confidence in the sensitivity of their CT imaging to also forgo formal contrast pulmonary angiography. Another advantage to CT over VQ scan is the ability to detect other disorders that may be responsible for the patient's symptoms, including pulmonary edema, pneumonia (consolidation), and pleural effusions [53].

Magnetic resonance angiography

Magnetic resonance angiography (MRA) uses gadolinium injection during magnetic resonance scanning to visualize the pulmonary vasculature. Newer generation MRI with faster imaging acquisition times have enabled the use of this technique. While initial studies were promising with reportedly high sensitivity and specificity [96], in a prospective study of 141 patients with suspected pulmonary embolism, the overall sensitivity was only 77% when compared with pulmonary angiography [97]. Still, others have proposed a combination of chest MRI and lower extremity magnetic resonance venogram as a way to detect 13% more cases of thromboembolism [98]. Unfortunately, no reported studies have examined the use of magnetic resonance to diagnose pulmonary embolism in pregnancy.

Workup of patients with suspected pulmonary embolism

A diagnostic algorithm is presented in Fig. 2 to guide the clinician in the workup of a pregnant patient with a suspected pulmonary embolism.

Treatment of venous thromboembolism in pregnancy

Whether manifested as a deep venous thrombosis or pulmonary embolism, acute venous thromboembolism in pregnancy requires immediate medical therapy. Initial steps in the management of pulmonary embolism

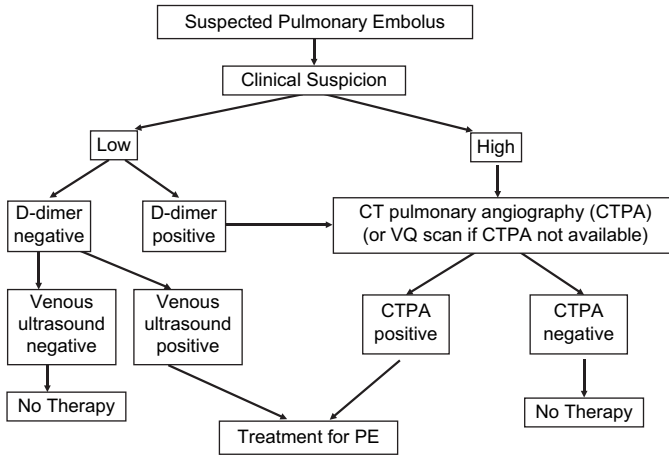

Fig. 2. Diagnostic algorithm for pulmonary embolism. PE, pulmonary embolism.

include oxygen support, blood pressure stabilization, and an assessment of the patient's cardiovascular and respiratory status [7,53]. Consultation with the intensive care unit service may be appropriate and transfer to the intensive care unit should be considered, depending on nursing and physician resources in the unit where the patient is located. Close monitoring for evidence of right-sided cardiac failure in cases of massive pulmonary emboli is warranted [53].

The mainstay of medical treatment is anticoagulation. While conventional treatment recommendations called for unfractionated heparin as the suggested therapy in pregnancy, low molecular weight heparin (LMWH) has emerged as the superior alternative based on more recent studies. Warfarin is seldom a treatment for acute venous thromboembolism in pregnancy given the drug's risk of teratogenicity [20,53], though this risk is greatest between the sixth and 12th weeks of pregnancy. There is also a risk for fetal hemorrhage with warfarin use.

Unfractionated heparin

Unfractionated heparin promotes anticoagulation by inhibiting platelet aggregation and by enhancing and increasing antithrombin and factor Xa inhibitor activity [99]. The initial bolus dose and maintenance dosing are calculated and titrated to achieve an activated partial thromboplastin time (aPTT) at 1.5- to two-times normal [18,99,100]. Standard nomograms are readily available from hospital pharmacies. Once therapeutic dosing is achieved, the aPTT must be periodically monitored to confirm adequate dosing. The potential side effects from unfractionated heparin include hemorrhage, osteoporosis, and thrombocytopenia.

Osteoporosis, or clinically significant bone loss, has been traditionally quoted as an adverse effect of long-term anticoagulation with heparin during pregnancy. Dahlman [101] reported that the incidence of vertebral fractures in 184 women treated with unfractionated heparin during pregnancy was 2.2%. Additionally, the mean duration of heparin prophylaxis in the women who had osteoporosis and spinal fracture was only 17 weeks (range: 7–27 weeks).

Heparin-induced thrombocytopenia (HIT) occurs in approximately 3% of patients receiving unfractionated heparin. Type I, or the immediate form, occurs within days of exposure and is typically self-limited. Type II, the immunoglobulin type, is rare and usually occurs 5 to 14 days after the initiation of therapy [102]. The authors therefore typically monitor platelet counts as follows: complete blood cell count on day 3, then on each of days 7 through 10, and then monthly after starting anticoagulation. A 50% decline in platelet count from the pretreatment level suggests a type II reaction and is an indication to promptly discontinue the heparin. Consultation with hematology would then be recommended for acceptable alternative therapies.

The cumbersome dosing requirements, the need for frequent aPTT monitoring, the need for long-term hospitalization, and concerns regarding side effects, including osteoporosis, osteopenia, and HIT, have led many authorities to recommend LMWH as the primary anticoagulation in pregnancy (see below) [20,53]. However, in certain rare circumstances, the authors prefer unfractionated heparin over LMWH. These include circumstances involving patients who are hemodynamically unstable due to massive pulmonary embolism [53], patients at significant risk for bleeding (eg, immediately postoperation patients or patients with antepartum placental abnormalities), and patients close to term who may require regional anesthesia and/or cesarean delivery. These patients are potentially better served by unfractionated heparin because of its shorter half-life and ease of reversibility with such agents as protamine sulfate. Protamine can be given as an intravenous infusion and dosing is based on residual circulating heparin.

Low molecular weight heparin

LMWHs, including enoxaparin and dalteparin, have established safety profiles in pregnancy and are emerging as the anticoagulant of choice for many indications, including acute venous thromboembolism [20,53,103–107]. LMWHs have potential advantages over unfractionated heparin because they have a lower incidence of HIT [102], a more predictable dose response, and a lower incidence of bone loss related to use. Shefras and colleagues [108] performed serial bone mineral density measurements in women treated with LMWH during pregnancy. Mean bone loss was 5.6% and 5.1%, depending on the dose, but this was not statistically different from the mean bone loss in the control group of pregnant patients who

were not exposed to LMWH (3.1%). In a randomized open study of unfractionated heparin versus LMWH in pregnancy, Pettila [109] showed that bone mineral density, as measured by serial dual energy x-ray absorptiometry scan up to 3 years postpartum, was significantly lower in the unfractionated heparin group versus the LMWH group. However, there was no difference between the LMWH group and healthy controls that were not exposed to heparin therapy.

Many studies have examined the efficacy of LMWH versus unfractionated heparin. In a prospective observational study, Rodie and colleagues [110] demonstrated the safety of enoxaparin for the treatment of acute venous thromboembolism in pregnancy. Few patients needed modification of the initial dose to maintain a therapeutic anti-Xa activity. Jacobson and associates [104] found similar results, but suggested that approximately 10% to 20% higher doses of LMWH may be needed in pregnancy. In a meta-analysis of 11 randomized trials comparing LMWH to unfractionated heparin [103], LMWH reduced mortality rates over 3 to 6 months of patient follow-up (odds ratio: 0.71), had favorable results with regard to major bleeding complications, and had equivalent efficacy to unfractionated heparin in preventing thromboembolic recurrences. Other reviews [106,111] have had similar conclusions. In a decision model, Gould and colleagues reported (in nonpregnant patients) LMWH to be more cost-effective than unfractionated heparin in the treatment of acute deep venous thrombosis [112].

One controversial area with regard to the use of LMWH in pregnancy is the necessity to monitor therapeutic levels (ie, anti-Xa levels). In nonpregnant patients, monitoring is generally not required because anticoagulant effects are predictable [111]. However, in pregnancy, the increased glomerular filtration rate in the kidney may explain the apparent need for increased dosing to maintain therapeutic levels reported in the literature [113]. In addition, there is a greater variability with regard to binding, distribution, and metabolism of LMWH in pregnancy.

The authors' preferred treatment for acute venous thromboembolism in pregnancy is LMWH. Though some have proposed outpatient therapy as a viable option outside of pregnancy [114], initial hospitalization is recommended in a gravid patient. The authors start with enoxaparin at a dose of 1 mg/kg subcutaneously given twice a day. The authors typically follow anti-Xa levels monthly and adjust the LMWH dosing to achieve a peak anti-Xa level of 0.6 to 1.0 U/mL (3–4 hours after injection). The authors also prefer twice-daily over once-daily dosing. It is recommended to continue therapeutic anticoagulation for at least 20 weeks. If this period expires before the end of pregnancy or the postpartum period, prophylactic anticoagulation should be initiated unless the patient has another indication for the continuation of therapeutic anticoagulation, such as a high-risk thrombophilia. Prophylactic anticoagulation should be continued for up to 6 weeks postpartum.

Though the risk of HIT is lower with LMWH, the authors still monitor platelet counts by checking a complete blood cell count on day 3, once between days 7 through 10, and then monthly after starting anticoagulation. Finally, the authors typically convert patients to unfractionated heparin at 36 weeks in anticipation of labor and possible regional anesthesia as regional anesthesia is contraindicated within 18 to 24 hours of therapeutic LMWH administration. Patients should be advised to hold their anticoagulation at the onset of labor. Heparin should be discontinued 24 hours before induction of labor or planned cesarean section. If spontaneous labor occurs in women receiving unfractionated heparin, careful monitoring of the aPTT is required [20].

In the postpartum period, prophylactic anticoagulation should be restarted 3 to 6 hours after vaginal delivery and 6 to 8 hours after uncomplicated cesarean delivery. The authors either continue enoxaparin (40 mg daily) or transition to oral anticoagulant therapy with warfarin. Warfarin should be dosed to achieve an international normalized ratio of 2.0 to 3.0 and enoxaparin must be continued for 5 days and until the international normalized ratio is therapeutic for 2 days. Because of the need with warfarin therapy for frequent monitoring of the international normalized ratio, most patients prefer to simply continue the enoxaparin.

Summary

Venous thromboembolism is one of the most critical clinical emergencies an obstetrician/gynecologist will confront. An understanding of the physiology and pathophysiology of hemostasis and thrombosis in pregnancy is essential and allows the clinician to predict which patients are at highest risk. Prompt recognition and diagnosis of venous thromboembolism with contemporary imaging modalities allow for the timely initiation of appropriate therapy to prevent further maternal and fetal morbidity.

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Shoulder Dystocia: An Update

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Shoulder dystocia is something of an enigma: It is poorly defined, ultimately unpredictable, and, once encountered, difficult to treat given the absence of a proven management algorithm. Because of these facts, and because shoulder dystocia is frequently associated with permanent birth-related injuries, it remains one of the most terrifying obstetric emergencies. The injuries carry potentially daunting medical implications for the patient and family and are among the most litigated issues in obstetrics [1,2]. The rare occurrence of shoulder dystocia makes management difficult to teach during training because severe shoulder dystocia is often handled by attending obstetricians. However, all practicing clinicians must be prepared to manage this unpredictable event.

Definition

The American College of Obstetricians and Gynecologists (ACOG) defines shoulder dystocia as a delivery that requires "additional obstetric maneuvers following failure of gentle downward traction on the fetal head to effect delivery of the shoulders" [3]. Many authors use a definition similar to the ACOG definition [4–10]. Others simply defer to the clinician's judgment and/or require the clinician to record the term "shoulder dystocia" in the chart [11–14]. Still others include various combinations of the preceding definitions [15–18]. Some divide shoulder dystocia into mild and severe based upon the number of maneuvers employed [19].

In trying to objectively define shoulder dystocia, Spong and colleagues [20] proposed defining shoulder dystocia as a "prolonged head-to-body delivery time (eg, more than 60 seconds) and/or the necessitated use of ancillary obstetric maneuvers." The 60-second interval was selected because,

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in their study, it was approximately two standard deviations above the mean value for head-to-body time for uncomplicated deliveries. The group suggested that an objective definition would facilitate future studies regarding prevention and management of shoulder dystocia [21]. Despite this recommendation, shoulder dystocia remains an entity without a clear definition.

Epidemiology

The lack of a uniformly accepted criteria for shoulder dystocia contributes to its varying incidences found in the literature, which range from 0.2% to 3% [22]. Ethnic differences have also been reported, with African American women [14] and "non-Caucasian" [23] women reported to have increased incidence, while a study examining the 1-year incidence of shoulder dystocia in California reports that Hispanic patients have a decreased incidence of shoulder dystocia [24]. One study from Singapore reported that a birth weight above 3600 g (almost the 90th percentile for this population) conferred a relative risk of shoulder dystocia 16.1 times higher when compared with pregnancies with birth weight below 3600 g [25]. Yet another study from France concludes that after controlling for confounding factors, ethnic origin was not an independent factor associated with shoulder dystocia [26]. The above articles underscore the importance, when researching and reporting on shoulder dystocia, of establishing a uniform definition for shoulder dystocia and a precise definition of the population being studied.

Risk factors

Macrosomia

The known risk factors include macrosomia and fetal anthropometric variations, maternal diabetes and obesity, operative vaginal delivery, precipitous delivery and prolonged second stage of labor, history of shoulder dystocia or macrosomic fetus, postterm pregnancy, and advanced maternal age. Macrosomia, like shoulder dystocia, has no uniformly accepted definition. Proposed definitions for macrosomia include cases where the infant is large for its gestational age (greater than the 90th percentile for a given gestational age) or weighs more than a specific cut-off limit—most commonly 4000 g [15,17,27–31] or 4500 g [32–34]. ACOG supports the use of the 4500-g cutoff to diagnose macrosomia because, at this weight, sharp increases are seen in risks of morbidity for infants and mothers [35]. No matter the definition used, the most serious complication for macrosomic infants is shoulder dystocia [35], and this risk clearly increases with increasing birth weight. Nesbitt and colleagues [24] reviewed the 1-year incidence of shoulder dystocia in California, and reported the percentages of spontaneous births of nondiabetics complicated by shoulder dystocia as 5.2% for infants weighing 4000 to 4250 g, 9.1% for those weighing 4250 to 4500 g, 14.3% for those

weighing 4500 to 4750 g, and 21.1% for those weighing 4750 to 5000 g. A Swedish study of newborns from 1973 to 1984 weighing greater than or equal to 5700 g reported a 40% incidence of shoulder dystocia [36]. Despite the increasing risk of shoulder dystocia with macrosomia, nearly half of shoulder dystocia cases occur with birth weight of less than 4000 g [37,38].

While correlating birth weight with shoulder dystocia is convenient for the sake of retrospective research, no one has been able to consistently identify the macrosomic fetus antenatally. Methods used to predict the macrosomic fetus include assessment of maternal risk factors (such as diabetes, prior history of macrosomic infant, maternal prepregnancy weight, weight gain during pregnancy, multiparity, male fetus, gestational age, gestational age greater than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years, and positive 50-g glucose screen with a negative result on the 3-hour glucose tolerance test [39]), clinical examination, and ultrasound measurement of the fetus [35]. While it may seem intuitive that ultrasound measurements are superior to clinical examination in the prediction of macrosomia, this is not the case and an error of up to $\pm 20\%$ must be taken into account when performing ultrasound near term [23]. Chauhan and colleagues [40], after a prospective study of over 100 parous women in active labor, concluded that maternal estimates of birth weight were within 10% of the actual birth weight in 69.8% of cases, compared with 66.1% for clinical estimates and 42.4% for ultrasonography (femur length and abdominal circumference). These results are further validated by a prospective study reporting the sensitivity of clinical and ultrasonographic prediction of macrosomia (defined as birth weight >4000 g) as 68% and 58%, respectively [41].

The usefulness of ultrasonography for prediction of macrosomia is further limited by the fact that fetal weight prediction is less accurate at higher birth weights. For example, Hadlock's formula to predict fetal weight has a mean absolute percent error of 13% for infants greater than 4500 g, compared with 8% for non-macrosomic infants [42]. Using a definition of macrosomia of 4500 g, existing formulas require that an estimated fetal weight must exceed 4800 g for the fetus to have a greater than 50% chance of being macrosomic [35,43,44]. Investigators from Iceland [45] and France [46] attempted unsuccessfully to predict shoulder dystocia based upon ultrasonographic measurements of the humerospinous distance and newborn shoulder length. Improved methods to estimate fetal weight are critical in identification of the fetus at risk for shoulder dystocia.

Over 50 formulas exist to calculate estimated fetal weight by ultrasound. The formula proposed by Cohen and colleagues [47] involves subtracting the biparietal diameter from the abdominal diameter (abdominal circumference divided by 3.14). They reported that a value greater or equal to 2.6 cm in infants of diabetic mothers has "excellent sensitivity, specificity, and predictive value in identifying those fetuses at high risk of birth injury." Elliott and colleagues [48] reported that, in their study involving infants of diabetic

mothers, performing cesarean section for all fetuses with a chest-diameter–biparietal-diameter of 1.4 cm or more would reduce the incidence of traumative morbidity from 27% to 9%. Winn and colleagues [49] studied which fetal ultrasonographic parameter best correlates with the neonatal bisacromial diameter and concluded that the fetal chest circumference (at the level of the four-chamber heart) was most accurate.

Also, while several investigators have reported that various measurements by three-dimensional ultrasonography improves the accuracy of birth weight prediction [50–52], these results are not universally accepted and the limited availability of three-dimensional ultrasounds and clinicians trained in three-dimensional ultrasonography limits its clinical usefulness. Based upon level A evidence, ACOG states that "the diagnosis of fetal macrosomia is imprecise." The ACOG further states that "for suspected fetal macrosomia, the accuracy of estimating fetal weight using fetal biometry is no better than that obtained by clinic palpation (Leopold's maneuvers)" [35].

Diabetes

Maternal diabetes is an independent risk factor for shoulder dystocia [3,9,21,35,53–55]. One study demonstrated that, at any incremental birth weight above 3500 g, the cumulative incidence of shoulder dystocia was significantly greater among diabetic than nondiabetic patients [56]. A second study, this one by Langer and colleagues [37], made a similar finding—that, at any incremental birth weight above 3750 g, the cumulative incidence of shoulder dystocia was significantly greater among diabetic than nondiabetic patients. Langer and colleagues [37] go on to report that when compared gram-for-gram, the perinatal mortality rate, incidence of birth injuries, and incidence of shoulder dystocia are increased in diabetic mothers. Diabetes mellitus confers a risk for shoulder dystocia six times that of the normal population [55], and in births in which the shoulder diagnosis is made, the risk of adverse neonatal outcome is higher when maternal diabetes is present [24].

Why is it that infants of diabetic mothers are at increased risk of shoulder dystocia and resulting birth injury? Some investigators have proposed that anthropometric differences in macrosomic infants of diabetic and nondiabetic mothers are to blame [57,58]. McFarland and colleagues [58] report that macrosomic infants of diabetic mothers are characterized by larger shoulder and extremity circumferences, decreased head-to-shoulder ratio, higher body fat, and thicker upper-extremity skin folds compared with nondiabetic control infants of similar birth weight and birth length. As mentioned above, Cohen and colleagues [19] actually quantified sonographic fetal asymmetry in diabetic patients. Whatever the cause of the increased risk of shoulder dystocia in this population, intensive treatment of diabetes reduces the risk of macrosomia and shoulder dystocia [59–62].

Operative vaginal delivery

While a few studies have not reported an association between shoulder dystocia and operative vaginal delivery [21,25], the overwhelming conclusion is that operative vaginal delivery (especially midpelvic extraction) significantly increases the risk of shoulder dystocia [7,9,10,12,14,18,24,30,53,55,62–65] with odds ratios ranging from 4.6 to 28.0 depending on the station at application and other risk factors. Multiple studies state that vacuum confers an increased risk when compared with forceps delivery [7,14,53,64,65] and that the sequential use of forceps and vacuum further increases the risk of shoulder dystocia and brachial plexus injury [66,67].

Many of the risk factors for shoulder dystocia are interrelated. For example, diabetes, both gestational and insulin-dependent, occurs more frequently in older mothers, in women with higher parity, and in those with a previous large infant [68]. Belfort and colleagues [18] performed multiple regression analysis and found that only three factors remained statistically significant for shoulder dystocia: birth weight, diabetes, and operative vaginal delivery. They produced a formula incorporating birth weight, 1-hour glucola, and operative vaginal delivery and found a sensitivity and specificity of 84% and 80%, respectively. Moreover, significant associations persisted when height of fundus, which can be measured antenatally, and carbohydrate intolerance, which includes pregestational diabetics, were substituted for birth weight and 1-hour glucola, respectively. They propose that this model may be useful in the design of prospective studies for managing suspected macrosomia.

Minor risk factors

As previously mentioned, there are multiple minor risk factors for shoulder dystocia. Many reports about such factors reveal conflicting results regarding their significance. In 1990, O'Leary and Leonetti [69] proposed the dictum: "once a shoulder dystocia, always a cesarean." That is, any woman who has a delivery involving shoulder dystocia should subsequently have all her babies delivered by cesarean. The reported incidence of recurrent shoulder dystocia among women with a previous shoulder dystocia ranges between 1.1% [63] and 16.7% [70]. These studies are all retrospective, however, and "one might surmise patients with the worse shoulder dystocias, greatest complications, and biggest babies may have been selected in future pregnancies to have cesarean section and therefore not appear in the retrospective analysis"[55]. The Australian Carbohydrate Intolerance Study in Pregnant Women, known as the ACHOIS trial [30], actually found no association between a prior birth complicated by shoulder dystocia and the risk of shoulder dystocia. ACOG states that "because most subsequent deliveries will not be complicated by shoulder dystocia, the benefit of universal elective cesarean delivery is questionable in patients who have a history

of shoulder dystocia'' [3]. The issue of recurrent shoulder dystocia, like many issues related to shoulder dystocia, is unclear.

It may seem counterintuitive that both a precipitous delivery [53,71,72] and prolonged labor pattern [4,12,21,63] have been associated with increased incidence of shoulder dystocia. Some authors [71,72] propose that precipitous delivery is associated with absence of truncal rotation into an oblique diameter. This, in turn, leads to a persistent anteroposterior location of the fetal shoulders at the pelvic brim. On the opposite end of the spectrum, prolonged labor pattern has been associated with between a threefold [63] and sevenfold [12] increased risk of shoulder dystocia. Beall and colleagues [21] divided patients into primigravid and multigravid groups and significance for prolonged second stage remained only in the multigravid group. McFarland and colleagues [73] matched 276 shoulder dystocia cases with 600 controls and found no association between labor abnormalities and shoulder dystocia. Other investigators also report no relationship between prolonged labor pattern and shoulder dystocia [9,16,26,53,74]. This discrepancy could be due to variations in study design, study population, or labor management [14].

Several clinical entities—maternal obesity, prolonged pregnancy, advanced maternal age, male fetal gender—are associated with macrosomia and, therefore, shoulder dystocia. ACOG states, and many investigators concur, that ''maternal obesity is associated with macrosomia and, thus, obese women are at risk for shoulder dystocia'' [3,26,74–76]. However, after controlling for confounding effects, such as fetal macrosomia, previous macrosomic infant, midpelvic instrumental delivery, and/or coexisting medical complications (such as diabetes and/or hypertension), multiple logistic regression performed in various studies reports that maternal obesity actually is not significant as an independent risk factor for shoulder dystocia [9,16,21,77].

Similarly to maternal obesity, prolonged pregnancy also increases the risk of macrosomia [39] and therefore, according to some investigators, shoulder dystocia [78]. Baskett and Allen [63] reported that prolonged pregnancy increased the risk of shoulder dystocia threefold. Also, however, just as evidence relating maternal obesity and shoulder dystocia is conflicting, there are similarly conflicting reports about prolonged pregnancy and the risk of shoulder dystocia with some reports finding no independent relationship between postdatism and shoulder dystocia [9,16,21,24,54].

Advanced maternal age is associated with increasing incidences of coexisting medical disease, including diabetes (both gestational and pregestational [68]) and obesity. Therefore, it makes sense that advanced maternal age confers an increased risk of shoulder dystocia [55]. However, using logistic regression analysis in a large population (n = 75,979), Langer and colleagues [37] found no significant contribution of maternal age on the incidence of shoulder dystocia.

The incidence of male gender in shoulder dystocia series (55%–68%) is greater than incidence of male gender in the general obstetric population

[55,79–82]. The reason for this discrepancy is unclear. Dildy and Clark [55] postulated that birth weight, which is established to be greater in male newborns, places them a greater risk of macrosomia. It is also plausible that a difference in anthropomorphic dimensions between male and female infants exists, as seen between infants of women with and without diabetes. This issue deserves further study.

The use of oxytocin, which is rather prevalent in many labor and delivery units for labor augmentation, has been associated with increased risk of shoulder dystocia [83]. It is likely not oxytocin augmentation alone that causes shoulder dystocia, but its use is probably associated with labor dystocia and fetal macrosomia [55]. With regards to maternal obesity, prolonged pregnancy, advanced maternal age, male fetal gender, and oxytocin augmentation, it is unclear whether their relationships with shoulder dystocia is an independent entity or a result of confounding variables. Whatever the relationship, it is clear that the predictive value of these risk factors is not high enough to be useful in a clinical setting [3].

Method of delivery

Despite O'Leary and Leonetti's insistence that "once a shoulder dystocia, always a cesarean," recent reports have suggested that cesarean may not always be the prudent choice for deliveries following a shoulder dystocia. As mentioned above, the benefit of universal elective cesarean is questionable in patients with a history of shoulder dystocia and the counseling of the patient should play into the decision-making process [3]. What about management in patients (with or without a history of shoulder dystocia) who appear to be carrying a macrosomic fetus? Rouse and colleagues [84] constructed a decision analytic model to compare three policies in both diabetic and nondiabetic patients: (1) management without ultrasound, (2) ultrasound and elective cesarean delivery for estimated fetal weight of 4000 g or more, and (3) ultrasound and elective cesarean delivery for estimated fetal weight of 4500 g or more. The study compared rates of shoulder dystocia, rates of permanent brachial plexus injury, the number and cost of additional cesarean births, and the potential cost savings for averting permanent brachial plexus injury. In the nondiabetic population, the study found that for each permanent brachial plexus injury prevented by the 4500-g policy, an increase of 8.5% in the cesarean birth rate with an additional cost of $8.7 million. The findings of the 4000-g policy in nondiabetics increased the cesarean rate 11.5% with an additional cost of $4.9 million. Expressed in other terms, one maternal death would result for every 3.2 brachial plexus injuries prevented. They concluded that a policy of elective cesarean birth in nondiabetics at a cutoff of either 4000 or 4500 g would be medically and economically unsound. They were unable to adapt the model for an estimated fetal weight of 5000 g because of the paucity of data available to analyze. Analysis in the diabetic population, with a macrosomia threshold of 4500 g

reported that 443 cesareans and $930,000 are required to prevent one permanent brachial plexus injury, which they reported as "more tenable, although the absolute merits of the approach are debatable." In a later publication, this group questions whether prophylactic cesarean delivery for fetal macrosomia diagnosed by means of ultrasonography is a "Faustian bargain" [85]. A recent publication analyzed mode of delivery and survival of macrosomic infants and concluded that cesarean delivery may reduce the risk of neonatal death in infants weighing over 5000 g [28]. All of the above findings are based upon birth weight and not estimated fetal weight.

Gonen and colleagues [32] performed a retrospective assessment of a policy at their institution that recommended cesarean delivery for macrosomia (estimated fetal weight 4500 g or more) and found an insignificant effect on the incidence of permanent brachial plexus palsy. Cesarean delivery is not 100% reliable for averting permanent brachial plexus palsy, as will be discussed later [86–88]. Improving the clinician's ability to accurately predict fetal weight could increase the benefit of elective cesarean delivery. Now, however, the concept of prophylactic cesarean to prevent shoulder dystocia and its permanent sequelae has not been supported by clinical or theoretic data [89]. Based on expert opinion, ACOG states that planned cesarean delivery to prevent shoulder dystocia may be considered for suspected fetal macrosomia when there is an estimated fetal weight of 5000 g in women without diabetes [3].

Studies regarding induction of labor (IOL) are divided into three categories: IOL for macrosomia in nondiabetic patients, IOL for macrosomia in diabetic patients, and IOL for prevention of macrosomia in diabetics. Several, small retrospective studies report that labor induction in nondiabetic patients appears to at least double the risk of cesarean delivery without reducing shoulder dystocia or newborn morbidity [17,27,90–92]. Gonen and colleagues [93] performed a prospective study where patients at term with ultrasonic fetal weight estimation of 4000 to 4500 g were randomized to either induction of labor or expectant management. There was no difference in either the number of cesarean deliveries, shoulder dystocia, or neonatal morbidity. Furthermore, Nassar and colleagues [16] report vaginal delivery is achievable in 88.9% of pregnancies allowed to labor with infants weighing 4500 g or more, at the expense of a 15.5% risk of shoulder dystocia, a 3% risk of brachial plexus injuries, and a 7.7% risk of perineal trauma. ACOG recommends that, as induction does not improve maternal or fetal outcomes, suspected fetal macrosomia in nondiabetic patients is not an indication for induction of labor.

Herbst [94] performed a cost-effective analysis including three strategies of managing infants with an estimated fetal weight of 4500 g. Based solely on cost, expectant treatment was the preferred strategy at a cost of $4014.33 per injury-free child, versus an elective cesarean delivery cost of $5212.06 and an induction cost of $5165.08. This suggests that expectant treatment is the most cost-effective approach to treatment of the fetus with suspected macrosomia in nondiabetic patients.

Management of patients with diabetes must account for glucose control. Lurie and colleagues [95] compared outcomes after implementation of a policy in which labor was induced at 38 to 39 weeks' gestation for insulin-requiring diabetic patients in comparison to pregnancies managed expectantly. Although the incidence of shoulder dystocia was higher in the group managed expectantly, the difference did not reach statistical significance. Kjos and colleagues [68] demonstrated that, in pregnancies complicated by insulin-dependent diabetes, expectant management does not reduce the incidence of cesarean birth and actually leads to an increased prevalence of large-for-gestational-age infants and shoulder dystocia. They conclude that if delivery is not pursued at 38 weeks, careful monitoring of fetal growth is essential. Partially because other groups have not confirmed these results, ACOG does not specifically recommend induction of labor for diabetics. ACOG states, however, that "expectant management beyond the estimated due date is generally not recommended" [96]. They further recommend, based on expert opinion, that diabetic patients with estimated fetal weight greater than 4500 g may be offered prophylactic cesarean delivery [3].

Nesbitt and colleagues [24] are among many investigators to report an increased risk of shoulder dystocia with operative vaginal delivery, especially midpelvic extraction. Obstetric patients should be counseled regarding the risks, benefits, and alternatives of both forceps and vacuum extraction before labor. While in labor, the entire clinical scenario should be taken into account whenever making the decision to proceed with operative vaginal delivery as there are certainly times when the risks of cesarean delivery outweigh the risks of operative vaginal delivery. It seems prudent to use forceps or vacuum with caution in the setting of suspected macrosomia.

Intrapartum management

Upon arrival to labor and delivery, estimated fetal weight should be always be documented. Despite the notion that estimations have an inherent margin of error, legal texts [97–99] and journals [100] have maintained that a physician's failure to assess fetal weight during pregnancy or labor constitutes a deviation from standards of practice [89]. Along these same lines, an assessment of the adequacy of the patient's pelvis should be performed and documented either at a prenatal visit or on labor and delivery. While care of laboring patients may include recording the labor curve, the labor partogram is not predictive of shoulder dystocia [73].

If the clinician is concerned about a possible shoulder dystocia, certain "shoulder precautions" can be employed. This generally includes positioning the patient in the dorsal lithotomy position [101] with the bed "broken down" such that the patient's buttocks are at the end of the bed [102], emptying the patient's bladder before delivery, ensuring the presence of an extra nurse or other clinician, and having a stool immediately available in case

suprapubic pressure is indicated. One study evaluated whether prophylactic use of McRoberts maneuver (exaggerated hyperflexion of the patient's legs) and suprapubic pressure was beneficial in reducing head-to-body delivery time. The investigators randomized pregnancies with estimated fetal weight over 3800 g to either undergo prophylactic maneuvers or deliver in dorsal lithotomy with additional maneuvers being employed only if necessary, and demonstrated that prophylactic maneuvers were not beneficial. They did state that "the only apparent advantage of performance of prophylactic maneuvers was that an overt diagnosis of shoulder dystocia was avoided in a number of patients" [101]. Furthermore, the use of McRoberts maneuver before the clinical diagnosis of shoulder dystocia does not significantly change the traction forces applied to the fetal head during vaginal delivery in multiparous patients [103]. While "shoulder precautions" seem reasonable, many shoulder dystocias are encountered in the absence of risk factors; therefore, all practitioners should be prepared to manage this obstetric emergency at every delivery.

Maneuvers

How much time do I have?

Unfortunately, there is no one superior algorithm to manage shoulder dystocia. Typically, shoulder dystocia is heralded by the classic "turtle sign"; after the fetal head is delivered, it retracts back tightly against the maternal perineum [71]. Shoulder dystocia, as mentioned above, is typically not diagnosed until downward traction fails to deliver the shoulders. At this point, one of the major concerns is: How much time can elapse without risking fetal hypoxic injury? Insult to the fetus from hypoxia results from compression of the neck and central venous congestion, as well as compression of the umbilical cord, reduced placental intervillous flow from prolonged increased intrauterine pressure, and secondary fetal bradycardia [102]. Stallings and colleagues [6] report that shoulder dystocia resulted in statistically significant but clinically insignificant reduction in mean umbilical artery gas parameters (pH of 7.23 versus 7.27). Wood's [104] work in 1973 reports a decrease of 0.14 pH U/min during trunk delivery. Such a drop would suggest that a pH less than 7.00 might occur with a delay in delivery as short as 2 or 3 minutes. Stallings and colleagues [6] analyzed Wood's results and reported that they are of limited value in regard to fetal acidosis because the methodology involves inappropriate extrapolation. Stallings and colleagues further report that their data suggest the change in fetal pH after the onset of shoulder dystocia is probably slower than previously thought.

Ouzounian and colleagues [105] analyzed 39 cases of shoulder dystocia, 15 with neonatal brain injury and 24 without. They reported that the mean interval in the injured group was 10.6 minutes compared with 4.3 minutes in the uninjured group. On the basis of a receiver-operating characteristic curve, the

investigators stated that a threshold interval of 7 or more minutes had a 67% sensitivity and 74% specificity for predicting brain injury. Allen and colleagues [106] reported that head-to-body interval of 6 or more minutes was the only significant predictor of low Apgar scores at 5 minutes in vaginal deliveries that resulted in permanent brachial plexus injury. These infants, however, did not appear to be at imminent risk of permanent central neurologic dysfunction. While it is reasonable to assume that permanent central neurologic dysfunction is associated with prolongation to head-to-shoulder interval thresholds, there is no clear consensus for the amount of time allowed to safely resolve a shoulder dystocia.

When a shoulder dystocia is encountered, the clinician must first designate a care-team member to mark the time. Tracking the time is necessary both for documentation and to allow periodic reassessment of the situation in case of severe shoulder dystocia. Clinicians' first reaction to difficult delivery is to exert considerably larger forces than normal, thereby possibly increasing the risk of fetal injury [107]. However, the clinician (and the other staff) must remain calm and proceed through maneuvers to resolve the dystocia. Adequate ancillary staff, including nursing staff, pediatricians, anesthesiology staff, and other obstetricians, if available, should be called to the room. Having a prearranged protocol in place involving a team approach to management of shoulder dystocia can help all team members be aware of their role (Box 1).

McRoberts maneuver

According to ACOG [3], the performance of the McRoberts maneuver (Figs. 1 and 2), with or without suprapubic pressure, is a reasonable initial approach to shoulder dystocia. The McRoberts maneuver does not change the actual dimension of the maternal pelvis (see Figs. 1 and 2); it straightens

Box 1. Maneuvers for shoulder dystocia

Initial maneuvers
McRoberts
Suprapubic pressure
Episiotomy?
Woods' corkscrew
Rubin's
Delivery of posterior arm
Gaskin position

Last-resort maneuvers
Intentional clavicular fracture
Zavanelli
Symphysiotomy
Hysterotomy

Fig. 1. The McRoberts maneuver. This maneuver involves hyperflexion of the maternal thighs against the abdomen, usually involving two assistants, each of whom grasps a maternal leg.

the sacrum relative to the lumbar spine, allowing cephalic rotation of the symphysis pubis sliding over the fetal shoulder [108]. Suprapubic pressure (Fig. 3) assists in dislodging the anterior shoulder [71]. Gonik and colleagues [109] demonstrated that McRoberts positioning reduced delivery force up to 37% for endogenous load (maternal force) and up to 47% for exogenous loads (clinician applied), thereby decreasing brachial plexus stretching. This group also noted greater stretching with endogenous versus exogenous force. Along these same lines, Buhimschi and colleagues [110] reported that use of McRoberts position almost doubled the intrauterine pressure developed by contractions alone.

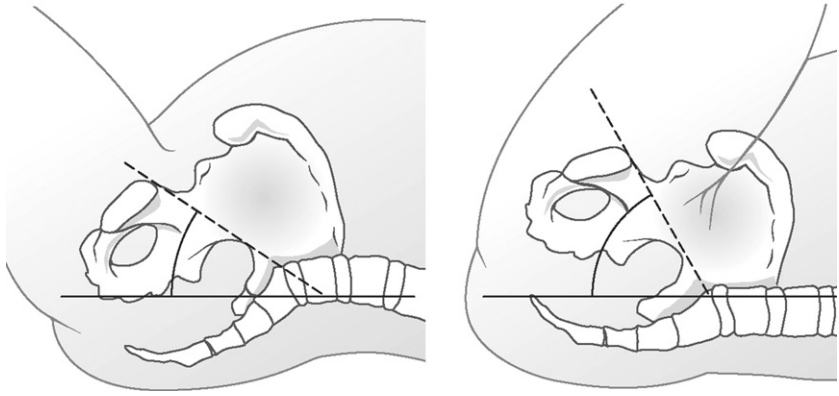

Fig. 2. The McRoberts maneuver does not change the actual dimension of the maternal pelvis. Rather, the maneuver straightens the sacrum relative to the lumbar spine, allowing cephalic rotation of the symphysis pubis sliding over the fetal shoulder.

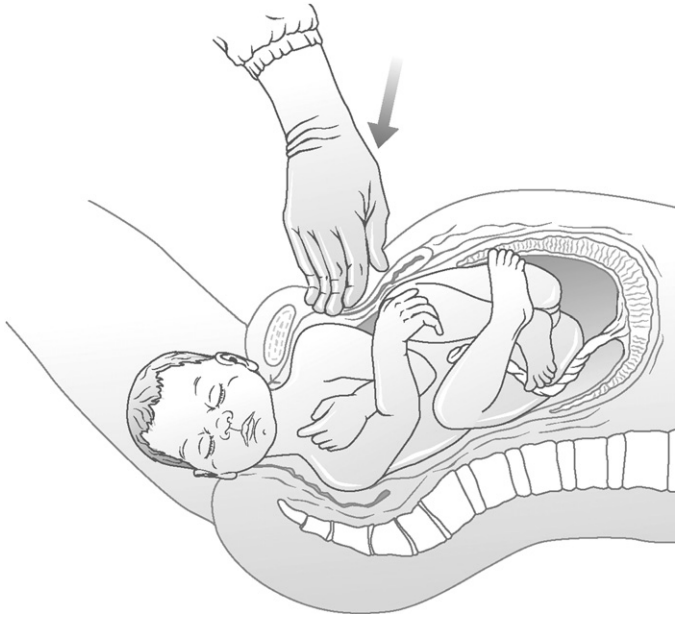

Fig. 3. Suprapubic pressure. Suprapubic pressure is applied directing the anterior shoulder downward and laterally. If possible, pressure should be directed from the side of the fetal spine toward the face. Pressure should be applied by an assistant with either the palm or fist.

The McRoberts maneuver is often done with the application of suprapubic pressure (see Fig. 3), which involves an assistant other than the primary delivering provider to apply pressure to the anterior shoulder of the fetus just cephalad to the pubic symphisis so that the shoulder is pushed anteriorly relative to the fetus. The success of McRoberts in resolving shoulder dystocia (used either alone or in combination with suprapubic pressure) is reported between 42% and 58% [5,15,111]. McRoberts positioning has risks, however. Continued attempts at McRoberts maneuver during severe shoulder dystocia are often associated with increasing traction, which can lead to increased risk of brachial plexus injury [63,112]. Gherman and colleagues [113] published a case report involving symphyseal separation and transient femoral neuropathy associated with the McRoberts maneuver. In spite of this reported case, the investigators still recommend the McRoberts position as the initial technique in management of shoulder dystocia but caution against ''overly aggressive hyperflexion and abduction of the maternal thighs onto the abdomen.''

Episiotomy?

Shoulder dystocia is typically a ''bony'' obstruction and not a result of obstructing soft tissue [3]. Management by episiotomy or proctoepisiotomy has been associated with a nearly sevenfold increase in the rate of perineal

trauma without benefit of reducing the occurrence of neonatal depression or brachial plexus palsy [114,115]. The decision to cut a generous episiotomy or proctoepisiotomy must be based upon clinical circumstances, such as a narrow vaginal fourchette in a primigravid patient or the need to perform fetal manipulation [70].

Woods' corkscrew and Rubin's maneuvers

The Woods' corkscrew maneuver (Fig. 4) involves the practitioner abducting the posterior shoulder by exerting pressure onto the anterior surface of the posterior shoulder (see Fig. 4). The Rubin's maneuver (reverse Woods') entails the practitioner applying pressure to the posterior surface of the most accessible part of the fetal shoulder (ie, either the anterior or posterior shoulder) to effect shoulder adduction (Fig. 5) [116]. Gurewitsch and colleagues [117] developed a laboratory birthing simulator and determined that the anterior Rubin's maneuver required less traction and produces less brachial plexus stretch than McRoberts positioning or posterior Rubin's. They encourage an emphasis on practicing the Rubin's maneuver during training so clinicians are familiar with its use.

Delivery of posterior arm

Delivery of the posterior arm was first described by Barnum [118] in 1945. To perform the maneuver, pressure should be applied by the delivering provider at the antecubital fossa to flex the fetal forearm. The arm is subsequently swept out over the infant's chest and delivered over the perineum (Figs. 6 and 7). Rotation of the trunk to bring the posterior arm anteriorly is sometimes required. Grasping and pulling directly on the fetal arm and applying pressure onto the midhumeral shaft should be avoided when possible, as bone fracture may occur [119], although these injuries typically heal without any long-term morbidity [102]. Kwek and Yeo [102] recommend placing traction on the posterior axilla to help facilitate delivery of the posterior arm. Posterior arm delivery effectively creates a 20% reduction in shoulder diameter and, according to Poggi and colleagues [120], reduces the obstruction by more than a factor of two when compared with McRoberts position. Poggi further recommends prioritizing posterior arm delivery in management algorithms and states that, when the trunk fails to deliver after posterior arm delivery, clinicians should proceed directly to emergent techniques, such as intentional clavicular fracture, cephalic replacement, or symphysiotomy.

Gaskin position

Several investigators propose placing the patient in the "all-fours" (or Gaskin) position (Fig. 8) to help resolve shoulder dystocia [121,122]. Bruner and colleagues [121] report a series of 82 consecutive cases of shoulder dystocia managed by moving the laboring patient to her hands and knees.

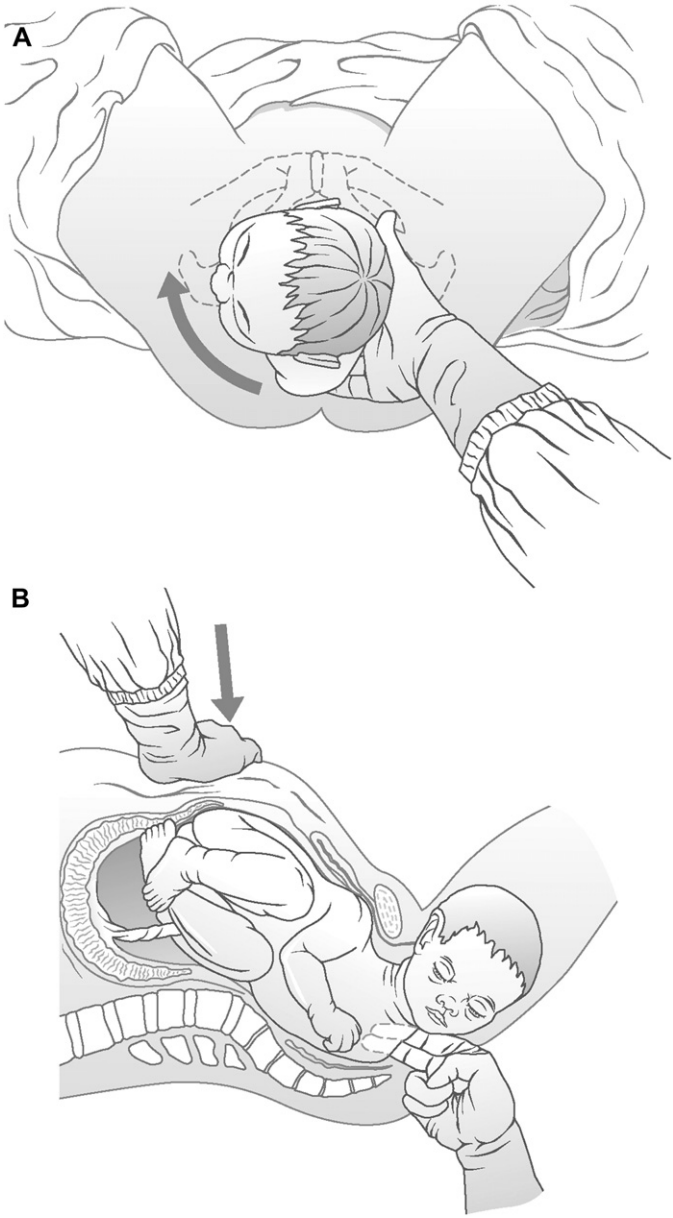

Fig. 4. The Woods' corkscrew maneuver. This maneuver involves applying pressure to the clavicular surface of the posterior arm, allowing rotation (*A*) such that the anterior shoulder dislodges (*B*) from behind the maternal symphysis. Curved arrow shows rotation. Straight arrow shows manual rotation of infant's body in coordination with rotation by hand below.

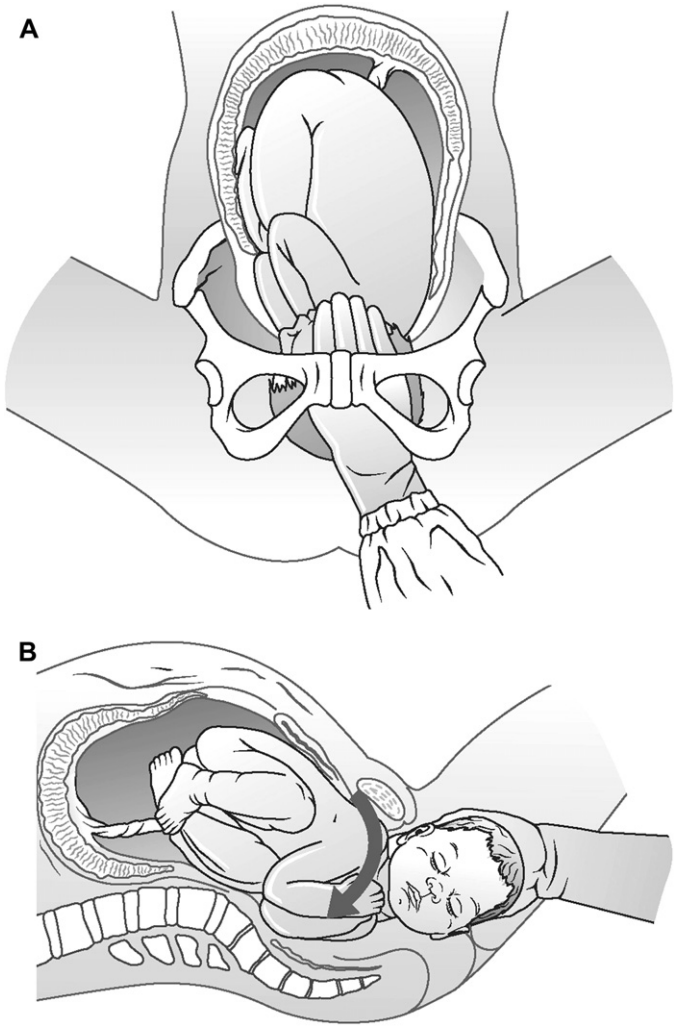

Fig. 5. The Rubin's maneuver. This maneuver involves applying pressure to the most accessible part of the fetal shoulder (ie, either the anterior or posterior shoulder) to effect shoulder adduction (*A*). (*B*) Curved arrows shows rotation of fetal shoulders.

Sixty-eight women (or 83%) delivered without need for any additional maneuvers with no increase in maternal or fetal morbidity. The "all-fours" position exploits the effects of gravity and increased space in the hollow of the sacrum to facilitate delivery of the posterior shoulder and arm [122].

Walcher's position

Walcher's position, a reverse form of McRoberts position, in which the thighs are hyperextended, results in downward displacement of the

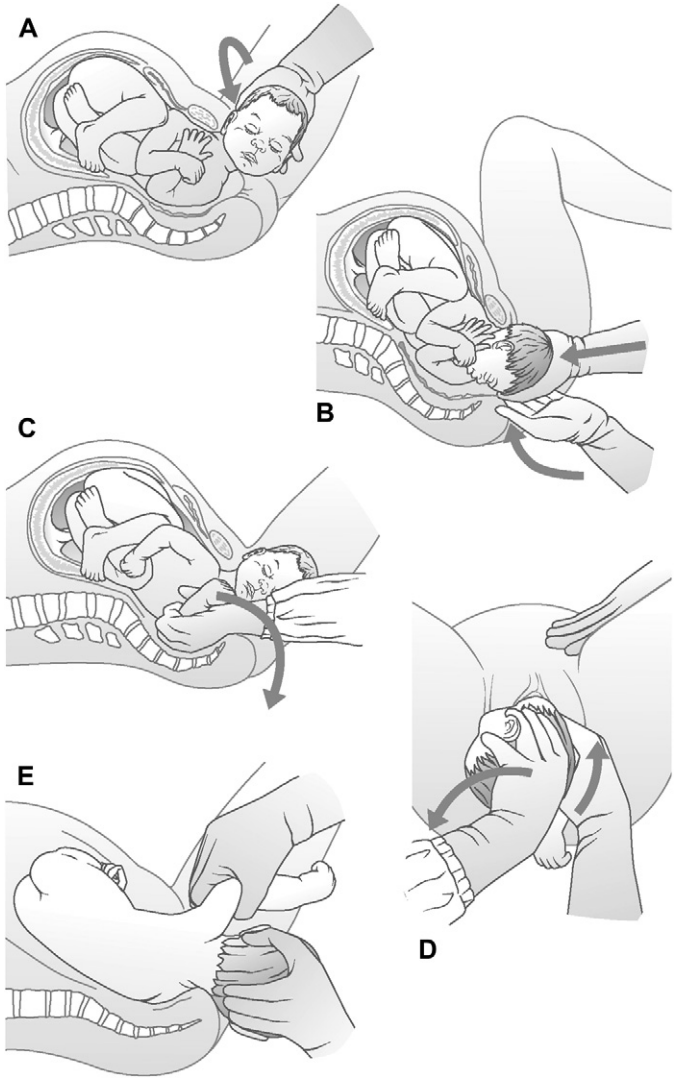

Fig. 6. Delivery of the posterior arm. To deliver the posterior arm, pressure should be applied at the antecubital fossa to flex the fetal forearm. The forearm or hand is subsequently grasped and the arm swept out over the infant's chest and delivered over the perineum. Rotation of the trunk to bring the posterior arm anteriorly is sometimes required. (*A*) First, turn fetal head to allow entry of practitioner's hand to facilitate manipulation. (*B*) Second, support fetal head with one hand and sweep second hand posteriorly. (*C*) Next, flex infant's arm at antecubital fossa to allow practitioner to grasp posterior forearm or hand. (*D*) Deliver posterior arm. This allows rotation of the fetus with the goal of disimpacting the anterior shoulder. (*E*) Further rotate fetus to facilitate delivery.

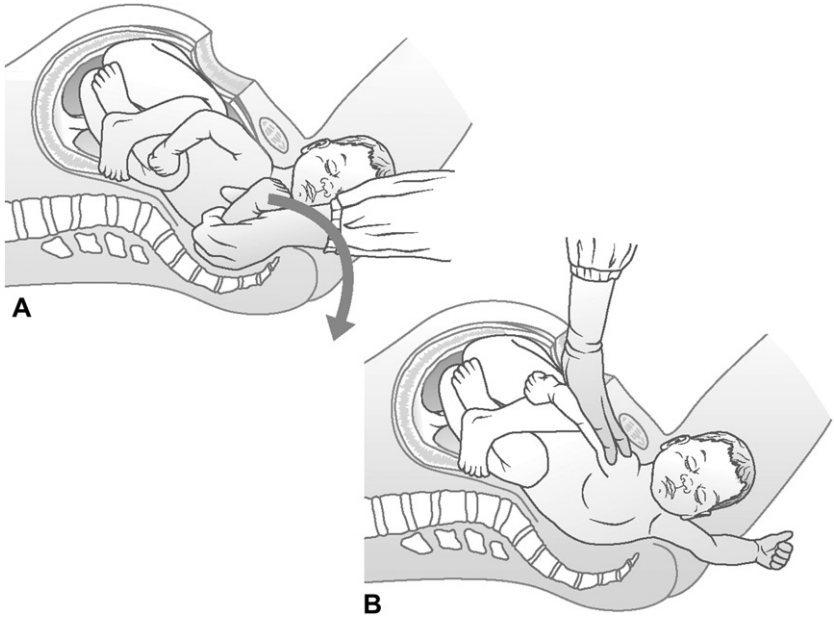

Fig. 7. (*A, B*) This figure shows delivery of the posterior arm with facilitation of delivery by hysterotomy. The intra-abdominal hand can be used to rotate the anterior shoulder to allow vaginal delivery; or a Zavanelli maneuver can be performed subsequently, allowing cesarean delivery.

symphysis pubis by 1.0 to 1.5 cm [123]. While it is mentioned in some of the older literature as a maneuver to help relieve shoulder dystocia, there are no recent case series or reports in the literature about its use and it is not mentioned in the most recent ACOG bulletin on shoulder dystocia [3].

Clavicular fracture

Intentional clavicular fracture has been described, mostly in older literature, by applying upward digital pressure on the fetal clavicle against the maternal pubic ramus. Although this would decrease the bisacromial diameter, there is significant risk of damage to the brachial plexus and pulmonary vasculature. Additionally, cleidotomy, which involves separation of the clavicle with a blade or pair of scissors, is probably best reserved following intrauterine death [102] as it is technically difficult to perform and carries significant fetal risks [71].

Zavanelli maneuver

For catastrophic shoulder dystocia, cephalic replacement, hysterotomy, and symphysiotomy are last-resort options. Cephalic replacement (Zavanelli maneuver) is essentially a reversal of the delivery process whereby the fetal

Fig. 8. The Gaskin position. The "all fours" position exploits the effects of gravity and increased space in the hollow of the sacrum to facilitate delivery of the posterior shoulder and arm.

neck is flexed, restitution is reversed, the head is rotated back to the occipito-anterior position, and digital pressure is applied to replace the head within the uterine cavity. The use of tocolytics (eg, terbutaline or nitroglycerine) can be used along with halothane or other general anesthetic agents to facilitate successful completion of the maneuver, which is followed by a cesarean delivery [71,102]. Among the 59 reported cases of attempted cephalic replacements described by O'Leary [124], only 6 (10.2%) were unsuccessful. Sandberg [125] reviewed 12 years' worth of literature on the Zavanelli maneuver and reported an overall 92% success rate. While Sandberg mentioned numerous injuries in these infants, the conclusion was that most of these injuries were due to pre-Zavanelli manipulations and protracted hypoxia. Reported maternal complications include both uterine and vaginal rupture but, again, Sandberg states that these injuries cannot be directly attributed to the Zavanelli procedure. He concludes that "in most cases of cephalic replacement, the Zavanelli maneuver appears to be simple and successful, even without prior experience." Despite this review, ACOG states that the Zavanelli maneuver is associated with a significantly increased risk of fetal morbidity and mortality and of maternal morbidity and that

it should only be performed in cases of severe shoulder dystocia unresponsive to more commonly used maneuvers [3].

Symphysiotomy

Due to the significant maternal morbidity associated with symphysiotomy, including bladder neck injury and infection, it should only be used as a last attempt to preserve fetal life [102,126]. To perform a symphysiotomy, the patient should be placed in an exaggerated lithotomy position with proper support of the legs. Then, if at all possible, a transurethral catheter should be placed. The clinician, with his or her index and middle finger, should displace the urethra laterally and partially incise the cephalad portion of the symphysis with a scalpel blade or Kelly clamp [71]. Goodwin and colleagues [126] presented a case series in which emergency symphysiotomy was performed in three patients in an effort to preserve fetal life after approximately 12, 13, and 23 minutes. All infants subsequently died because of severe anoxic insult. Goodwin suggests that, because of operator inexperience and maternal morbidity, the role of emergency symphysiotomy remains unclear. Furthermore, they state that because the procedure takes at least 2 minutes from the time a decision is made, it should be initiated within 5 to 6 minutes of delivery of the fetal head.

Hysterotomy

The use of hysterotomy or an upper-segment uterine incision allows either more direct pressure or cephalic replacement. More direct pressure can achieve shoulder rotation or directly dislodge the anterior shoulder for vaginal delivery. Cephalic replacement can facilitate abdominal delivery [102]. The use of hysterotomy or an upper-segment uterine incision is by no means always effective, and tragic consequences have been described [126].

Maneuvers to avoid

While no good evidence exists regarding the role of fundal pressure in shoulder dystocia, fundal pressure applied in the setting of shoulder dystocia has been reported to further press the shoulder on the pelvic brim and increase intrauterine pressure, thereby increasing the risk of permanent neurologic injury and orthopedic damage [102,127]. Hankins [128] published a case report involving lower thoracic spinal cord injury with permanent neurological injury when fundal injury was applied in an attempt to relieve shoulder dystocia. The ACOG Practice Bulletin on shoulder dystocia [3] reports that "fundal pressure may further worsen impaction of the shoulder and also may resulting uterine rupture." Therefore, it seems reasonable to avoid fundal pressure with shoulder dystocia.

Any nuchal cord, if unable to be reduced over the fetus' head, should not be cut and clamped if at all possible. Iffy and Varandi [129] report a series of five

cases of cerebral palsy in infants where shoulder dystocia was recognized only after interruption of a nuchal cord. The delay in delivery in that series ranged from 3 to 7 minutes. Flamm [130] reports a case in which a tight nuchal cord was encountered during a severe shoulder dystocia and was not clamped or cut. He proposed that if the cord was severed, the infant "might have suffered permanent neurologic injury or died before birth." Stallings and colleagues [6] speculate that, even in the face of shoulder dystocia with a nuchal cord, some cord circulation may continue and that severing the cord may contribute to fetal hypoxia and hypotension during the time it takes to resolve the dystocia.

Postpartum management

Shoulder dystocia is among the four most common causes of medical litigation [131] and has been estimated to account for up to 11% of obstetric claims. Following all complicated deliveries, measurements of umbilical cord blood gases must be obtained, a discussion with the patient and family must be held, and the events of the delivery must be documented by all care-team members involved. Parents are usually traumatized by the events and they deserve complete, immediate, and accurate information regarding the delivery, the maneuvers used, and the rationale behind management [102]. If a brachial plexus injury is present, the clinician should not speculate regarding the cause.

Acker [132] recommends that a shoulder dystocia intervention form should include the following information:

When and how the dystocia was diagnosed
Progress of labor (active phase and second stage)
Position and rotation of the infant's head
Presence of episiotomy
Anesthesia required
Estimation of force of traction applied
Order, duration, and results of maneuvers used
Duration of shoulder dystocia
Documentation of adequate pelvimetry before initiating labor induction or augmentation
Neonatal and obstetric impressions of the infant after delivery
Information given to gravida that shoulder dystocia had occurred

Unfortunately, recent publications [5,63,133] have noted incomplete documentation in the majority of shoulder dystocia cases. A legal case with inadequate documentation can be difficult to defend.

Neonatal sequelae of shoulder dystocia

McFarland and colleagues [15] found that fetal and maternal morbidity increases with number of maneuvers employed to resolve shoulder dystocia.

In regards to recent literature, many papers are using fetal injury (namely, brachial plexus injury) as an endpoint as opposed to using shoulder dystocia as the study endpoint. Fetal injuries associated with shoulder dystocia include brachial plexus injury, fracture of the clavicle or humerus, and, rarely, hypoxic injury or neonatal death. Reports of brachial plexus injury during deliveries complicated by shoulder dystocia vary from 4% to 40% [1,56,63,70,81,84,134–138], although case-control studies report an 18- to 21-fold increase in the risk of brachial plexus injury among infants with birth weight greater than 4500 g [139–141]. The obstetrical literature reports less than 10% of Erb's palsies are permanent [63,135–137], although persistent injury may be more common in birth weights over 4500 g [142] and in infants of diabetic mothers [24]. Pediatric and orthopedic literature reports permanent injury in up to 15% to 25% of cases [143,144].

Brachial plexus injury

Benjamin [143] provides an excellent review of the characteristics of brachial plexus injuries. Damage to spinal nerves C5-C6 leads to Erb's or Erb-Duchenne palsy (80% of brachial plexus injuries). The classic posture is a result of paralysis or weakness in the shoulder muscles, the elbow flexors, and the forearm supinators. The affected arm hangs down and it is internally rotated, extended, and pronated. Oftentimes, the C7 nerve is also involved, causing loss of innervation to the forearm, wrist, and finger extensors. The loss of extension causes the wrist to flex and the fingers to curl up—the "waiter's tip" position. Phrenic nerve injury with resulting diaphragmatic paralysis may be present due to damage to the C4 segment. Avulsion of C8-T1 causes Klumpke's palsy, which is characterized by weakness of the triceps, forearm pronators, and wrist flexors leading to a "clawlike" paralyzed hand with good elbow and shoulder function. Upper-arm function differentiates Klumpke's palsy from Erb's palsy. Unfortunately, only 40% of Klumpke's palsies resolve by 1 year of life [73]. An associated Horner's syndrome with sensory deficits on the affected side, contraction of the pupil, and ptosis of the eyelid is caused by cervical sympathetic nerve injury. Complete brachial plexus injury, or Erb-Klumpke palsy, involving C5-T1, is characterized by a flail, paralyzed arm without sensation or reflexes. Brachial plexus injury occurs regardless of the number and type of maneuvers used [5,63,145] and does not appear predictable before delivery [8,88].

Excessive traction applied at the time of delivery can cause injury to the brachial plexus. Allen and colleagues [112] performed an in vivo study looking at the force applied during delivery and demonstrated a significant difference in the peak delivery force applied in routine versus shoulder dystocia deliveries. The clinical utility of this information remains unknown. Birth injury is not the only cause of brachial plexus injury. A significant proportion (34%–47%) of brachial plexus injuries are not associated with shoulder dystocia [3]. In fact, 4% occur after cesarean birth [84,146,147]. Aside from excessive

traction, other causes of injury include the normal forces of labor and delivery [73], a compressive effect of the symphysis pubis against the brachial plexus, and abnormal intrauterine pressures arising from uterine anomalies, such as an anterior lower uterine segment leiomyoma, an intrauterine septum, or a bicornuate uterus [72,148,149]. Performance of electromyeolography soon after delivery (within 24–48 hours) can help determine the timing of brachial plexus injury. Electromyelographic evidence of muscular denervation normally requires 10 to 14 days to develop. Its finding in the early neonatal period, therefore, strongly suggests an insult predating delivery [150–152]. No matter the cause, care of the newborn with brachial plexus injury should involve a multidisciplinary approach including pediatrics, pediatric neurology, physical therapy, and possible referral to a brachial pleuxus injury center. The care plan should be clearly communicated with the parents.

Fracture

Orthopedic fractures almost invariably heal with simple supportive therapy and do not lead to permanent disability [153,154]. One investigator even calls clavicular fracture "benign"[154]. While clavicular fracture often occurs in the absence of shoulder dystocia [155], the incidence of fracture of the clavicle at the time of shoulder dystocia ranges from approximately 3% to 9.5% [5,6,15] with increasing risk with greater birth weight [5,155].

Fetal mortality

The reported incidence of perinatal death attributed to shoulder dystocia ranges from zero to 2.5% [84,156,157]. Rouse and colleagues [84] conclude that "although shoulder dystocia may result in perinatal death, this happens rarely and would not serve as a reasonable justification, at least in pregnancies of nondiabetic women, for cesarean delivery based on the ultrasonographic diagnosis of macrosomia."

Maternal sequelae of shoulder dystocia

A study of 236 shoulder dystocias reported an 11% rate of postpartum hemorrhage and a 3.8% rate of fourth-degree lacerations [111]. These were independent of type of maneuver or maneuvers employed to resolve the dystocia. Other maternal complications that have been reported include vaginal and cervical lacerations, and bladder atony [71]. It should be noted that "heroic" measures, such as the Zavanelli maneuver and symphysiotomy, are often associated with significant risk of maternal morbidity [124,158].

Training for shoulder dystocia

A team-oriented approach is necessary for management of shoulder dystocia. A formalized activation system, good leadership, and good

organization of team members, with each member well trained in the management of obstetric emergencies, helps facilitate a smooth delivery of the fetus [102]. While there is no evidence available that training for the management of shoulder dystocia improves neonatal outcome [108], it seems intuitive that "skill drills" would help increase preparedness of all team members. Deering and colleagues [159] published a report in which residents were block-randomized by year-group to a training session on shoulder dystocia management that used an obstetric birthing simulator or to a control group with no specific training. They found that trained residents had significantly higher scores in all evaluation categories including timeliness of their interventions, performance of their maneuvers, and overall performance. Crofts and colleagues [160] developed a mannequin for training and found that the management of shoulder dystocia improved following training. Specifically, they found a reduction in the head-to-body delivery duration, and the maximum applied delivery force. However, these reductions in delivery duration and applied force did not reach statistical significance.

Antenatal counseling

As there is no accurate method to predict which pregnancies will experience shoulder dystocia, antenatal counseling should be individualized for each patient. Ideally, this should be an ongoing discussion throughout the antenatal course and should include discussion of any history of shoulder dystocia with or without birth injury, estimate of current fetal weight compared with previous infants' birth weights, gestational age, the presence of maternal glucose intolerance and/or diabetes, and history of severe perineal trauma with any subsequent incontinence. Depending on the results of that discussion, a conversation regarding elective cesarean delivery, induction of labor, expectant management, and operative vaginal delivery should take place. Respecting a patient's autonomy is of paramount importance and, ultimately, in the setting of history of (or significant risk factors for) shoulder dystocia, either vaginal or cesarean delivery is a reasonable option.

Summary

Shoulder dystocia, in the final analysis, remains somewhat enigmatic. The rarity of its incidence leads to many of the ancillary problems associated with the event: the difficulty of arriving at a definition all practitioners can accept, the inability to predict it, and the elusiveness of a univocal management plan. Key factors in successfully managing shoulder dystocia include constant preparedness, a team approach, and appropriate documentation. Future directions include further research on accurate prediction of macrosomia and regarding "skill drills" and training with birth simulators.

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Diabetic Ketoacidosis in Pregnancy

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Diabetic ketoacidosis (DKA) is a disease process involving numerous pathophysiologic changes that can be markedly exaggerated in the pregnant state. Episodes of DKA are infrequent in the general population and even more so in pregnancy. Nonetheless, DKA may represent a life-threatening event for the mother and her fetus. The incidence of DKA and factors unique to pregnancy are discussed in this article, along with the effects of the disease process on pregnancy. Clinical presentation, diagnosis, and treatment modalities are covered in detail to offer data to improve maternal and fetal outcome.

The reported incidence of DKA outside of pregnancy ranges from 4.6 to 8 episodes per 1000 patients annually [1]. The overall incidence of DKA in pregnancies complicated by diabetes is difficult to ascertain. Numerous review articles and retrospective studies have found the incidence to range from 1% to 10%, and the overall prevalence of DKA during pregnancy and fetal loss associated with DKA have fallen significantly in recent years. This trend is likely secondary to prenatal counseling (with a goal of optimal glucose control before pregnancy) and improved understanding and management of the acute event. Cousins [2] reported the incidence of DKA during pregnancy to be 9.3% in a group of 1508 patients studied between 1965 and 1985. More recent retrospective studies by Rodgers and Rodgers [3] and Cullen and colleagues [4] found an incidence of DKA in pregnancy of 1% to 2%. In a case series by Kilvert and colleagues [5], the reported incidence of DKA among 635 pregnant patients who had pregestational type 1 diabetes mellitus was 1.73%. A larger, more recent case series by Schneider and colleagues [6] reported the incidence of DKA in pregnant patients to be 1.2% among women who received insulin for diabetes control during their gestation. Four of the 11 patients who developed DKA on insulin therapy were

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considered to have gestational diabetes mellitus, accounting for an incidence of 0.45%. The occurrence of DKA in pregnancies complicated by gestational diabetes mellitus is rare [7], and when it is encountered, the possibility of unrecognized pre-existing diabetes should be strongly considered. The vast majority of cases of DKA occur in patients whose pregnancy is complicated by pre-existing diabetes mellitus, particularly those who are prone to DKA before pregnancy [8]. Although the use of insulin in a strict manner to prevent occurrence has helped to lower the incidence of DKA in pregnancy, it appears that a significant number of cases may occur in individuals who have previously undiagnosed diabetes. In one study, 30% of cases of DKA occurred in women who did not have known diabetes [9].

The overall incidence of fetal and maternal mortality secondary to DKA in pregnancy is limited to data from case series. The true incidence of maternal mortality is unknown, though it is historically reported as 5% to 15% [10]. Like the overall incidence of DKA in pregnancy, the maternal mortality appears to be declining. A study by Drury and colleagues [11] found the maternal mortality rate to be less than 1% among 13 episodes of DKA experienced in 600 consecutive pregnancies. Fetal loss rates, however, are much higher. The study by Drury and colleagues [11] reported a fetal mortality rate of 85%. Montoro and colleagues [9] reported a 35% incidence of fetal demise in women who had type 1 diabetes mellitus who presented with DKA. The fetal mortality rate was even higher (57%) in the one third of patients for whom the episode of DKA was their first diagnosis of diabetes. A more recent study by Cullen and colleagues [4] found a lower fetal loss rate of 9%.

Specific adaptations that occur during pregnancy place the gravid diabetic woman at risk for episodes of DKA. Pregnancy is a relatively diabetogenic state. It is well known that overall insulin resistance and lipolysis are increased during normal pregnancy; the increased lipolysis contributes to the ''accelerated starvation'' and propensity toward ketone body formation during pregnancy [12]. Hormones such as human placental lactogen (HPL), growth hormone, prolactin, and progesterone play key roles in insulin sensitivity and are discussed in further detail later. Another key adaptation of pregnancy that contributes to a propensity to DKA involves the intricate link between the renal and respiratory systems. Increases in minute ventilation at the alveolar level place the pregnant woman in a state of respiratory alkalosis. At the renal level, this is compensated for by increased excretion of bicarbonate, a key metabolic buffer. This state of ''compensated respiratory alkalosis'' during pregnancy plays its role by decreasing the pregnant woman's ability to buffer ketone acids present in the serum during episodes of DKA.

Pathophysiology

Proficiency and effectiveness in diagnosing and treating DKA necessitates a thorough understanding of the pathophysiology that underlies this disease

process. It should become clear from the following description that the pathophysiology of DKA feeds on itself: ''the worse it gets, the worse it gets.'' In short, DKA is a state of inadequate insulin action (absolute lack, as in type 1 diabetes mellitus, or relative lack, as can occur in type 2 diabetes mellitus), resulting in perceived hypoglycemia at the level of target cells (adipose, muscle, and liver tissue). It is essential to keep in mind that most of the clinical hallmarks of DKA (hyperglycemia, hypovolemia, ketosis, and acidosis) are the result of an exaggerated counter-regulatory response to the perceived hypoglycemia, which sets off a cascade effect that becomes apparent in the clinical presentation and laboratory findings. Insulin counter-regulatory hormones such as glucagon are released into the circulation in response to cellular hypoglycemia, causing gluconeogenesis and glycogenolysis to become disinhibited at the level of the liver. Therefore, the hyperglycemia in DKA originates from three sources: (1) a high availability of glucose precursors due to glucagon- and epinephrine-driven lipolysis (glycerol) and muscle breakdown (amino acids); (2) a breakdown of glycogen stores; and (3) a decreased peripheral uptake of glucose, caused by insulin lack and made worse by increased counter-regulatory hormones. The increased insensitivity to insulin results in decreased adipocyte storage of free fatty acids, now present in the circulation in high amounts due to increased lipolysis. These increased fatty acids undergo oxidation and are converted to ketoacids by the liver (3-β-hydroxybutyrate and acetoacetate). The ketoacid acetoacetate may undergo decarboxylation and conversion to acetone, and can often present clinically as a fruity odor from the patient's breath [13]. The increased levels of ketone bodies, combined with the buildup of lactic acid from peripheral hypoperfusion, result in the metabolic acidosis seen with DKA.

The intravascular hyperglycemia is just as important pathophysiologically as the intracellular hypoglycemia. High levels of glucose within the circulation serve as an osmotic reservoir resulting in diuresis, leading to profound hypovolemia and dehydration and further exacerbating the hyperglycemia and the acidosis. The ensuing hypovolemia stimulates the release of other counter-regulatory stress hormones such as catecholamines, growth hormone, and cortisol while enhancing the release of glucagon [14].

Some hormones that are increased during normal pregnancy have also been found to play a role in the pathophysiology of DKA. HPL, which is unique to pregnancy, serves as a counter-regulatory hormone for protection against the hypoglycemic state. HPL can be seen in increased levels along with glucagon in patients who have DKA. Prolactin is increased during pregnancy and acts as a counter-regulatory hormone. The previously mentioned release of catecholamines, growth hormone, and cortisol along with HPL and prolactin acts on insulin-sensitive tissues to produce alternative substrates for energy use during DKA [13]. Like glucagon, these hormones also serve to increase insulin resistance at the cellular level.

Electrolyte abnormalities are present in DKA and can be well understood through pathophysiology. Serum sodium and potassium levels can become

grossly abnormal during episodes of DKA as a result of the osmotic diuresis. Ketoacids also play a role in decreasing these serum electrolyte levels. The electrolyte salts containing sodium and potassium may become bound to anions from ketoacids and be excreted in the urine [13]. Potassium levels tend to be high because of protein breakdown and inhibited entry of potassium into cells due to insulin lack. Therefore, low potassium levels obtained in the management of DKA indicate severe hypokalemia. Sodium levels may be elevated, normal, or decreased. High levels suggest severe dehydration, whereas low levels may be real or a result of "pseudohyponatremia" associated with high serum levels of triglycerides.

How pregnancy affects this disease

When assessing a patient who has a particular medical illness during pregnancy, one must question the effects that the pregnancy has on the disease process in particular and vice versa. Several factors are unique to pregnancy and to how the gravid state affects the development of DKA. Pregnancy is a state of accelerated starvation. Glucose is readily absorbed by the placenta and fetus as a source of energy. The metabolic hallmarks of pregnancy include fasting hypoglycemia and hyperinsulinemia. These states, in combination with constant acquisition of glucose by the fetus and placenta, place the gravid patient at risk for cellular hypoglycemia. Pregnancy also has a noted effect on insulin activity. Pregnancy is a relatively insulin-resistant state, and this insulin resistance increases throughout gestation. Several hormones such as HPL, cortisol, and prolactin are elevated during pregnancy and serve to antagonize the effects of insulin at the cellular level even further. Progesterone levels increase during pregnancy and serve to antagonize the effects of insulin by decreasing gastrointestinal motility, effectively resulting in the promotion of hyperglycemia [15]. The respiratory changes in pregnancy previously mentioned lead to a state of respiratory alkalosis. A compensatory increase in renal excretion of bicarbonate results in a lower buffering capacity in the gravid state. These changes make the pregnant diabetic patient more susceptible to DKA by altering the ability to buffer ketoacids. This decreased buffering capacity also places pregnant patients who have diabetes at risk for the development of DKA at lower serum levels of hyperglycemia then those seen in nonpregnant patients [14]. High levels of human chorionic gonadotropin have been associated with emesis, placing a strain on the already hypoglycemic state of pregnancy. Dehydration from emesis leads to a resultant increase in release of stress hormones that, as mentioned previously, have insulin antagonistic effects. Due to the release and effect of these insulin antagonistic hormones, any event that leads to stress at the physiologic level places a pregnant patient who has diabetes at risk for the development of DKA.

How this disease affects pregnancy

One of the most profound effects that a disease can have on a pregnancy outcome involves fetal loss. Current literature from the last decade supports a fetal loss rate of approximately 9% [4,14]. Although the exact mechanism remains unknown, several pathophysiologic aspects of DKA probably contribute to fetal loss. Fetal status during correction of DKA is based on limited case reports demonstrating fetal heart rate tracings that are concerning for fetal distress and on animal models of DKA [16,17]. Decreased uteroplacental blood flow almost certainly plays a major role. The massive osmotic diuresis that takes place during DKA leads to intravascular volume depletion, culminating in a decrease in and redistribution of maternal cardiac output, resulting in decreased uteroplacental blood flow. Along with the osmotic effects of DKA, maternal acidemia itself can reduce uteroplacental perfusion, as can maternal cardiac arrhythmias resulting from potassium disturbances [18].

Another proposed mechanism involves the fetal response to the metabolic derangements of DKA. Glucose and ketoacids are readily transported across the placenta to the fetus. Studies in ewes have demonstrated that increased maternal ketoacids and hyperglycemia can lead to lactic acidosis and hypoxia in the fetuses [19,20]. This acidosis is thought to occur by several pathways: (1) fetal hyperglycemia resulting in fetal osmotic diuresis and hypovolemia, contributing to lactic acidosis; (2) fetal hyperinsulinemia causing an increased fetal oxygen demand; and (3) increased affinity of maternal hemoglobin for oxygen due to decreased 2,3-DPG levels, lowering the amount of oxygen available to the fetus [21].

Limited literature exists regarding long-term outcomes on surviving fetuses exposed to episodes of DKA in utero. Two studies suggest that there may be an association between levels of ketoacids during pregnancy and mental outcome. Stehbens and colleagues [22] showed an association between lower-level IQ scores and elevated ketoacid levels of pregnant patients who had diabetes. Another study related specifically to maternal levels of β-hydroxybutyrate during the third trimester showed an association with decreased mental development scoring during the second year of life [23]. Although these findings are worrisome, their results should not be construed as an indication to expedite delivery of a fetus before the woman who has DKA is sufficiently stabilized and the pathophysiology is corrected.

Risk factors for diabetic ketoacidosis

Many studies have been performed on precipitating causes of DKA in hopes to better recognize and prevent the onset of this disease process. Rodgers and Rodgers [3] looked at variables associated with DKA in pregnancy by retrospectively reviewing admissions of affected patients over a 10-year period. These data were then compared with the existing literature

regarding DKA in pregnancy, for a total of 64 cases. The most common precipitating event was emesis from any cause, accounting for 42% of DKA cases in their study. The second most common precipitating event was use of β-sympathomimetics, and when combined with emesis, these events accounted for 57% of episodes of DKA in this study. Other contributing variables included infection, poor patient compliance, insulin pump failure, undiagnosed diabetes, and physician management errors. A total of 80% of DKA episodes in this study could be attributed to β-sympathomimetics, emesis, poor compliance, and physician management errors. In a similar study, Montoro and colleagues [9] found that poor patient compliance was the most common variable inciting episodes of DKA. Cessation of insulin use in the study population accounted for 35% of DKA episodes, whereas infection accounted for 20%. Based on these studies, seven general factors can be associated with precipitating the onset of DKA during pregnancy: emesis, infection, poor compliance/noncompliance, insulin pump failure, use of β-sympathomimetics, use of corticosteroids, and poor physician management. Given these adverse effects of tocolysis with β-sympathomimetics, magnesium sulfate is the recommended agent for tocolysis of preterm labor in pregnancies complicated by diabetes or in the setting of DKA. Corticosteroid therapy also poses a similar risk when administered in an effort to increase pulmonary lung maturity and decrease intraventricular hemorrhage in the anticipation of preterm delivery. Nonetheless, corticosteroids should not be withheld from women who have diabetes out of fear of potential DKA. Rather, the physician should have concern and anticipation for the onset of DKA (or worsening of its course) and plan accordingly. This anticipation of DKA may involve admitting a diabetic woman who is to receive steroids to a unit in which frequent assessment of maternal and fetal condition can be made and initiating an insulin drip to control blood glucose levels.

Clinical presentation

DKA has classic clinical findings, none of which are pathognomonic of the disease process but still raise a high level of suspicion for its presence. The diagnosis of DKA is best made by ascertaining the patient's symptoms and findings on physical examination and by confirming the diagnosis with laboratory studies. Patients suffering episodes of DKA generally present with hyperventilation, altered mental status, weakness, dehydration, vomiting, and polyuria. As previously discussed, the conversion of acetoacetate to acetone by way of decarboxylation can lead to a fruity odor that is apparent on the patient's breath. Hyperventilation occurs as a response to ketoacids in the body and is an attempt to decrease overall pH in the blood stream by removing carbon dioxide by way of respiratory means. Altered mental status is also an effect of the buildup of ketoacids and represents the effects an

acidic environment has on the brain itself. Infrequently, the level of acidosis can be so severe that patients may be completely obtunded. Vomiting, dehydration, and polyuria are related to the osmotic diuresis that takes place during episodes of DKA. Vomiting can be a response to this diuresis or, as is discussed later, an inciting event.

The laboratory findings seen in DKA can be used to help confirm a correct diagnosis of the disease. Findings of hyperglycemia, acidosis, and ketonemia are generally seen in all cases of DKA [24]. Plasma glucose levels are usually well over 300 mg/dL, but episodes of DKA in pregnancy can be seen at much lower glucose levels in pregnancy. Blood glucose levels less than 200 mg/dL have even been reported in some cases of DKA during pregnancy [4]. Acidosis is present and can be confirmed by arterial blood gas revealing a pH less than 7.30. An anion gap is present along with this acidosis because the acidosis is caused by unmeasured anions: ketoacids and lactic acid. Arterial blood gas findings also reveal an elevated base deficit that is consistent with a primary acidosis. Serum ketones and urine ketones are present in patients experiencing episodes of DKA. Alterations in sodium and potassium levels can be observed. Potassium may appear to be within normal limits on laboratory results; however, it is likely that the total body potassium is decreased and the patient is hypokalemic. Serum bicarbonate levels are decreased, often to less than 15 mEq/L. Blood urea nitrogen and creatinine levels are elevated due to dehydration and possibly renal failure. Phosphate levels may be decreased as a result of binding to the anions of ketoacids in serum.

Treatment

The cornerstones of the treatment of DKA are aggressive fluid replacement and insulin administration while ascertaining which precipitating factors brought about the current episode of DKA, and then treating accordingly to mitigate those factors. The effects that DKA has on pregnancy make incorporating the mother and her fetus in the plan of care a necessity. Some of the fetal effects of DKA may be only transient and wholly dependent on maternal condition, whereas maternal effects can be longstanding depending on severity. Resolution and treatment of DKA in the mother often leads to correction of the fetal physiologic response to the disease process. Except for the special circumstance of how to handle fetal surveillance during an episode of DKA, it is helpful to keep in mind that pregnancy itself does not alter the management of DKA. In other words, recommendations for volume replacement and correction of hyperglycemia and electrolyte disturbances are the same regardless of whether a person is pregnant. Knowing this is helpful as we communicate with colleagues from different disciplines in the care of these high-risk women.

Effective treatment of DKA in pregnancy requires an organized and multifaceted approach to correct physiologic abnormalities in the mother and

secondarily in her fetus. Initial assessment regarding diagnosis of DKA should be made promptly and an organized plan set in motion. This plan should call on the talents and resources of a multidisciplinary team, which can include the patient's primary obstetric care provider, a perinatologist, an intensive care specialist, an endocrinologist or general internist, and skilled obstetric and intensive care nursing support.

Intravenous (IV) hydration with 0.9% sodium chloride is the recommended initial fluid replacement of choice. Marked hypovolemia can be assumed with fluid deficits of at least 4 to 10 L. Estimating fluid deficit may be difficult, but Carroll and Yeomans [13] recommend calculating 100 mL/kg of body weight when determining overall fluid deficit. Isotonic normal saline should be administered as 1000 to 2000 mL per hour for 1 to 2 hours. This aggressive administration has multiple effects. First, it immediately increases tissue perfusion by increasing the markedly depleted intravascular volume. Second, glucose values are decreased through hemodilution and through increased renal loss of glucose when renal perfusion is improved. After the first 1 to 2 hours, fluids are administered at a rate of 250 to 500 mL/h, with a long-term goal of correcting 75% of fluid deficit over a 24-hour period [13]. Isotonic normal saline may be continued until glucose values are less than 250 mg/dL, at which point administration of an IV solution with 5% dextrose is begun. If hypernatremia develops during administration of isotonic normal saline, then 0.45% normal saline should be administered. After hyponatremia is corrected, one may choose to administer 0.45% normal saline during the remainder of volume resuscitation. An indwelling bladder catheter should be placed to monitor hourly urine output in response to treatment.

Along with aggressive fluid replacement, administration of insulin is a requisite to correcting the disease process of DKA, by eliminating the perceived intracellular hypoglycemia that drives the exaggerated counter-regulatory response. The amount of insulin required to correct and reverse the process of DKA is large, and many algorithms exist for its dosing; however, IV administration is preferred. Regular insulin should be administered IV as a 0.1 U/kg bolus followed by 0.1 U/kg/h. This dosage should place the initial bolus and maintenance insulin level at about 10 U. If glucose levels do not fall by 50 to 75 mg/dL over the first hour, then the hourly infusion rate should be doubled.

Electrolyte abnormalities, particularly hypokalemia, are also addressed. Every patient in whom DKA is suspected should have a comprehensive metabolic profile drawn for laboratory evaluation and repeated frequently when the diagnosis is confirmed. Before administering potassium by way of IV, adequate renal function must be established. If urine output is adequate after IV fluid administration has begun, then appropriate replacement of potassium deficit may begin. Although serum levels of potassium may appear normal, total body potassium is typically low. In addition, insulin administration aimed at correction of hyperglycemia causes intracellular shifts of

potassium, thus worsening an already present potassium deficit. Fluid administration also serves as a sieve on potassium stores as ketoacids become bound to potassium and are excreted in the urine. Potassium should be administered IV and may be replaced with 20 mEq/L of potassium chloride solution. Phosphate levels may appear abnormally low on serum chemistries and may be replaced in conjunction with potassium by administering 10 to 20 mEq/L of potassium phosphate for each 10 to 20 mEq/L of potassium chloride [25]. Anticipation of potassium deficit, on average, can be 5 to 10 mEq/kg of body weight. Serum potassium levels should be maintained at around 4 to 5mEq/L.

The need for replacement of other electrolytes, including magnesium and calcium, is debatable. Studies regarding replacement of these electrolytes have not confirmed a specific benefit, and some investigators believe that serum phosphate need not be replaced unless values fall below 1.0 mg/dL [26].

Much debate surrounds administration of bicarbonate for correction of the metabolic acidosis in cases of DKA. Administration of bicarbonate may cause a delay in the correction of ketoacids in the bloodstream [3]. There has also been a suggestion that administration of bicarbonate can be associated with an ''overshoot'' alklosis or worsening acidemia secondary to increased partial pressure of carbon dioxide (P_{CO_2}) [26]. On the other hand, fetal benefits may come from maternal bicarbonate replacement. According to Lobue and Goodlin [17], administration of bicarbonate to the mother resulted in resolution of fetal heart rate abnormalities including late decelerations and absent beat-to-beat variability. It is concerning, however, that rapid correction of maternal pH and P_{CO_2} levels with bicarbonate administration could lead to elevated fetal levels of P_{CO_2}, thus having a detrimental effect on the fetal ability to maintain adequate oxygen transfer [13]. Other investigators suggest replacement of bicarbonate only in cases of severe acidosis during which pH is less than 5.0 to 7.0 mEq/L [14,25,27].

Several pitfalls exist during the treatment of DKA that the physician should be aware of. A common error is to discontinue or decrease volume therapy inappropriately after glucose levels normalize. Acidemia may still be present despite correction of hyperglycemia, and restoration of circulating volume is critical to its resolution. Without continued and adequate fluid replacement, the possibility for recurrence of DKA exists. To avoid this mistake, the estimated fluid deficit should be calculated based on body weight, as described earlier, and fluid replacement should be continued until this calculated deficit has been remedied.

The desire to discontinue insulin therapy may also exist after hyperglycemia has been corrected, but discontinuation also could result in worsening or continued presence of DKA. It should be remembered that it is the intracellular hypoglycemia, not the serum level of glucose, that determines the level of counter-regulatory hormone activity and that this intracellular hypoglycemia is what drives the DKA process. Correction of the acidemia present in DKA takes much longer than correction of hyperglycemia;

therefore, insulin should be continued at a basal infusion rate of 1 to 2 U/h after normoglycemia is established [28]. Furthermore, early discontinuation of IV insulin in favor of intermittent subcutaneous injections may prolong complete resolution of DKA. IV insulin therapy should not be discontinued until after the first subcutaneous dose of regular insulin is administered [28].

Electronic fetal heart rate monitoring is recommended for gestational ages greater than 24 weeks [14]. Fetal heart rate abnormalities, however, are to be expected in the acute phases of an episode of DKA. It is critical that no intervention on fetal behalf occur unless the mother's condition is stable enough to withstand the rigors of delivery, particularly by cesarean section. Maternal mortality can be the result of operative intervention before full stabilization of the mother.

Summary

It is fortunate that episodes of DKA are rare in pregnancy. When present, however, DKA can represent a life-threatening emergency for mother and fetus. Most cases of DKA occur in patients who have diabetes existing before pregnancy. Several adaptations place the gravid patient who has diabetes at risk for development of DKA. The obstetrician must be aware of several precipitating events that can serve as a catalyst for the onset of DKA. No substitute exists for adequate history and physical examination in the diagnosis of DKA, and subsequent confirmation can be obtained with the hallmark laboratory findings of hyperglycemia, acidosis, and ketonemia. Treatment involves aggressive fluid management, insulin administration, and the identification and treatment of precipitating causes. Care should be taken to stabilize and treat the mother first because most fetal heart rate abnormalities subside after correction of maternal hypovolemia and acidosis.

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Amniotic Fluid Embolism

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Amniotic fluid embolism (AFE) is a catastrophic syndrome occurring during labor and delivery or immediately postpartum. Although presenting symptoms may vary, common clinical features include shortness of breath, altered mental status followed by sudden cardiovascular collapse, disseminated intravascular coagulation (DIC), and maternal death. It was first recognized as a syndrome in 1941, when two investigators described fetal mucin and squamous cells during postmortem examination of the pulmonary vasculature in women who had unexplained obstetric deaths [1]. Since then, many studies, case reports, and series have been published in an attempt to elucidate the etiology, risk factors, and pathogenesis of this mysterious obstetric complication.

The incidence of AFE has been reported in the range of 1 in 8000 to 80,000 deliveries [2]. Two recent large population-based cohort studies have demonstrated the rate of AFE to be 14.8 and 6.0 per 100,000 in multiparous and primigravid deliveries, respectively [3,4]. The true incidence is unclear because this syndrome is difficult to identify and the diagnosis remains one of exclusion, with possible under-reporting of nonfatal cases. There have also been discrepancies in the published maternal mortality rates associated with AFE. In a well-defined United States national registry examining 46 cases of AFE within a 5-year span, maternal mortality rates were reported at 61%, with a neurologically intact maternal survival rate of 15% [5]. Investigators from the United Kingdom report a maternal mortality rate of 37% in their registry of AFE, with 93% of survivors remaining neurologically intact [6]. Other retrospective studies reporting from databases derived from hospital charts have reported maternal mortality rates between 13% and 26%, with normal maternal outcome in 87% of survivors [3,4]. Fetal outcome is poor when AFE occurs before delivery. The fetal

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survival rate approaches 40%, though with 29% and 50% of surviving neonates developing neurologic abnormalities [5,6].

Although the United States national registry did not find any maternal demographic risk factors for AFE, they found that 70% of cases occurred during labor, 19% were recorded during cesarean section, and 11% of cases occurred immediately following vaginal delivery [5]. Other studies have also found an increased frequency of AFE in women who underwent cesarean delivery, with rates between 20% and 60% [4,7]. Approximately 50% of these cases were associated with fetal distress, suggesting that amniotic fluid embolus and associated hypoxia preceded cesarean delivery. This interpretation is supported by studies from the United Kingdom in which only one of the five cesarean deliveries in the registry was performed before the diagnosis of AFE [6]. Rupture of membranes was a consistent finding among 78% of women in the United States AFE registry, with onset of symptoms occurring within 3 minutes of amniotomy in 11% of cases [5]. Another study found maternal age (mean age, 33 years) and multiparity (mean parity, 2.6) to be associated with AFE [4]. Conflicting data have been reported on multiple gestation. The frequency of twin gestation in the national AFE registry was not increased from baseline population estimates but found to be approximately threefold higher in one retrospective analysis [4].

In the large cohort study examining the association between AFE and the induction of labor along with other risk factors, AFE was found in twice as many women who underwent medical induction of labor. This association was even stronger for fatal cases (odds ratio, 3.5). Increased rates of AFE were also found in women who had placenta previa, placental abruption, cervical lacerations, or uterine rupture and in women who underwent operative vaginal delivery [3]. Although eclampsia was also strongly associated with AFE in this study, no risk factor has been consistently substantiated in the literature.

Etiology and pathogenesis

The mechanism of disease for AFE is poorly understood. Early studies describe the histologic presence of amniotic fluid components in lung tissue during postmortem examination in obstetric patients who had unexplained death [1]. This finding was followed by reports of amniotic fluid debris found in maternal circulation in fatal and nonfatal cases of AFE [8,9]. Conventional wisdom describes the efflux of amniotic fluid components into maternal vasculature as driven by a pressure or electrochemical gradient by way of lacerations in the lower uterine segment, endocervical vessels, and placental site [9]. Plugging of the cervical vasculature by amniotic fluid elements has been described, although the mechanism by which this leads to AFE is unclear. In addition, elements of amniotic fluid have been isolated in blood and sputum of pregnant women who did not have clinical evidence of AFE [10,11].

Amniotic fluid contains various concentrations of fetal squamous epithelial cells, lanugo hair, vernix, mucin, zinc coproporphyrin, prostaglandins, and platelet activating factor. One possible mechanism of disease includes the effect of direct procoagulants found in amniotic fluid on maternal systems. The presence of vasoactive substances, such as platelet activating factor, in the placenta and amniotic fluid has been shown to cause increased vascular permeability; bronchoconstriction; platelet aggregation; recruitment of leukotrienes, cytokines, and thromboxanes; and the cascade of prostaglandin production [12]. In one small study examining the effect of autologous fetal membranes on the coagulation profile in pigs, findings were significant for decreased platelets, fibrinogen, and antithrombin III. Although these laboratory abnormalities are consistent with AFE, the syndrome of AFE could not be elicited in this study [13]. Similar studies involving primates also failed to model the syndrome despite procoagulant effects of autologous amniotic fluid [14–16]. Currently, there is no suitable animal model for amniotic fluid embolus secondary to the limitations of autologous amniotic fluid.

Laboratory testing for the fetal antigen sialyl Tn has shown some diagnostic value with AFE [17–19]. Sialyl Tn is a fetal antigen present in meconium and amniotic fluid detected most accurately with the TKH-2 monoclonal antibody [19,20]. In a small Japanese case series, seven of nine women who had the diagnosis of AFE had elevated serum levels of fetal antigen compared with control subjects. In addition, special imunohistochemical stains for the presence of fetal antigen in lung tissue were positive in women who had a history of AFE [18]. An anaphylactic or complement activation reaction to sialyl Tn may explain the mechanism of disease. In one small series, complement activation was found along with high levels of sialyl Tn. Levels of complement C3 and C4 were twofold to threefold lower than normal [17]. When these markers were used for evaluation of anesthesia-induced allergic anaphylaxis, however, similar results were found [17,21].

An alternative immunologic mechanism for AFE involves the possibility of anaphylaxis with massive mast cell degranulation, independent of antigen-antibody–mediated classic anaphylaxis. In early studies, immunohistochemical staining in postmortem cases of AFE revealed elevated numbers of mast cells in the pulmonary vasculature [22]. Tryptase has been examined as a factor involved in anaphylaxis because it is specific to mast cells and has a longer half-life than histamine. In one study using serum tryptase and urinary histamine concentrations as markers for mast cell degranulation, no difference was found between women who had a history of AFE compared with control subjects [17]. Other investigators, however, found elevated tryptase levels in women who had AFE, but these values were compared with nonpregnant control subjects [23,24]. Of note, in some cases when complement is involved in classic antibody-antigen anaphylaxis, mast cell degranulation can occur [25]. The studies evaluating serum tryptase levels in AFE cases did not simultaneously measure complement levels [23,24].

Clinical presentation

Although AFE typically occurs during labor and delivery or immediately postpartum, rare cases of AFE have been reported after midtrimester termination, transabdominal amniocentesis, trauma, and saline amnioinfusion [26–30]. Classic presenting symptoms of AFE include respiratory distress, altered mental status, profound hypotension, coagulopathy, and death [2]. Historical studies have described the presenting symptom as primarily respiratory distress, whereas other studies describe the most common presenting symptom before delivery to be altered mental status. Seizure or seizure-like activity was reported as the initial symptom in 30% of patients involved in the United States national registry, followed by dyspnea (27%), fetal bradycardia (17%), and hypotension (13%) [5]. Over 50% of postpartum patients who had AFE presented with postpartum hemorrhage secondary to coagulopathy [5]. Other signs and symptoms include nausea, vomiting, fever, chills, and headache. Diagnostic criteria used for the United States and the United Kingdom registries for AFE are listed in Box 1.

Due to the vast overlap of the symptomatology of AFE with other disease states, consideration for the differential diagnosis of AFE is warranted. A differential diagnosis for possible AFE is shown in Box 2.

Clinical features of AFE include profound cardiovascular changes. According to the United States national registry, all patients who had AFE experienced hypotension. Most women (93%) had some level of pulmonary edema or adult respiratory distress syndrome along with hypoxia [5]. One explanation for these findings includes the possibility of severe bronchospasm related to the presence of fetal elements in the pulmonary vasculature; however, only 15% of patients were found to have bronchospasm [5]. Transesophageal echocardiograpy and pulmonary artery catheters have demonstrated transiently elevated pulmonary artery pressures in cases of AFE along with left ventricular dysfunction, supporting the notion that these pulmonary findings are consistent with cardiogenic shock. There have also been reports of isolated right ventricular dysfunction with high

Box 1. Diagnostic criteria for amniotic fluid embolism

Acute hypotension and/or cardiac arrest
Acute hypoxia diagnosed by dyspnea, cyanosis, and/or respiratory arrest
Coagulopathy or severe clinical hemorrhage in the absence of other explanations
All of these occurring during labor, cesarean delivery, or dilation and evacuation or within 30 minutes postpartum with no other explanation for the findings

Box 2. Differential diagnosis for women presenting with possible amniotic fluid embolism

Pulmonary thromboembolism
Transfusion reaction
Hemorrhage
Air embolism
Anaphylaxis
High spinal anesthesia
Placental abruption
Peripartum cardiomyopathy
Eclampsia
Myocardial infarction
Septic shock
Uterine rupture

right-sided pressures and tricuspid regurgitation [14,31–37]. In the United States registry, all but two patients experienced cardiac arrest or serious cardiac arrhythmia, with 50% of these events occurring within 5 minutes of symptom onset [5]. Myocardial hypoxic injury may be related to decreased cardiac output and impaired filling, resulting in decreased coronary artery perfusion. Dilation of the right ventricle with subsequent leftward displacement of the interventricular septum may also contribute to myocardial dysfunction [31]. Initially, pulmonary and systemic pressures may be elevated. Although the etiology of these changes is unclear, small studies have reported vasoconstrictive effects of amniotic fluid in animal models [33,38]. This vasoconstriction is often followed by profound hypotension and shock, most likely resulting from cardiogenic or obstructive causes as described earlier.

After initial survival, hypoxia relates more to noncardiogenic shock, whereby severe alveolar-capillary membrane leak leads to increase pulmonary edema and decreased oxygenation [14]. In the presence of DIC, hemorrhagic shock may further complicate the management of the patient who has AFE.

DIC is a common feature of AFE. According to the United States registry for AFE, 83% of patients demonstrated laboratory abnormalities or clinical findings consistent with DIC, regardless of mode of delivery. Onset was variable, with 50% of cases occurring within 4 hours of presentation, often within 20 to 30 minutes of symptom onset [5]. The presence of clotting factors in amniotic fluid has been linked with the possible activation of the clotting cascade in the pulmonary vasculature of affected women [38,39]. Additional data report that increased levels of plasminogen activator inhibitor–1 antigen in amniotic fluid may become active in maternal circulation, leading to consumptive coagulopathy [40]. Within the national registry,

75% of patients who presented with hemorrhage and isolated coagulopathy died despite appropriate aggressive management.

Management

Currently, there are no proven laboratory tests that confirm the diagnosis of AFE. Most events occur in an unpredictable manner and have variable presentation. The initial management goal includes rapid maternal cardiopulmonary stabilization with prevention of hypoxia and maintenance of vascular perfusion. In cases of refractory hypotension, vasopressors may be necessary. Central monitoring for cardiovascular status may assist in these endeavors. Eighty-seven percent of patients in the national AFE registry suffered cardiac arrest. Of these, 40% occurred within 5 minutes from symptom onset. The most common dysrhythmia was found to be electrochemical dissociation, followed by bradycardia and ventricular tachycardia or fibrillation [5]. Ionotropes may need to be added to improve myocardial function. Initial laboratory data should include complete blood count, arterial blood gas, electrolytes, and a coagulation profile. A tryptase level is available at some hospitals, in addition to TKH-2 monoclonal antibody to fetal mucin. With or without evidence of hemorrhage as a presenting symptom, blood products should be ordered expeditiously in anticipation of profound bleeding and DIC. Uterine artery embolization and recombinant factor VII have been used in cases of severe coagulopathy resistant to conventional blood and product replacement [41–43].

Transthoracic or transesophageal echocardiography is often necessary to evaluate cardiac function and to guide treatment, along with a 12-lead ECG. When ischemia or infarction is suspected, cardiac isoenzymes and troponins should be obtained. A chest radiograph should be ordered to evaluate the possibility of pulmonary edema and cardiac enlargement. Diuretics may be used with caution for pulmonary edema.

Other case reports have described the use of continuous hemodiafiltration, extracorporeal membrane oxygenation, and intra-aortic balloon counterpulsation in cases of AFE [44–46]. In one report, early transesophageal echocardiogram demonstrating severe pulmonary vasoconstriction and cor pulmonale led to successful rescue using cardiopulmonary bypass [45].

According to the national registry, 70% of patients were in labor when AFE occurred. When fetuses are undelivered, the fetal mortality rate approaches 20% [47]. Of the surviving fetuses recorded in the registries, 30% were severely acidotic, with a 12% perinatal mortality rate [5,6]. In cases of cardiac arrest, administration of all cardiac support measures, including medications used in resuscitation, should be without delay. The patient can be placed in the left lateral decubitus position before chest compressions to avoid compression of the inferior vena cava by the gravid uterus. In cases in which asystole or malignant arrhythmia is present for greater than 4 minutes, perimortum cesarean delivery should be considered

[48]. Uterine evacuation after unsuccessful resuscitation may not only be therapeutic for the mother but also improve neonatal outcome [48,49]. Intact fetal survival has been shown to be possible when delivery is accomplished within 5 minutes of maternal cardiac arrest [48].

Significant maternal morbidity is associated with AFE. Over 75% of patients in the United Kingdom registry required intensive care management, with an average length of stay of 5.2 ± 9.7 days among survivors. An average of 34 U of blood products was required in these patients [6]. In the United States AFE registry, only 15% of patients who had cardiac arrest survived neurologically intact [5]. Other sequelae include liver hematoma, renal and multisystem failure, and ischemic encephalopathy. There are no data to support recurrence risk for subsequent pregnancies in women who survive [37].

Overall morbidity and mortality of AFE has improved with early recognition of the syndrome and improved resuscitative efforts involving multiple disciplines of medicine. In cases recorded within the United Kingdom registry, women who survived AFE had a shorter time frame between symptom onset and treatment (41.5 minutes versus 108 minutes) [6,50].

Although there are many new research developments in this field, the etiology and the pathogenesis of AFE remain unclear. Currently, there is no "gold standard" diagnostic test. AFE remains a diagnosis of exclusion dependent on rapid bedside evaluation and judgment. Ideal management includes prompt evaluation of and intervention for each of the pathologic events found in this complex obstetric condition.

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Trauma in Pregnancy

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Trauma is the most common cause of nonobstetric morbidity and mortality in pregnancy and complicates at least 6% to 7% of all pregnancies [1–5]. According to the Centers for Disease Control and Prevention, trauma is the leading cause of death in women 35 years or younger [6]. Maternal death rates from trauma may be noted as high as 10% to 11% [7,8]. Death to the fetus is reported to be even higher than death of the mother from traumatic injuries. With trauma, fetal mortality is as high as 65%, from placental abruption, direct fetal injury, unexplained fetal loss, maternal shock, disseminated intravascular coagulation, and other causes [9]. Largely because of the increase in size of the developing fetus and uterus, the risk of trauma to the mother and fetus increases as pregnancy progresses. There is a 10% to 15% risk of maternal or fetal injury from trauma during the first trimester, 32% to 40% in the second trimester, and 50% to 54% during the third trimester [10,11]. Motor vehicle crashes cause most injuries, but domestic violence, penetrating trauma, and head injuries are also frequently seen. It has been estimated that motor vehicle collisions occur during a pregnancy in about 2% of all live births in the United States, or 79,000 children are exposed in utero to a police-reported crash [4,12].

One of the unique characteristics of pregnancy is that relatively minor injuries can be life threatening for the mother and the developing fetus. Anatomic and physiologic changes in pregnancy can mask or mimic injury, making diagnosis of trauma-related problems difficult. To the physician, these features represent a unique challenge because care must be provided

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for two patients. Many physicians are overwhelmed and intimidated in the management of these patients. However, familiarity with normal anatomical and physiologic changes, mechanisms of injuries, and maternal trauma assessment skills enhance the physician's ability to care for the mother and her unborn child.

Anatomic and physiologic changes in pregnancy

Numerous changes take place in the cardiovascular system during pregnancy (Table 1). Beginning in the eighth week of pregnancy, physiologic changes start to appear. Progesterone-related smooth-muscle relaxation leads to a significant decrease in the total peripheral resistance. At 10 to 12 weeks' gestation, blood pressure gradually declines, reaching its nadir around 28 weeks' gestation. The systolic and diastolic pressures have decreased by 5 to 15 mm Hg at this point during the pregnancy. During the third trimester, blood pressure gradually increases, returning to nearly prepregnancy readings. These effects are also seen in central venous pressure as it slowly drops 9 mm Hg to about 4 mm Hg in the third trimester [12]. Progesterone is not the only pregnancy-related hormone that affects

Table 1
Hemodynamic changes during pregnancy

Physiology	Change during normal pregnancy	Normal range during pregnancy
Systolic blood pressure	Decreases by an average of 5–15 mm Hg	110–110 mm Hg
Diastolic blood pressure	Decreases by 5–15 mm Hg	50–70 mm Hg
Mean arterial pressure	Decreases by 10 mm Hg	80 mm Hg
Central venous pressure	Slightly decreases or no change	2–7 mm Hg
Heart rate	Increases by 10–15 beats/min	75–95 beats/min
System vascular resistance	Decreases by 10%–15%	1200–1500 dynes/sec/cm^{-5}
Pulmonary vascular resistance	Decreases by 10%–15%	55–100 dynes/sec/cm^{-5}
Cardiac output	Increases by 30%–50%	6–7 L/min at rest; 10 L/min with stress
Cardiac index	Increases	4.0–4.5
Pulmonary capillary wedge pressure	Decreases	6–9 mm Hg
Oncotic pressure	Decreases	16–19 mm Hg
Blood volume	Increases by 30%–50%	4500 mL
Red blood cell volume	Increases by 30%	—
Hematocrit	Decreases	32%–34%
White blood cell count	May increase	5000–15,000/mm^3
Electrocardiogram	Flat or inverted T waves in leads III, V_1, and V_2; Q waves in leads III and aV_F	—

pregnancy. There is an increase in alpha-receptors within the myometrium stimulated by estrogen. This results in a rise in heart rate of 10 to 15 beats per minute above baseline. Cardiac output increases to 30% to 50% above normal during the second trimester. In labor, there is an additional increase in cardiac output as each uterine contraction results in blood transfer from the uterus back into circulation. Finally, after delivery of the fetus and placenta, maximal cardiac output is achieved as the contracted uterus auto-transfuses the majority of blood it receives back into circulation. This is usually the most critical period. Cardiac output remains elevated at third-trimester values for the first 2 postpartum days, and then it slowly declines to prepregnant values over the next 2 weeks. Blood volume increases by 50% [13] mainly from plasma as red blood cell volume increases only about 30%. A further expansion is seen in multiple gestations. The net effect on the hematologic system is a dilution anemia, the so-called ''physiologic anemia'' of pregnancy. The average hematocrit of pregnancy is 32% to 34%. Nearly all coagulation factors increase throughout pregnancy (Table 2). The net effects of these pregnancy-induced changes are an increase of procoagulants and a reduction in fibrinolysis, thus creating a hypercoagulable state. This hypercoagulable state is a double-edged sword, protecting against hemorrhage at the time of delivery but increasing the risk of thromboembolism.

These hyperdynamic and hypervolemic adaptations help the pregnant patient tolerate the increase in the metabolic demands of the fetus and the expected hemorrhage of childbirth. The average estimated blood losses for a term vaginal delivery and cesarean section are approximately 500 mL and 1000 mL, respectively. This amount of hemorrhage typically results in no change in pulse, blood pressure, or other hemodynamic parameters. The mechanism by which the maternal systemic blood pressure is preserved is the result of vasoconstriction of the uteroplacental and splanchnic circulation. During the prenatal period, this reflex reduces perfusion to the uterus and places the fetus in harm's way to save the mother. It is this mechanism that leads many health care providers into a false sense of security. Because of vasoconstriction of the uterine arteries, the fetus often

Table 2
Changes in coagulation during pregnancy

Coagulation factor	Change during normal pregnancy
Fibrinogen	Increases (normal range 300–600 mg/dL; 3.0–6.0 g/L)
Factors I, II, V, VII, X, XII	Increases
Prothrombin time	Decreases by 20%
Partial thromboplastin time	Decreases by 20%
Protein S	Decreases
Protein C	Minimally increases
Plasminogen activator inhibitor-1,-2	Increases (fibrinolytic activity may not be affected)

shows signs of distress (the fifth vital sign in obstetrics) before an alteration in the maternal hemodynamic parameters. The first maternal signs of distress may not occur until hemorrhage of 1500 to 2000 mL, a precarious time because the mother's condition rapidly deteriorates when blood loss is over 2500 mL. Hemodynamics of the mother are also affected by maternal position. The uterus grows from 70 g to 1000 g, and the entire uterofetoplacental unit averages 4500 g at term. During pregnancy, when the mother is placed in the supine position, the uterofetoplacental unit compresses the inferior vena cava. The result is decreased venous return and preload, and subsequently reduced cardiac output. This diminished cardiac output may result in significant hypotension, which often results in vaso-vagal–type symptoms.

The respiratory system undergoes numerous changes during pregnancy (Table 3). The pregnancy-related increase in blood volume leads to capillary engorgement of the mucosa throughout the respiratory tract, causing swelling of the nasal and oral pharynx, larynx, and trachea. This is compounded by mucosal edema [12]. The end results are difficulty with nasal breathing, epistaxis, and voice changes [14,15]. These changes may be significantly exacerbated by a mild upper respiratory tract infection, fluid overload, oncotic pressure, or the edema associated with preeclampsia. Thus, leading to a severely compromised airway [14,16,17].

Beyond anatomical changes, there are also changes in respiratory physiology. These changes are adaptations to the increasing metabolic demands and oxygen delivery to the fetus. Oxygen consumption increases by 15% to 20% during pregnancy. Progesterone stimulates the medullary respiratory center, resulting in hyperventilation and respiratory alkalosis. The renal tubules are able to metabolically compensate for some of these effects by excreting bicarbonate. However, a slight alkalemia remains. The hyperventilation also results in a decrease in the P_{CO_2} to a level of 27 to 32 mm Hg in the pregnant patient. The tidal volume and minute ventilation

Table 3
Anatomical physiological changes in the respiratory system during pregnancy

Physiology or system	Change during normal pregnancy
Upper airway	Increased edema; capillary engorgement
Diaphragm	Displaced 4 cm cephalad
Thoracic anteroposterior diameter	Increases
Risk of aspiration	Increases
Respiratory rate	Slightly increases in the first trimester
Oxygen consumption	Increases 15%–20% at rest
Partial pressure of carbon dioxide	Decreases (normal range: 27–32 mm Hg)
Partial pressure of oxygen	Increases (normal range: 100–108 mm Hg)
Minute ventilation	Increases 40%
Tidal volume	Increases 40% (normal: 600 mL)
Minute ventilation	Increases 40% (normal: 10.5 L/min)
Functional residual capacity	Decreases 20%–25%
2,3-Diphosphoglycerate	Increases

increase about 40% as the respiratory rate returns to baseline. There is a gradual 4-cm elevation of the diaphragm and increase in the thoracic anteroposterior diameter during the pregnancy. This contributes to a 20% to 25% decrease in functional residual capacity. These changes and increasing levels of 2,3-diphosphoglycerate help to facilitate oxygen release to the fetus. Unfortunately, this process leaves the pregnant patient with diminished oxygen reserve and buffering capacity. In clinical practice, this translates into rapid hypoxia of the mother when respiratory stress is introduced and an inability to compensate for the ensuing acidosis. Fetal oxygenation remains constant provided the maternal Pao_2 remains above 60 mm Hg. Below this Pao_2 level, fetal oxygenation drops precipitously. When fetal oxygen saturation drops by half, the so-called "diving reflex" shunts fetal blood flow away from the liver and abdominal organs to the heart and brain, thereby exposing other organ systems to hypoxic injury [18].

In addition to the cardiovascular and pulmonary systems, other organ systems also undergo significant changes (Table 4). In the abdominal cavity there is compartmentalization and cephalad displacement of intraabdominal organs. There is gradual growth and stretching of the abdomen and peritoneal cavity. This appears to desensitize the peritoneum to irritation in the pregnant patient. Because of these changes, a physical examination for abdominal tenderness, rebound, and guarding may find none of these signs despite the presence of significant injury. Hormonal effects of pregnancy become evident as progesterone decreases gastrointestinal motility and relaxes smooth-muscle tone. The gravid uterus causes a shift in the position of the stomach, which changes the angle of the gastroesophageal junction, resulting in incompetence of the gastroesophageal pinchcock mechanism [19]. These effects place the pregnant patient at risk for regurgitation and pulmonary aspiration. Lower esophageal sphincter tone

Table 4
Anatomical physiological changes in the abdomen and genitourinary system during pregnancy

Physiology or system	Change during normal pregnancy
Intraabdominal organs	Compartmentalization and cephalad displacement
Gastrointestinal tract	Decreased gastric emptying; decreased motility; increased risk of aspiration
Peritoneum	Small amounts of intraperitoneal fluid normally present; desensitized to stretching
Musculoskeletal system	Widened symphysis pubis and sacroiliac joints
Kidneys	Mild hydronephrosis (right > left)
Renal blood flow	Increases by 60%
Glomerular filtration rate	Increases by 60%
Serum creatinine	Decreases (normal 0.6–0.7 mg/dL (50–60 μmol/L))
Serum urea nitrogen	Decreases (normal 3–3.5 mg/dL (1.1–1.2 mmol/L))
Bicarbonate	Decreases (normal 19–25 mEq/L)

decreases, allowing gastric reflux and heartburn during pregnancy [20]. Labor itself also decreases gastric emptying [21,22]. Therefore, the pregnant patient is at increased risk for silent regurgitation, active vomiting, and aspiration during general anesthesia or impaired consciousness [23].

Within the genitourinary system, the pelvic uterus becomes a lower abdominal organ by approximately 12 weeks' gestation. Before 12 weeks, the small size and pelvic location of the uterus make it relatively resistant to injury [24]. After the pregnant uterus becomes abdominal, the location predisposes it to injury from blunt or penetrating abdominal trauma. Perhaps more importantly, uteropelvic blood flow increases markedly during pregnancy. By pregnancy's end, this dramatic increase in pelvic blood flow increases the likelihood of appreciable hemorrhage in the circumstances of uterine injury or pelvic trauma [2,8]. Uterine rupture is relatively uncommon, occurring in less than 1% of pregnant trauma victims, and is generally associated with severe direct abdominal impact [25,26]. Fetal death frequently occurs with uterine rupture, whereas maternal death takes place in 10% of cases of traumatic uterine rupture [18].

The bladder is displaced anteriorly and superiorly by the uterus, effectively becoming an intraabdominal organ and more susceptible to injury. The renal pelves and ureters become dilated from the influence of progesterone and direct compression of the uterus on the ureters [27]. The right ureter is more dilated than the left in the second and third trimester. This occurs under the influence of the sigmoid colon causing rotation of the uterus to the right. The pressure of the gravid uterus on the ureter may obstruct or impede urine outflow. Thus ultrasound evidence of a dilated right renal pelvis is not uncommon [27]. The increase in blood volume during the pregnancy increases renal blood flow by about 60%, leading to an increase in glomerular filtration rate. The end effect is a significantly reduced serum urea nitrogen to less than 10 and serum creatinine by about half (0.8 mg/dL). Therefore, a relatively "normal" serum urea nitrogen and creatinine may reflect a seriously compromised renal function.

Trauma pathophysiology and management in pregnancy

The mechanisms of injury and death are composed of multiple categories, including blunt and penetrating trauma, burns, electrocution, falls, and assaults. Many attempts have been made to identify factors that predict outcomes from maternal trauma, but few have been identified. Hypotension seems intuitive and seems predictive in some studies, but other studies have not validated these data [9,28–31]. It appears that initial maternal acidosis may be a useful indicator [28,32–34], while initial pulse, white blood cell count, hemoglobin, oxygen saturation, and other physiologic or laboratory values are not useful [35–38]. Fetomaternal hemorrhage has also not been shown to be predictive of fetal outcome [38–40]. However, fetomaternal hemorrhage has been associated with uterine contractions and an increased

risk of preterm labor [36,41]. With all these factors influencing the fetus, it is not surprising that the most commonly observed complications of all types of maternal trauma are preterm labor, spontaneous abortion, and placental abruption [7,34,42]. These complications are thought to be secondary to intramyometrial bleeding and disruption of the uterine–placental interface. Intramyometrial bleeding is known to cause contractions by a mechanism that involves the activation of thrombin, lysosomal enzymes, cytokines, and prostaglandins [43,44]. Fortunately, in approximately 90% of cases, as intramyometrial bleeding subsides, contractions also diminish [45]. Penetrating injuries, burns, and electric shock, which are less common than blunt traumatic injury, may involve other mechanisms of pathophysiology. These mechanisms may take the form of cytokines and inflammatory mediators typically seen in systemic inflammatory response [46]. In the following sections, general management and specific management strategies are discussed.

Prehospital care

Paramedics and first responders should seek information regarding pregnancy from female patients of childbearing age because there are specific issues related to the traumatized pregnant patient. Care must be undertaken during the initial assessment because, as previously stated, vital signs and patient symptoms may not reflect the underlying injuries to the patient and fetus. General standard guidelines for trauma patients apply to the pregnant patient with some modification. Extrication should be performed in normal fashion with spinal immobilization being employed for most patients, especially those with blunt force trauma. Placing the patient on a backboard with a 15° angle to the left is a pregnancy-specific intervention to avoid compression of the vena cava by the uterus and resultant hypotension. This technique must be employed in all patients beyond 20 weeks' gestation. Failure to employ this procedure can result in a 30% decrease in cardiac output and possible maternal death from decreased perfusion of vital organs. The use of towels or blankets placed under the backboard is quick, easy, and effective. Supplemental oxygen by nasal cannula or facemask should be given as soon as possible and considered routine. Two large-bore intravenous catheters should be placed and 1 to 2 L of resuscitative fluids initiated. The bolus of fluid may allow for continued perfusion of the uterine placental unit and prevent mild hypovolemia not noted in the vital signs.

Gestational age can be approximated by the size of the gravid uterus (Fig. 1) or by the history obtained from the patient. Fetal viability is extremely likely if the uterine fundal height is between the umbilicus and xyphoid process. It is important to relay this information to the hospital or trauma center. This simple task can allow for the obstetrical and neonatal teams to be mobilized before the patient arrives at the trauma center or to

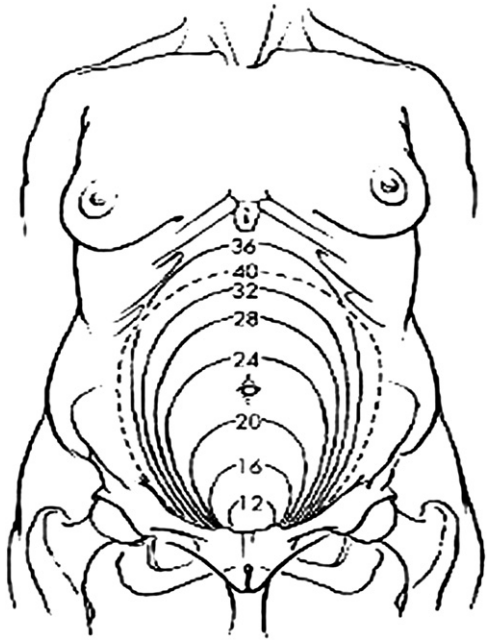

Fig. 1. Uterine size in weeks' gestation.

provide consultation for the medics in the field if needed. It is important to direct the transport to a proper hospital that can care for both the mother and a premature neonate if delivery is necessary. This has led some emergency medical service systems to designate pregnancy as an indication for transport to a trauma facility. Although most patients are unlikely to need the resources of the trauma center, prehospital findings of tachycardia (heart rate >110 beats/min), chest or abdominal pain, loss of consciousness, and third-trimester gestation are associated with an increased need for services available at the trauma center [38]. In the event that prehospital transfusion is required, O-negative blood should be used whenever possible. Emergency medical services that still use military antishock trousers should be aware that it is contraindicated to inflate the abdominal portion of this device for pregnant women. Not only can this maneuver result in reduced uterine perfusion but it also can increase the cardiac workload.

General management

The pregnant trauma patient is best cared for using a team approach. The emergency physician should involve the trauma surgeon and maternal fetal medicine specialist or obstetrician early in the care of these patients. The clinician should perform all necessary tests and procedures on the pregnant

woman that are indicated, including radiologic imaging, intubation, central venous access, ultrasonographic evaluations, and even diagnostic peritoneal lavage (with use of a periumbilical approach or open lavage technique). Because the most common cause of fetal death is maternal death, efforts to assess fetal well-being are secondary to resuscitation of the pregnant woman. However, the well-being of the fetus may represent the most accurate measurement of maternal health. The patient may have experienced a significant loss of blood, but arterial pressure often remains stable due to the increase in blood volume during pregnancy and the shunting of blood flow away from the uterus. This is the normal physiological response of the pregnant woman to stress—self-preservation at the expense of the fetus. For this reason, fluid management is important. Waiting for maternal signs of hypotension will result in fetal compromise and distress. Early transfusion of blood products may assist in providing volume and improve oxygen-carrying capacity. Fetal heart monitoring can be useful to guide the adequacy of fluid resuscitation because fetal heart rate abnormalities may be the first sign of maternal hypovolemia. For this reason, the fetal heart rate has been considered the ''fifth vital sign'' in obstetrics.

The primary survey varies little in the pregnant trauma patient compared with the nonpregnant patient (Fig. 2). During pregnancy, the risk of aspiration increases and monitoring of adequate oxygenation by pulse oximetry is important. Further, because hypoxia results in fetal distress and maternal oxygen reserve is significantly diminished, early endotracheal intubation may be considered. During the first and early second trimester, the woman may be tachypneic, but later in pregnancy other causes of respiratory compromise must be considered. If a chest tube thoracostomy is required, it needs to be placed one or two intercostal spaces higher than usual to avoid diaphragmatic injury. If rapid sequence intubation is required, lower dosages of succinylcholine are required because pseudocholinesterase levels decrease in pregnancy [47]. Both nondepolarizing and depolarizing paralytics cross the placenta. Therefore a flaccid, apneic infant may result.

A rapid but thorough secondary survey must include evaluation of the pregnancy. Great care and precision are needed in performing the abdominal examination because the normal physiologic stretching of the abdominal cavity may mask signs of significant peritoneal injury. Findings consistent with injuries to the liver or spleen include upper abdominal pain, referred shoulder pain, sudden onset of pain, and elevated liver transaminases. A focus assessment sonographic trauma (FAST) scan should be performed for intraabdominal hemorrhage [48,49]. Direct peritoneal lavage using an open (direct) technique is feasible during pregnancy and appears to be without any specific pregnancy-related complications [30,33,50]. The uterus should be palpated carefully because tenderness and contractions may be overlooked. The top of the fundus should be marked to evaluate the possibility of concealed abruption as noted by an increasing fundal height.

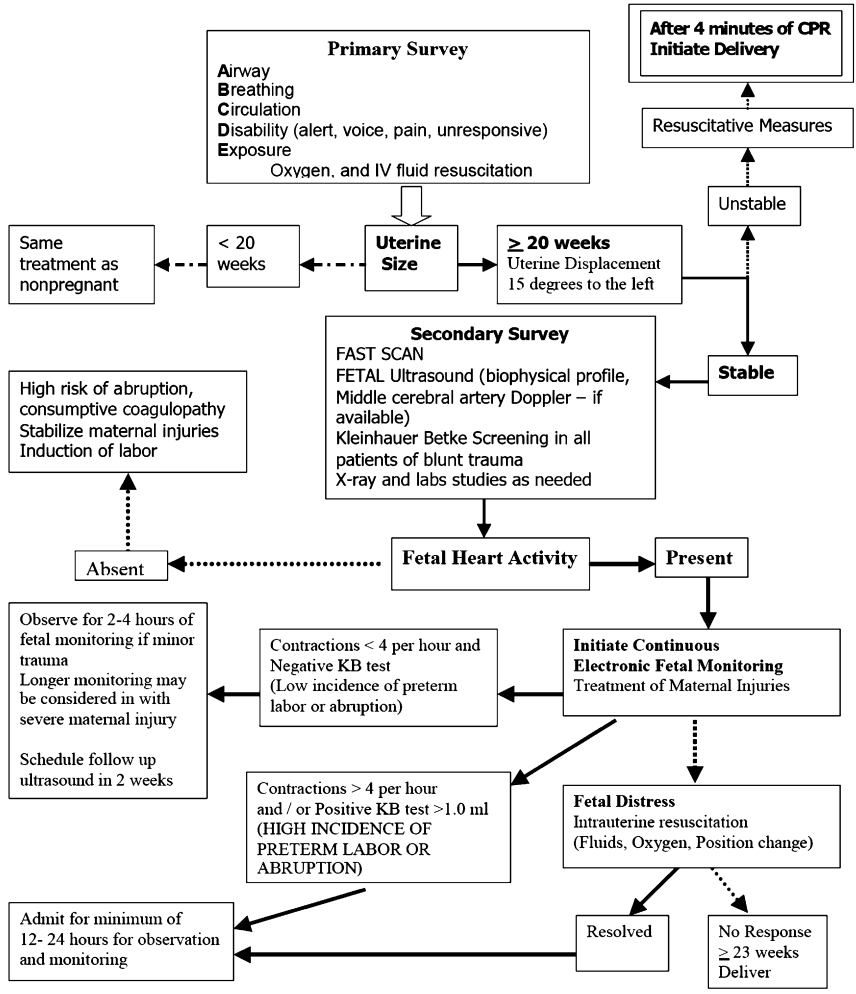

Fig. 2. Maternal trauma algorithm. CPR, cardiopulmonary resuscitation; FAST SCAN, focus assessment sonographic trauma scan; IV, intravenous; KB, Kleihauer–Betke.

A sterile speculum examination is vital in the evaluation of the pregnant trauma patient. Fluid within the vaginal vault may be difficult to differentiate, but the use of nitrazine paper for a blue color change and the presence of ferning on microscopic examination aids in distinguishing alkaline amniotic fluid from urine. Vaginal bleeding may be present, indicating the possibility of placental abruption, uterine rupture, pelvic fracture with vaginal injury, or other injuries. The cervix should be visually inspected for evidence of dilation and effacement. A bimanual examination, which is sometimes overlooked, is an integral part of the secondary survey.

Cardiotocographic monitoring needs to be initiated in the emergency department as soon as possible, preferably on arrival after the secondary survey and FAST scan, because uterine contractions or irritability may subside with time. All pregnant women at 20 weeks' gestation or longer should have cardiotocographic monitoring for 2 to 6 hours after a traumatic injury [51]. Monitoring times should be increased in those with contractions, abdominal pain, or significant maternal injury. An ultrasound of the fetus and placenta can be performed after the FAST scan or incorporated as part of an obstetrical/FAST trauma scan. Fetal ultrasound evaluation should include position of the fetus and heart rate, gestational age assessment, biophysical profile, fetal middle cerebral artery Doppler peak velocity for anemia, and evaluation of placenta for abruption. Unfortunately, ultrasound has a low sensitivity for detecting placental abruption (50%) [52]. However, the positive predict value is high. Ultrasound findings suggestive of placental abruption are (1) retroplacental hematoma (hyperechoic, isoechoic, hypoechoic), (2) preplacental hematoma (gelatin-like appearance—shimmering effect—of the chorionic plate with fetal movement), (3) increased placental thickness and echogenicity, (4) subchorionic collection, and (5) marginal collection.

The fetus may also be screened for acute anemia by Doppler ultrasound of the middle cerebral artery. This may identify fetal anemia before cardiotocographic monitoring indicates distress. In cases of penetrating trauma, it is important to evaluate the placenta as it relates to the site of injury. Visualization of streaming indicates placental vessel injury likely needing immediate delivery.

Laboratory testing in the pregnant trauma patient should include hemoglobin, hematocrit, coagulation studies, typing and cross matching, and a gross inspection of the urine. Prenatal laboratory tests may be helpful if original prenatal laboratory results are not available. A serum bicarbonate level, blood gas analysis, or lactate level may be considered in severe trauma, as some evidence suggests that maternal acidosis may be linked to fetal outcome [28,32,33]. A fibrinogen level that is normal in a nonpregnant patient may be abnormal for pregnancy and may be an early indicator of placental abruption with a consumptive coagulapathy. A Kleihauer–Betke test should be considered in all trauma patients because it may be an indicator of the severity of uterine–placental trauma present and an indicator of those patients at risk of preterm labor [36]. An Rh-negative patient with a positive test should be treated with Rh-immune globulin (300 μg initially and an additional 300 μg for each 30 mL of estimate whole fetal blood) to reduce the risk of isoimmunization. The Rh-negative patient with significant trauma with a positive Kleihauer–Betke test, should have repeat Kleihauer–Betke testing and additional antibody screening (Coombs testing) 24 to 48 hours after the trauma. A negative antibody screen indicates the need for additional Rh-immune globulin.

Diagnostic studies should be obtained in the pregnant trauma patient for the same indications as in nonpregnant patients. No study to date has

shown any increase in teratogenicity for a fetus exposed to less than 10 rad or 100 mGy. Growth restriction, microcephaly, and mental retardation can occur with high-dose radiation well above that used in medical imaging [53]. The fetus is most at risk for central nervous system effects from 8 to 15 weeks and the threshold appears to be at least 20 to 40 rad or 200 to 400 mGy. The American College of Obstetricians and Gynecologists (ACOG) has published recommendations for diagnostic imaging during pregnancy [54]. They state that a 5-rad or 50-mGy exposure to the fetus is not associated with any increased risk of fetal loss or birth defects. Radiation dosages by study are listed in Table 5. The fetal radiation dose without shielding is 30% of that to the mother. Mandatory shielding of the fetus decreases exposure further and should be performed for all studies except for pelvic and lumbar spine films and CT scans. If multiple diagnostic radiographs are performed, then consultation with a radiologist or radiation specialist should be considered to calculate estimated fetal dose as recommended by the ACOG. This is extremely important when radiation exposure approaches 5 to 10 rad or 50 to 100 mGy.

Perimortum cesarean section

In cases of maternal cardiac arrest with potential fetal viability, perimortem cesarean section should be performed when resuscitative measures have

Table 5
Radiation exposure to a unshielded uterus/fetus

Imaging study	Uterine radiation dose in rads	Uterine radiation dose in milligray units (mGy)
Plain film studies		
Abdomen (AP)	0.133–0.92	1.33–9.2
Abdomen (PA)	0.064–0.3	0.64–3
Cervical spine	Undetectable	Undetectable
Chest (AP)	0.0003–0.0043	0.003–0.043
Chest (PA)	<0.001	<0.01
Femur (AP)	0.0016–0.012	0.016–0.12
Hip (AP)	0.01–0.21	0.1–2.1
Pelvis (AP)	0.142–2.2	1.42–22
Full spine (AP)	0.154–0.527	1.54–5.27
Lumbar spine (AP)	0.031–4.0	0.31–40
Thoracic spine (AP)	<0.001	<0.01
Computed tomography		
Upper abdomen	3.0–3.5	30–35
Entire abdomen[a]	2.8–4.6	28–46
Head	<0.05	<0.5
Pelvis[a]	1.94–5.0	19.4–50
Thorax	0.01–0.59	0.1–5.9

Shielding reduces exposure by 30%.
Abbreviations: AP, anteroposterior; PA, posteroanterior.
[a] Depends on trimester.

failed. The best outcomes occur if the infant is delivered within 5 minutes of maternal cardiac arrest. This means the decision to operate must be made and surgery begun by 4 minutes into the arrest [30,55–57]. The latest reported survival was of an infant delivered 22 minutes after documented maternal cardiac arrest [58]. Several factors must be considered when deciding whether to undertake perimortem cesarean section [55,59–62]. These include estimated gestational age (EGA) of the fetus and the resources of the hospital. The ability to salvage a fetus under ideal circumstances (availability of all skilled personnel and a controlled setting) may range from 23 to 28 weeks' EGA. If the fetus is known to be 23 weeks' EGA and the institution's nursery has never had a newborn of this EGA survive, perimortem cesarean section is probably not indicated for the sake of the fetus, but may improve maternal circulation by increasing cardiac return. Before 23 weeks' gestational age, delivery of the fetus may not improve maternal venous return. Therefore aggressive maternal resuscitation is the only indicated intervention. There has been at least one reported case of complete maternal and fetal recovery after a prolonged arrest at 15 weeks' gestation [63].

Blunt trauma

Blunt trauma during pregnancy may be the result of motor vehicle accidents, accidental falls, and violence. Different mechanisms of maternal injury occur in pregnant women with blunt abdominal trauma compared with injuries to their nonpregnant counterparts [28]. Because the gravid uterus changes the relative location of abdominal contents, transmission of force may be altered in the pregnant abdomen. Due to increased vascularity during pregnancy, splenic and retroperitoneal injury and hematomas are more frequent in pregnant victims of blunt abdominal trauma [64,65]. Up to 25% of pregnant women with severe blunt trauma manifest hemodynamically significant hepatic or splenic injuries [66]. Conversely, bowel injury is less frequent [45,67].

Pelvic fractures are another concern during pregnancy and may result in significant retroperitoneal bleeding [68]. Management is unchanged from the nonpregnant patient, with consideration for associated injuries of the bladder, urethra, or rectosigmoid. The presence of a pelvic fracture is not an absolute contraindication for vaginal delivery. A safe vaginal delivery can be performed provided the pelvic architecture is not substantially disrupted and the old fracture is stable [51].

The manifestations of the trauma on the pregnancy may be placental abruption, preterm labor, or late-onset growth restriction. The underlying cause for each of these is the extent of placental injury. The placenta does not contain elastic tissue and thus does not have the capacity to expand and contract. In contrast, the uterus contains elastic tissue and can react to acceleration–deceleration forces by changing its shape, in turn generating

very high intrauterine pressures. This produces a shearing effect on the placental attachment with resultant separation from the uterine wall, and is the most likely mechanism for the abruption in blunt trauma [69,70]. Placental abruption is present in up to 40% of women with severe maternal trauma. However, clinically evident abruption occurs in approximately 1% to 5% of women with minor trauma as well when associated with deceleration and/or uterine-directed force [71]. Fetal death is the result of placental abruption in 50% to 70% of cases from motor vehicle collisions [72]. Severe maternal injuries results in fetal death 20% to 40% of the time, and fetal death from uterine rupture or direct fetal injury accounts for less than 10% of the cases [4]. However, maternal death still ranks as the number one cause of fetal death.

Direct fetal injuries and fractures complicate less than 1% of cases of severe blunt abdominal trauma in pregnant women. The reasons for the low fetal injury rate are the protective nature of the maternal soft tissues, uterus, and amniotic fluid, the mandatory use of seat belts and shoulder restraints, and the presence of airbags as standard equipment in automobiles. Most such cases of fetal injury occur during late pregnancy in gravidas [73,74]. Fetal brain and skull injuries may be more common in cases with fetal head engagement in which maternal pelvic fracture occurs [75,76]. Deceleration injury to the unengaged fetal head may also occur [77].

It is believed that airbags, in conjunction with proper seat belt use, affords the best protection to the pregnant woman and her unborn child. The National Highway Traffic Safety Administration does not consider pregnancy as an indication for deactivation of air bags [78]. They recommend, however, that airbags be disconnected if vehicle occupants cannot position themselves with their sternum (or uterine fundus) at least 10 in back from the center of the airbag cover. This is because, with frontal airbag deployment, the cushion expands at a speed of about 125 mph toward an individual [79]. Consequently, a person within this expansion zone—that is, within 10 in from the steering wheel hub or airbag cushion—is at considerable risk for injury. Placental abruption, as well as fetal or uterine injury, is a potential complication of airbag impact with the gravid abdomen because of the proximity of the gravid uterus to the rapidly and forcefully deploying airbag [80]. Relatively minor accidents with no maternal injury have resulted in severe fetal injury. Data on airbag safety is based only on case reports [69,81] and a small case series of 30 patients [82]. No conclusive large-scale data exists and until such data suggests harm, the use of airbags during pregnancy is recommended.

Penetrating trauma

Penetrating trauma in pregnancy is usually the result of gunshot or knife wounds. Other causes are much less frequent. Gunshot wounds are more common than knife wounds. The maternal death rate from gunshot wounds

to the abdomen occurs in 3.9% compared with 12.5% of nonpregnant victims. The death rate from abdominal stab wounds is also lower for pregnant women compared to nonpregnant victims. The reduction in mortality stems from the anatomical changes induced by pregnancy. Visceral organs are displaced superiorly by the uterus, which results in the so-called ''protective effects'' of the uterus. Thereby visceral injuries are less common during pregnancy as well [83]. However, when penetrating trauma involves the upper abdomen, a pregnant woman is more likely to sufer a viseceral injury than if she were not pregnant. In these cases, the small bowel is more frequently injured, especially during the third trimester. Upper abdominal entry is also the most common site of abdominal stab wounds during pregnancy. The uterus and fetus are at increased risk for direct injury as they grow cephalad. Fetal injuries complicate 66% of gunshot injuries to the uterus [84]. Fetal mortality ranges from 40% to 70% in cases of penetrating trauma and generally results from either premature delivery or direct fetal injury by the missile [84]. Stab wounds to the abdomen are less common than gunshot wounds in the pregnant patient and are less likely to result in fetal death. The disparity probably results from the protective effect of the large muscular uterus on visceral organs. Gunshot wounds cause transient shock waves and cavitations as they impart their kinetic energy to the high-density tissues of the body, thus causing more severe injury patterns than low-velocity knife wounds.

Several key factors need to be considered in the management of penetrating abdominal trauma in the pregnant patient. Traditionally, in the nonpregnant patient, the universal recommendation is immediate surgical exploration of these injuries. However, the pattern of organ injury changes with gestational age. For the pregnant patient with penetrating trauma, management has become more controversial. Management options include immediate surgical exploration, diagnostic peritoneal lavage, laparoscopy, contrast-enhanced CT scanning, local wound exploration, and observation. Penetrating trauma to the upper abdomen is associated with an increased risk for maternal bowel injury and operative management is indicated [85]. In the lower abdomen, the uterus seems to provide some protection from missile injury and a more individualized approach may be more appropriate. If the entrance wound of the bullet is below the uterine fundus, and the bullet remains in the body of the uterus, the incidence of visceral injury is less than 20% [2]. However, the fetus has a higher incidence of injury from direct trauma to the uterus. Therefore an individualized approach for conservative management in lower abdominal injuries is needed, balancing maternal and fetal concerns [66]. Pregnant patients with anterior abdominal stab wounds below the level of the uterine fundus are the best candidates for conservative management [85]. However, the physician should have a very low threshold for surgical exploration in which conservative management is considered. Diagnostic peritoneal lavage, fistulogram, and ultrasound all may be used in the conservative management of stable lower-abdominal penetrating injury during pregnancy.

During exploratory laparotomy for the evaluation and management of penetrating trauma during pregnancy, the uterus should receive careful inspection with as little traction or twisting of the uterus as possible because this may decrease blood flow to the fetus. Delivery of the fetus is rarely necessary unless there is direct perforating injury to the uterus or fetal death. In cases of uterine injury, care should be individualized to reflect the type of injuries present, the gestational age of the fetus, and the maternal and fetal prognosis if undelivered. Delivery of the fetus by cesarean section may be required if the gravid uterus prevents surgical exposure for repair of maternal injuries or in the presence of nonreassuring fetal status. In cases of fetal death, it is often possible and preferred to attempt vaginal delivery by induction of labor.

Fetal evaluation should include heart-rate tracing with an ultrasound examination of the fetus (ie, biophysical profile, middle cerebral artery peak systolic velocity Doppler). In a clinically stable fetus and mother with suspecting uterine injury, Kleihauer–Betke testing or flow cytometry for fetomaternal hemorrhage should be considered due to the possibility of placenta bed disruption. Finally, the decision for conservative or operative management should be made to ensure the best outcome for the mother and the fetus.

Electric shock

The incidence of fetal injury after electric injury to the mother is not known, but injuries appear to be rare during pregnancy. When electrical injury does happen, it involves both direct and indirect mechanisms. The direct damage is caused by the actual effect that the electric current has on various body tissues (eg, the myocardium) or by the conversion of electrical to thermal energy that is responsible for various types of burns. Indirect injuries tend to be primarily the result of severe muscle contractions caused by electrical injury. In general, the type and extent of an electrical injury depends on the intensity (amperage) of the electric current and resistance of the conducting material. Thus, exposure of different parts of the body to the same voltage will generate a different current (and by extension, a different degree of damage) because resistance varies significantly among various tissues [86]. The least resistance is found in amniotic fluid, nerves, blood, mucous membranes, and muscles; the highest resistance is found in bones, fat, and tendons. Skin has intermediate resistance.

The spectrum of injury from accidental electrical shock for the mother ranges from a transient unpleasant sensation after exposure to low-intensity current to sudden death due to cardiac arrest. Fortunately for most pregnant women, electrical shock from low-voltage current, such as that used in North America (110 V), results in no or minimal adverse effects on the mother. In most cases, the current travels hand to hand and not hand to foot, avoiding the uterus and is unlikely to acutely affect the fetus. This

may not be the case in hand-to-foot transmission. When electrical current traverses through the uterus, there is a high incidence of fetal death even when the woman has no adverse symptoms after the event. In these cases, fetal death may be immediate or might not become apparent until several hours after injury [87]. Other fetal complications, including growth restriction, abruption, and abortion, have been reported following electrical shock [88–95]. Due to publication bias, reports of adverse outcomes are more often published than reports of normal outcomes. Consequently, the literature does not reflect the usual outcome of contact with low-voltage current [96].

Although fetal and obstetric surveillance is recommended following electrical injury, there is no evidence that any form of monitoring or treatment has a direct effect on outcome. Recommendations for fetal monitoring after electric shock have been published [97]. No fetal monitoring is required before 20 weeks' gestation. During the second half of pregnancy, fetal ECG is recommended if it has not been performed earlier. Maternal ECG and the monitoring of fetal heart rate and uterine activity are recommended for 24 hours if the injury involved loss of consciousness, abnormal maternal ECG results, or known maternal cardiovascular illness. If a fall resulted from the electrical shock, then fetal and uterine monitoring is indicated for 2 to 4 hours, which is the same as for patients with blunt trauma. The fetus should have an ultrasound evaluation 2 weeks after the incident for fetal well-being.

Burns

Burns sustained during pregnancy have been reported as increasing the mortality and morbidity of both mother and infant. The extent of injury and treatment is determined by body surface area and depth of injury (Table 6). Burns mainly consist of two groups, minor burns and major burns. The pregnant patient with a minor burn (<10% of the total body surface area) often does not require hospitalization and it rarely presents a threat to maternal or fetal well-being [98]. However, when a major burn is present, management is more challenging. The pregnant woman who has a major

Table 6
Characteristics of burn injury according to depth

Depth	Description
Superficial	Moist red wound that blanches with rapid refill
Superficial dermal	Pale dry wound with slow color return after blanching
Deep dermal injuries	Mottled cherry-red wound that does not blanch; damage within the capillaries in the deep dermal plexus
Full thickness	Dry leathery or waxy hard wound that does not blanch; may be mistaken for unburnt skin in appearance

burn is subject to all of the serious complications that occur in the nonpregnant woman with a burn, including cardiovascular instability, respiratory distress, sepsis, and renal and liver failure. The greatest risk occurs when the total body surface area burned is over 60% [99]. With improvement in the overall survival of burn patients, pregnant women with burns also stand a better chance of survival. The best chance of fetal survival occurs when the mother survives and remains free of severe complications, such as sepsis, hypotension, hypoxia, and death.

The overall treatment of a burn patient is unchanged by pregnancy. The basic principles of management include support of respiratory function and stabilization of airway injury, fluid and electrolyte management, infection control, nutritional support, eschar debridement, wound coverage with autografts, and the prevention and treatment of any complications.

Inhalation injuries are known to increase the mortality rate in burn victims and are highly problematic. Pregnant women with facial burns should be monitored carefully for breathing difficulties. Inspection via bronchoscopy may be necessary and intubation may be required if the patient is not adequately oxygenated. Dyspnea and wheezing may develop when overwhelming irritation is present, but often are not seen during the first 12 to 48 hours after injury. The avoidance of hypoxia is most important, and early oxygen therapy is always advised. Continuous pulse-oximetry is helpful in assessing oxygenation. Bronchodilators and assisted ventilation may be necessary. Corticosteroids and prophylactic antibiotics have not been shown to be effective adjunctive therapies in the treatment of respiratory complications.

Carbon monoxide is frequently inhaled in a closed fire and freely crosses the placenta. Because fetal hemoglobin has a higher affinity for binding carbon monoxide, the effects may be more pronounced in the fetus than in the adult. Exposure to carbon monoxide in utero may affect cardiac development and may produce fetal cardiac edema. Oxygen is the treatment of choice, and ventilation with 100% oxygen will reduce the half-life of carboxy-hemoglobin from 4.5 hours to approximately 50 minutes [100].

The second challenge in the pregnant burn patient is fluid loss. Fluid losses are the greatest in the first 12 hours after the injury. Fluid shifts may result in decreased uteroplacental circulation. These result in acute ischemic changes in the placenta and may lead to fetal hypoxia and acidosis. Even if the burned area is only 15% of total body surface area, sufficient fluid loss may occur for the patient to become hypovolemic. According to the Parkland formula, the fluid requirement in the first 24 hours postburn is 4 mL/kg body weight per percent of body surface area burned [101]. One half of the calculated fluids are given in the first 8 hours and the rest in the next 16 hours. In pregnancy, total body surface area is increased. The pregnant burn patient requires additional fluid resuscitation beyond amounts seen in nonpregnant individuals, rendering the Parkland formula inaccurate. It is important to maintain normal maternal hemodynamics

and adequate urine output. Invasive central hemodynamic monitoring may be necessary in cases involving cardiac or pulmonary compromise or in situations with inadequate urine output. If urine output remains low, renal dose dopamine (1–2 μg/kg/min) should be given. Interstitial edema can be expected to resolve within a few days, as noted by profound diuresis. Both hyponatremia and hypokalemia can result from a serious burn injury and its mismanagement. Hyponatremia is often the result of dilution effects of intravenous fluids as well as fluid losses through the gastrointestinal and genitourinary tracts and directly through the wound. Hypokalemia also can result from chronic potassium losses through the wound. Frequent monitoring is needed and the deficits should be corrected with potassium.

Other major concerns are nutrition and infection. The hypermetabolic state for the pregnant mother is amplified after a burn injury. Adequate nutritional support is essential during this period. Early enteral nutrition is vital in the management of the pregnant burn patient. A nasogastric tube is required if the burn is greater than 20% of the total body surface area. These burn patients often develop an ileus. The increased metabolic state of the patient also has an impact on the risk of infection. For the burn patient, infection is one of the most devastating complications. Septicemia and respiratory infections account for the majority of all deaths in burn patients and their fetuses. The use of prophylactic antibiotics is controversial, and treatment should be based on blood cultures and sensitivities.

The risk of preterm labor increases with increasing total body surface area burned. The best way to reduce the risks of preterm labor and fetal demise is to maximize the health of the mother by preventing hypovolemia, sepsis, hypoxia, and electrolyte imbalances. When preterm labor occurs, treatment is considered controversial. The use of tocolytic therapy may be considered when the total body surface area burned is less than 30% to 40% and the estimated gestational age is between 24 and 32 weeks, as long as fetal monitoring is reassuring [102]. Corticosteroids to enhance fetal lung maturity should be given because of the risk of premature delivery. The mode of delivery in the pregnant burn patient is decided by obstetrical indications. Vaginal deliveries are possible even in cases of extensive perineal burns, and grossly infected perineal burns seem to have no effect on neonatal survival. When a full-thickness perineal burn occurs, the tissue loses its elasticity and an episiotomy might be required. Cesarean delivery may be performed over a burned abdomen when obstetrically indicated.

Spinal cord injuries

The initial management of a spinal cord injury focuses on stabilization of the neck and airway maintenance [103]. When multiple injuries are present, it is important to rule out internal hemorrhage. The pregnant patient with acute spinal injury is treated the same as the nonpregnant patient and

should receive intravenous methylprednisolone within 8 hours of the injury and continued for 24 hours. This is associated with significant improvement in motor and sensory function 6 months after the injury [104]. It is also important to avoid maternal hypotension so as to maintain uterine blood flow and reduce the risk of secondary ischemic damage in the evolving lesion of the cord.

The management of a spinal cord injury in pregnancy depends upon the site, extent, and duration of the lesion. Complete transection of the cord is associated with neurogenic shock, cardiovascular instability, and autonomic hyperreflexia. Neurogenic shock develops with the blockade of the sympathetic autonomic function by the cord injury, and is characterized by a dominance of parasympathetic autonomic system. The patient typically develops hypotension and bradycardia with decreased cardiac output, and warm dry skin leading to loss of heat and hypothermia. Fetal distress may follow. These effects from neurogenic shock generally last from 1 to 3 weeks. Fluid management should be guided by central venous monitoring, as the typical signs of hypovolemia may not be present. Positive inotropic agents, such as dopamine and dobutamine (1–5 mg/kg/min), may be needed to enhance cardiac output, perfusion pressure, and renal perfusion. These agents appear to be safe in pregnancy because they do not reduce uterine perfusion and are not associated with teratogenic effects of the fetus.

Autonomic hyperreflexia or dysreflexia, which occurs in up to 85% of patients with a spinal cord injury above the level of the splanchnic autonomic outflow (T5/6), is caused by unregulated sympathetic nervous system activity. The occurrence of autonomic hyperreflexia may signal the resolution of the period of neurogenic shock. The initiating stimulus is below the level of the spinal injury and may be the result of labor, a full bladder, or a distended rectum or bowel. This stimulus results in a paroxysmal release of catecholamines. The patient may experience severe hypertension, tachycardia, reflex baroreceptor-mediated bradycardia, throbbing headaches, flushing, skin blotching, sweating, piloerection, nasal obstruction, chest pain, nausea, tremor, and feelings of anxiety. Serious complications, including convulsions, permanent neurological deficit, intracerebral hemorrhage and death, may occur. Management involves interruption of the reflex arc with regional anesthesia or inhalation anesthesia [105]. If anesthesia is not available, then intravenous labetalol or nitroprusside, diphenhydramine, hydralazine, diazepam, and guanethidine can be used. However, careful titration of these medications is required to avoid hypotension.

Finally, apart from complications listed above, these patients also have long-term needs. Special attention is needed to avoid urinary-tract infections, constipation, pressure sores, thrombosis, and repeat episodes of autonomic hyperrflexia. The mode and timing of delivery should be in accordance with the usual obstetric indications, unless the pregnancy impedes proper monitoring and care. The obstetric outcome is usually

good. Where the patient has sustained permanent injury, most of the above factors should be taken into consideration with a subsequent pregnancy.

Traumatic brain injury

Management of traumatic brain injury depends on the type and severity of injury. The initial management of the head-injured gravida focuses on maintaining ventilatory and circulatory function, cerebral blood flow, and normal physiologic functions of the mother and fetus. Guidelines for the management of severe traumatic brain injury have been published [106] and the role of neurosurgical intervention is unchanged by pregnancy.

Early postinjury hypoxia and hypotension greatly increase morbidity and mortality in traumatic brain injury patients. Accordingly, hypotension and hypoxemia should be closely monitored and treated. Patients with a Glasgow Coma Score less than 9 and who are unable to maintain their airway or who remain hypoxemic despite supplemental oxygen require endotracheal intubation. When possible, the bed should be kept elevated at 30° to reduce the intracranial pressure and the mean arterial blood pressures should be maintained above 90 mm Hg through intravenous fluid management. These therapies should help maintain cerebral perfusion pressure at more than 70 mm Hg [107].

Brain edema and elevated intracranial pressure develops in 40% of patients with severe traumatic brain injury. High or uncontrolled intracranial pressure is the most common causes of death and neurologic disability after severe traumatic brain injury. The main objective of intracranial pressure monitoring is to maintain adequate cerebral perfusion and oxygenation. It is also a means for guiding therapy. Intracranial pressure monitoring is reserved for those individuals with severe traumatic brain injury (ie, Glasgow Coma Score 8 or less) or an abnormal head CT scan [106]. Treatment should be initiated at an intracranial pressure threshold of 20 to 25 mm Hg. Treatment options consist of hyperventilation, chemical agents, hypothermia, and neurosurgical intervention.

Hyperventilation reduces cerebral blood flow and therefore decreases intracranial edema. In the nonpregnant patient, aggressive hyperventilation, defined as $Paco_2$ of 25 or less, has previously been the cornerstone in the management of severe trauma brain injury. However, aggressive hyperventilation may cause cerebral ischemia by further reducing cerebral blood flow without decreasing intracerebral edema and be associated with poorer neurological outcomes [108]. In the pregnant patient, normal $Paco_2$ is 32 mm Hg. Thus, hyperventilation may require levels of carbon dioxide that are extremely low. It has been suggested that extreme hypocapnia causes direct uterine vasoconstriction, possibly leading to fetal hypoxia. Recent evidence suggests hyperventilation rather than hypocapnia leads to a reduction in uterine blood flow through a mechanical reduction in venous return and subsequent decrease in cardiac output [45]. For these reasons, the

effective range for hyperventilation is reduced in pregnancy and caution must be exercised [45].

The mainstay of chemical agents for the reduction of intracranial pressure is mannitol, as hypertonic saline and steroids have had conflicting results [109]. In the nonpregnant patient, mannitol is routinely used to reduce intracranial pressure in traumatic brain injury patients with intracranial hypertension. Mannitol has a beneficial effect on maternal intracranial pressure, cerebral perfusion pressure, cerebral blood flow, brain metabolism, and short-term neurologic outcome. However, it may adversely affect the fetus. Indirectly, the osmotic diuresis can result in volume deficits in the mother and hypoperfusion of the placenta. Mannitol forces free water from the fetus and amniotic fluid to the mother, resulting in oligohydraminos, contraction of fetal blood volume, cyanosis, and fetal bradycardia. For these reasons, the use of mannitol during pregnancy should be restricted. Hypothermia has also been proposed as a treatment of elevated intracranial pressure, especially in those with hyperthermia [110]. The effects of hypothermia on a fetus are unknown and this treatment should be considered experimental. The physician is faced with a situation where treatments to help the mother may be contraindicated for the fetus. This is why some have advocated delivery of the fetus or termination to allow for maternal treatment. There may be benefit of craniotomy in patients with traumatic brain injuries when the intracranial pressure is refractory to conventional treatment [111]. There have also been reports of better outcomes with early craniotomy in traumatic brain injury when the Glasgow Coma Scale is below 8 [112]. Although there are no case reports of its use during pregnancy, craniotomy has been used during pregnancy for the resection of brain tumors. Craniotomy may be the only treatment available for elevated intracranial pressure after severe traumatic brain injury that allows for the prolongation of pregnancy.

Domestic violence

Domestic violence is common during pregnancy and affects up to 20% of all pregnancies [113]. It may be the leading cause of trauma in pregnancy. A pregnant woman is more likely to suffer domestic abuse than preeclampsia. Therefore, for physicians, diagnosing domestic abuse may be more crucial than diagnosing a placental abruption. Domestic violence may increase during pregnancy and lead to increased emergency room evaluations and antepartum and postpartum admissions [114,115]. The abuser tends to focus the attack on the abdomen, breast, and genitals. The effects of domestic abuse on the fetus typically depend on the severity of placental injury. These effects range from preterm delivery, preterm labor, growth restriction, and low birth-weight as the severity of placental injury decreases. The first step in treating domestic abuse is identification. Simple screening questionnaires have been developed to identify patients at risk (Box 1) [113]. The

Box 1. Examples of screening questions for domestic violence

The Massachusetts Medical Society Committee on Violence single-question screen[a]

- "At any time, has a partner hit, kicked, or otherwise hurt or threatened you?"

Three-question abuse assessment screen[b]

- "Within the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone?"
- "Since you've been pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone?"
- "Within the last year, has anyone forced you to have sexual activities?"

The SAFE questions[c]

- Stress/safety—"Do you feel safe in your relationship?"
- Afraid/abused—"Have you ever been in a relationship where you were threatened, hurt, or afraid?"
- Friends/family—"Are your friends or family aware that you have been hurt? Could you tell them, and would they be able to give you support?"
- Emergency plan—"Do you have a safe place to go and the resources you need in an emergency?"

From [a]Massachusetts Medical Society Committee on Violence. Partner violence: how to recognize and treat victims of abuse. Waltham (MA): Massachusetts Medical Society; 1996; [b]McFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy: severity and frequency of injuries and associated entry into prenatal care. JAMA 1992;267:3176; and [c]Ashur, ML. Asking about domestic violence: SAFE questions. JAMA 1993;269:2367.

most effective strategies for identifying domestic violence are screening questionnaires followed by in-person interviews by highly trained individuals [116]. A heightened index of suspicion and a concise screening tool may afford the emergency physician the unique opportunity to identify, intervene, and prevent reoccurrence of domestic violence. If domestic violence is suspected, consultation with social services should not be delayed. For a comprehensive review of domestic violence, see the article by Gunter elsewhere in this issue.

Summary

Trauma is the leading nonobstetric cause of maternal mortality, with the majority of injuries occurring from motor vehicle accidents. The basic tenets of trauma evaluation and resuscitation should be applied in maternal

trauma. It is important to understand the mechanism of injury, as well as the anatomical and physiological changes present in pregnancy. Failure to do so may have a significant impact on maternal hemodynamics and the fetus. Therefore aggressive resuscitation of the mother is the best management for the fetus. Care must be taken to keep the patient in the left lateral decubitus position to avoid compression of the inferior vena cava and resultant hypotension. Radiographic studies should not be avoided, but rather used with care. Noninvasive diagnostics, such as abdominal ultrasonography, should be used when available. Cardiotocographic monitoring of a viable gestations (>20 weeks' gestation) should be initiated as soon as possible in the emergency department to evaluate fetal well-being because fetal well-being is often the best indicator of maternal health. Seemingly minor injuries can result in placental abruption. Therefore monitoring is required for at least 2 to 4 hours after any trauma. Longer monitoring is needed if contractions or unstable maternal hemodynamics are present. Kleihauer–Betke testing should be considered in all cases of blunt trauma to determine the risk of preterm labor and placental injury. Rh-negative mothers should receive Rh-immune globulin administration to reduce the risk of Rh immunization. While routine cesarean section is not warranted, even in patients requiring laparotomy, urgent cesarean section should be considered if fetal distress is present, or if the presence of the fetus is contributing to maternal instability. For best fetal outcomes, perimortem cesarean section should be undertaken within 5 minutes of maternal circulatory arrest. Screening for domestic violence, particularly in patients with repeated injuries, should be undertaken and appropriate interventions made when identified. Finally, trauma centers and emergency rooms should have protocols in place that address the unique situations for trauma occurring during pregnancy. These protocols should include input from all specialists involved in this multidisciplinary emergency.

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Cardiopulmonary Resuscitation in Pregnancy

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Cardiac arrest in pregnant patients is an infrequent event that obstetricians and critical care medicine practitioners will encounter in their careers. Because outcomes depend on the underlying cause of the arrest and the speed of resuscitation efforts, an understanding of basic resuscitation principles and the specific challenges of an arrest in the pregnant woman is required to achieve a successful outcome. During attempted resuscitation of a pregnant woman, providers have two potential patients, the mother and the fetus [1]. The best hope of fetal survival is maternal survival. For the critically ill patient who is pregnant, rescuers must provide appropriate resuscitation, with consideration of the physiologic changes caused by pregnancy.

The true incidence of cardiac arrest during pregnancy is not known but has been estimated to be about 1 in 30,000 pregnancies [2]. Most information in the literature regarding cardiac arrest during pregnancy is in the form of case reports and case series. Some of the important etiologic factors causing cardiac arrest in the pregnant population are listed in Box 1. These factors differ somewhat from causes of cardiac arrest in nonpregnant patients. In the developed world, including the United States, the major causes of maternal mortality, in order of decreasing frequency, are venous thromboembolism, severe pregnancy-induced hypertension (pre-eclampsia or eclampsia), sepsis, amniotic fluid embolism, hemorrhage, trauma, iatrogenic causes including complications of anesthesia and drug errors or allergy, and maternal heart disease [3,4].

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Box 1. Major causes of cardiac arrest during pregnancy

Venous thromboembolism
Pregnancy-induced hypertension
Sepsis
Amniotic fluid embolism
Hemorrhage
  Placental abruption
  Placenta previa
  Uterine atony
  Disseminated intravascular coagulation
Trauma
Iatrogenic causes
  Medication errors or allergy
  Anesthetic complications
  Hypermagnesemia
Pre-existing heart disease
  Congenital
  Acquired

Amniotic fluid embolism (AFE), also called ''anaphylactoid reaction of pregnancy,'' is a rare complication of late gestation and the immediate postpartum period that deserves special mention. AFE, which occurs in an estimated 1:8000 to 1:80,000 pregnancies has a high mortality rate, ranging from 50% to 80%, and may rapidly precipitate cardiac arrest. In the analysis of the United States registry for AFE, cardiac arrest occurred in 87% of cases [5,6].

Another increasingly important contributor to cardiac arrest in pregnancy is the increasing average age of pregnant women in the United States. Because of personal choice or because of the effects of assisted reproductive technologies; pregnancy in women 45 years and older is much more common than it was a generation ago. This change tends to add patients who have chronic medical conditions that may be less prevalent in younger women. These chronic conditions can lead to complications in the pregnancy and, albeit rarely, to cardiac arrest.

Physiologic changes of pregnancy and implications for resuscitation

The cardiovascular and respiratory changes that occur during pregnancy are summarized here to emphasize their implications for resuscitation after cardiac arrest (Box 2). Cardiac output increases by 30% to 50% by 32 weeks' gestation [7]. Heart rate and resting oxygen consumption also are

Box 2. Physiologic changes in late pregnancy affecting cardiopulmonary resuscitation

Respiratory
Increased ventilation
- Increased oxygen demand
- Reduced chest compliance
- Reduced functional residual capacity

Cardiovascular
Incompetent gastroesophageal (cardiac) sphincter
- Increased intragastric pressure
- Increased risk of regurgitation

increased, whereas systemic vascular resistance and plasma oncotic pressure decrease as compared with the nongravid state. Uteroplacental blood flow increases during pregnancy so that the uterus receives up to 30% of cardiac output, as compared with less than 2% in the nonpregnant state. After spontaneous delivery, cardiac output increases by 60% to 80% of prelabor values [8]. This increase is smaller after cesarean delivery (about 30% of prelabor values), possibly because of the effects of anesthetics and blood loss.

Another critically important physiologic factor that has an impact on the effectiveness of cardiopulmonary resuscitation (CPR) and hemodynamic support in pregnant patients is aortocaval compression by the gravid uterus during the latter half of pregnancy [9,10]. In late pregnancy, the vena cava may be obstructed completely in most women when in the supine position, forcing venous return to flow through azygous lumbar and paraspinal veins. About 10% of pregnant women manifest the supine hypotensive syndrome, in which syncope, hypotension, and bradycardia occur when supine because of aortocaval compression. Stroke volume and cardiac output increase by 25% to 30% when late-term pregnant patients move from supine to lateral decubitus position.

The respiratory changes of pregnancy include increased minute ventilation caused by the effects of progesterone on respiratory drive, increased oxygen consumption, and a restrictive ventilatory defect caused by upward displacement of the diaphragm. Arterial blood gases during late pregnancy normally reflect a state of compensated respiratory alkalosis. The mechanical effects of the gravid uterus and hypertrophied breasts result in reduced functional residual capacity and reduced chest wall compliance. Reduced functional residual capacity and increased oxygen consumption can lead to precipitous oxygen desaturation if hypoventilation occurs [9].

Understanding the respiratory changes of pregnancy is essential during the management of cardiac arrest [11,12]. These changes necessitate quick

establishment of oxygenation and ventilation. Increased oxygen consumption leads to increased rates of arterial oxygen desaturation in the parturient who becomes apneic. Because of the hormonal and physical changes of pregnancy, patients are at increased risk for difficult ventilation and failed intubation. Increased levels of progesterone lead to delayed gastric emptying, increasing the risk for aspiration during mask ventilation and intubation. Although many centers require that patients take nothing by mouth during labor, patients often present in spontaneous labor after consuming a large meal. Edema of the upper airway, increased breast size, and generalized weight gain can delay the establishment of adequate ventilation and intubation. It is essential that oxygenation and ventilation be restored expeditiously while maintaining cricoid pressure. Moreover, it is imperative to intubate the patient as soon as possible to maximize oxygenation and minimize the risk of aspiration [8]. This need for rapid intubation is a key difference between the pregnant women in cardiac arrest and nonpregnant patients.

Differential diagnoses

The same reversible causes of cardiac arrest that occur in nonpregnant women can occur during pregnancy, but providers should be familiar with pregnancy-specific diseases and procedural complications. Obviously, providers should try to identify these common and reversible causes of cardiac arrest in pregnancy during resuscitation attempts. Some possible causes of cardiac arrest are discussed in this section.

Excess magnesium sulfate

Iatrogenic overdose is possible in women who have eclampsia and receive magnesium sulfate, particularly if the woman becomes oliguric. Administration of calcium gluconate (1 ampoule or 1 g) is the treatment of choice for magnesium toxicity [13]. Empiric calcium administration may be lifesaving.

Acute coronary syndromes

Pregnant women may experience acute coronary syndromes, typically in association with other medical conditions. Because fibrinolytics are relatively contraindicated in pregnancy, percutaneous coronary intervention is the reperfusion strategy of choice for ST-elevation myocardial infarction [14].

Pre-eclampsia/eclampsia

Pre-eclampsia/eclampsia develops after the twentieth week of gestation and can produce severe hypertension and ultimately diffuse organ system failure. If untreated it may result in maternal and fetal morbidity and mortality. Uncontrolled blood pressures can lead to stroke and subsequent cardiac arrest. Arrest during eclamptic seizures is relatively rare, particularly if the seizures are treated adequately and maternal oxygenation is maintained.

Aortic dissection

Pregnant women are at increased risk for spontaneous aortic dissection.

Life-threatening pulmonary embolism and stroke

The successful use of fibrinolytic therapy for a massive, life-threatening pulmonary embolism and ischemic stroke has been reported in pregnant women [15].

Amniotic fluid embolism

Clinicians have reported successful use of cardiopulmonary bypass for women who have life-threatening amniotic fluid embolism during labor and delivery.

Trauma

Pregnant women are not exempt from the accidents and violence that afflict much of society. Domestic violence also increases during pregnancy; in fact, homicide and suicide are leading causes of mortality during pregnancy, and motor vehicle accidents cause more maternal deaths in the United States than any other cause. Identification of the pregnancy early in the resuscitative effort of the pregnant trauma patient is critical. This statement may seem obvious, but because so many women in the United States are overweight and because trauma victims often arrive to the hospital unconscious and alone, a pregnancy may not be readily apparent, even after fetal viability. Therefore, the resuscitation team always must remember the possibility that any woman of childbearing age (an age range, as earlier noted, that is increasing) may be pregnant.

Cardiopulmonary resuscitation and advanced cardiac life support in pregnant patients

In general, resuscitation algorithms during cardiac arrest are the same for pregnant patients as for nonpregnant patients, but with some exceptions [16]. Principal among the modifications for the late-term pregnant woman are more aggressive airway management, attention to lateral displacement of the uterus, caution in the use of sodium bicarbonate, and early consideration of perimortem cesarean delivery (Box 3).

Cardiac output during CPR is estimated to be about 30% of normal, so uteroplacental blood flow is reduced markedly during cardiac arrest even with optimal performance of chest compressions [17]. CPR is performed in the same way on pregnant patients as on nonpregnant patients, except that in the second half of pregnancy an attempt to relieve aortocaval compression in the supine position is essential to restoring effective circulation. Rees and Willis [18] measured the force achieved with chest compressions performed on a manikin in the decubitus position at various angles of

Box 3. Specific difficulties in pregnant patients

Airway: patient needs to be inclined laterally for
Suction or aspiration
Removing dentures or foreign bodies
Inserting airways

Breathing
Greater oxygen requirement
Reduced chest compliance
More difficult to see rise and fall of chest
More risk of regurgitation and aspiration

Circulation: external chest compression is difficult because
Ribs are flared
Diaphragm is raised
Patient is obese
Breasts are hypertrophied
Supine position causes inferior vena cava compression by the gravid uterus

inclination. The resuscitative force decreased from 67% of the rescuer's body weight with the manikin in the supine position to 36% in the full lateral position. At an angle of 27°, the maximal possible resuscitative force during CPR was 80% of that which could be achieved with in the supine position. This study led to the development of the Cardiff resuscitation wedge, a wooden frame inclined at a 27° angle and specifically designed for performing CPR on pregnant patients. This apparatus may not always be available in critical care units or in the emergency department. Obstetric practitioners should ensure the availability of the wedge in the ICU, the operating suite, and the emergency room as well as in labor and delivery suites, because all these sites may be the locale of a code arrest in a pregnant patient. If one is faced with an arrest in a gravid woman beyond 20 weeks and the wedge is not available, alternative maneuvers to relieve aortocaval compression include manual displacement of the uterus to the left and upward while the patient is supine, use of a wedge such as a bed sheet placed under the right hip, use of a "human wedge" (one rescuer kneels on the floor or another surface with the woman's back positioned against the rescuer's thighs) [19]. All these measures can relieve some of the aortocaval compression.

Available evidence suggests that defibrillation energy requirements do not change significantly during pregnancy. In the only study to address this question directly, Nanson and colleagues [20] assessed transthoracic impedance, as measured by a defibrillator, in 45 women at term pregnancy

and repeated the measurements at 6 to 8 weeks after delivery in 42 of the women. They found no significant difference in the mean transthoracic impedance before or after delivery. The same defibrillation regimens recommended in the advanced cardiac life-support (ACLS) algorithm for appropriate cardiac arrhythmias, such as ventricular fibrillation or pulseless ventricular tachycardia, are recommended for pregnant patients.

Supplemental oxygen should be administered at a concentration of 100% during CPR in pregnant and nonpregnant patients. As mentioned previously, rapid control of the airway through performance of endotracheal intubation early in the resuscitation effort is highly recommended. In addition to the increased susceptibility to hypoxia for the mother and fetus, pregnant patients also are at increased risk for aspiration of gastric contents caused by delayed gastric emptying and reduced lower esophageal sphincter tone. This risk may be exacerbated further by gastric distention from air insufflation during bag-mask ventilation.

The use of sodium bicarbonate to reverse metabolic acidosis during cardiac arrest has been questioned; its role in managing maternal acidosis is controversial also [21]. Animal studies suggest that bicarbonate crosses the placenta poorly (although this finding may not be true in humans). Rapid correction of maternal (but not fetal) acidosis could lead to reduced compensatory hyperventilation and normalization of maternal $Paco_2$, which could result in a concomitant increase in fetal $Paco_2$ and potential worsening of fetal acidosis. Available evidence, however, suggests that the fetus may tolerate significant respiratory acidosis for short periods. Restoration of effective maternal circulation, with subsequent correction of hypoxia, is the most effective way to correct fetal acidosis during maternal cardiac arrest.

There is little information regarding pharmacologic therapy during ACLS in pregnant patients. The use of α-adrenergic agents theoretically may reduce uteroplacental blood flow, but their actual clinical effect is unknown. In general, the same protocols for pharmacologic management of ACLS should be used in pregnant and nonpregnant patients with cardiac arrest. The best chance for survival for the mother and fetus depends on rapid resuscitation of the mother.

Perimortem cesarean delivery and outcomes

Physicians must decide whether to attempt emergent cesarean delivery in the resuscitation of pregnant patients with cardiac arrest in whom initial resuscitative efforts are not immediately successful. Timing and speed of the procedure are keys to optimizing outcome and limiting adverse neurologic sequelae in survivors.

Cesarean delivery is one of the oldest surgical procedures in history, with literature dating back to at least 800 BCE [22]. Before the twentieth century,

however, the phrase ''postmortem cesarean'' would have been redundant, because the procedure was never undertaken unless the mother was dead or moribund.

Initially, the Roman decree (*Lex Cesare*, or law of Caesar) that unborn infants should be separated from their mothers' bodies was for purposes of religious ritual rather than attempts for survival of either the newborn or mother. Some infants did survive, and indeed, several mythological and ancient historical figures were reported to have been born in this fashion, including the Greek physician Asklepios, ''from the womb of dead Koronis.'' During the late nineteenth and early twentieth centuries, case reports began to arise of perimortem cesarean delivery successfully salvaging the fetus, and the procedure began to be considered seriously as a legitimate medical intervention. Well into the twentieth century, the salvage rate was very low, and therefore authors on the subject advocated it only after all other resuscitative measures had failed.

During the 1980s, several authors reported unexpected maternal recoveries after postmortem cesarean deliveries [23,24]. This experience suggested that the procedure actually might improve, rather than worsen, a mother's chance of survival during a collapse.

Katz and colleagues [25] reviewed the medical literature about perimortem cesarean deliveries that were reported through 1985. Of 188 surviving infants, they identified 61 cases in which the data showed the time from death of the mother to delivery of the infant. They found that 70% of surviving neonates were delivered within 5 minutes of maternal death, and 93% were delivered within 15 minutes. Some infants survived when delivery occurred more than 21 minutes after maternal death, but the neurologic deficits in these infants were more frequent and more severe. Lopez-Zeno and colleagues [26] reported a case of perimortem cesarean delivery after 22 minutes of CPR in a mother who developed cardiac arrest secondary to a fatal gunshot wound. The infant survived and was described as clinically normal at 18 months of age. Based on their findings, Katz and colleagues [25] recommended initiation of cesarean delivery within 4 minutes of maternal cardiac arrest if circulation has not been restored and recommended fetal delivery within 5 minutes. These recommendations have been supported by other investigators and form the basis of the ''4-minute rule.'' Given the number of reports of neonatal survival without adverse neurologic sequelae when delivery occurred well after 5 minutes of maternal cardiac arrest, this rule should not be taken as absolute. The outcomes of infants delivered by perimortem cesarean delivery are summarized in Table 1.

Estimated gestational age is an important factor in predicting prognosis for infants after perimortem cesarean deliveries. The threshold for expected fetal viability may vary slightly between institutions but generally is considered to be around 24 weeks of gestation. If the gestational age cannot be determined from the available medical or prenatal history, practical and rapid methods of its assessment in the emergency setting include calculation based

Table 1
Outcomes of infants delivered by perimortem cesarean delivery

Time (in minutes)	No. infants surviving	% Surviving intact
0–5	45	98
6–15	18	83
16–25	9	33
26–35	4	25
36 +	1	0

Data modified from Katz VL, Dotters DJ, Droegemueller W. Perimortem cesarean delivery. Obstet Gynecol 1986;68:571–6, and Clark SL, Hankins GDV, Dudley DA, et al. Amniotic fluid embolism: analysis of the National Registry. Am J Obstet Gynecol 1995;172:1158–69.

on the mother's last menstrual period or measurement of fundal height. Between 20 and 36 weeks of gestation, the fetal age in weeks is approximated by the distance in centimeters from the pubic symphysis to the top of the uterine fundus when the mother is supine. A fundal height at the level of the umbilicus corresponds to 20 weeks' gestation. In the settings of multiparity, extreme obesity, abdominal distention from other causes, or intrauterine growth retardation, these methods of estimating gestational age may be unreliable.

Although the primary goal of cesarean delivery in the perimortem period has been survival of the fetus, the procedure also may have a role in saving both the mother and infant. Because of the impact of aortocaval compression by the gravid uterus on the efficacy of CPR, delivery of the fetus may improve maternal cardiac output significantly in addition to improving survival of the fetus. In numerous case reports, emergent cesarean delivery in the setting of apparently refractory maternal cardiac arrest has resulted in survival of the infant and mother because of more effective resuscitation of the mother after delivery. Finegold and colleagues [27] reported a case of a previously healthy 35-year-old woman who was at 39 weeks' gestation and experienced cardiac arrest soon after rupture of membranes. Emergent cesarean delivery was performed 15 minutes after the cardiac arrest, with immediate recovery of maternal pulse and blood pressure. The mother and infant survived and had normal neurologic function. Other investigators have described similar situations and favorable outcomes, although such case reports cannot permit firm conclusions about whether cesarean delivery improves maternal outcome in the setting of late-term cardiac arrest.

If cardiac arrest occurs earlier in pregnancy, it is not known whether performance of cesarean delivery to produce a previable fetus is beneficial to maternal outcome. With significantly smaller fetal–placental mass, the hemodynamic benefits to the mother would not be expected to be as significant as later in pregnancy. In general, perimortem cesarean delivery is not recommended in cases with an estimated gestational age of less than 24 weeks, and efforts should focus on optimizing resuscitation performance and

restoration of spontaneous circulation to provide the best hope of recovery for mother and fetus. In one case report, maternal and fetal survival occurred after prolonged maternal cardiac arrest at 15 weeks' gestation secondary to accidental lidocaine overdose. CPR was performed for 22 minutes before return of spontaneous circulation. The patient recovered neurologic function and had a normal, spontaneous vaginal delivery at 40 weeks' gestation, delivering a neurologically normal infant.

Decision making for a perimortem cesarean delivery

The resuscitation team should consider several maternal and fetal factors in determining the need for an emergency hysterotomy. Although the gravid uterus reaches a size that will begin to compromise aortocaval blood flow at approximately 20 weeks of gestation, fetal viability begins at approximately 24 to 25 weeks. Portable ultrasonography, available in many emergency departments, may, in experienced hands, aid in determining gestational age as well as placental location, fetal lie, and the presence of fetal cardiac activity. The use of ultrasound should not delay the decision to perform emergency hysterotomy, however, and may be impractical in the setting of maternal cardiac arrest. If the gestational age is less than 20 weeks, urgent cesarean delivery should not be considered, because a gravid uterus of this size is unlikely to compromise maternal cardiac output significantly. A more difficult decision may be when the mother's gestational age is approximately 20 to 23 weeks. Performing an emergency hysterotomy to enable successful resuscitation of the mother may be reasonable, although minimal data exist to support the premise. Obviously, survival of the infant is unlikely at this gestational age and should not be a factor in the decision-making process. After 24 to 25 weeks, cesarean delivery may contribute to saving the life of the mother and allows an attempt of resuscitation of the infant.

The critical point is that both mother and infant will be lost if blood flow to the mother's heart cannot be restored. Four to 5 minutes is the maximum time rescuers have to determine if the arrest can be reversed by basic life support and ACLS interventions. The rescue team need not wait for this time to elapse before initiating emergency hysterotomy. Unfortunately, recent reports document long intervals between an urgent decision for hysterotomy and actual delivery of the infant, far exceeding the obstetric guideline of 30 minutes [28].

Establishment of intravenous access and an advanced airway typically requires several minutes. In most cases the actual cesarean delivery cannot proceed until after administration of intravenous medications and endotracheal intubation. Resuscitation team leaders should activate the protocol for an emergency cesarean delivery as soon as cardiac arrest is identified in the pregnant woman. By the time the team leader is poised to deliver the baby, intravenous access has been established, initial medications have been administered, an advanced airway is in place, and the immediate reversibility of the cardiac arrest has been determined.

Features of the cardiac arrest

The following features of the cardiac arrest can increase the infant's chance for survival:

- Short interval between the mother's arrest and the infant's delivery
- No sustained prearrest hypoxia in the mother
- Minimal or no signs of fetal distress before the mother's cardiac arrest
- Aggressive and effective resuscitative efforts for the mother
- Cesarean delivery performed in a medical center with a neonatal ICU

The professional setting

- Are appropriate equipment and supplies available?
- Is emergency cesarean delivery within the rescuer's procedural range of experience and skills?
- Are skilled neonatal/pediatric support personnel available to care for the infant, especially if the infant is not full term?
- Are obstetric personnel immediately available to support the mother after delivery?

The technique of perimortem cesarean delivery requires speed and decisiveness. CPR must be continued during delivery, and the procedure should not be delayed for attempts to obtain consent from next of kin. Most experts agree that in the setting of maternal cardiac arrest, the doctrine of emergency or implied consent applies, and the best interests of the child take precedence. Katz and colleagues [25] note that there have been no legal findings of liability against physicians in the United States for performing a postmortem cesarean delivery.

Summary

Successful resuscitation of a pregnant woman and survival of the fetus require prompt and excellent CPR with some modifications in basic and advanced cardiovascular life-support techniques. By the twentieth week of gestation, the gravid uterus can compress the inferior vena cava and the aorta, obstructing venous return and arterial blood flow. Rescuers can relieve this compression by positioning the woman on her side or by pulling the gravid uterus to the side. Defibrillation and medication doses used for resuscitation of the pregnant woman are the same as those used for other adults in pulseless arrest. Electric cardioversion during pregnancy has been described in the literature and seems safe for the fetus. The physiologic changes in pregnancy do not change defibrillation requirements for adult defibrillation.

Rescuers should consider the need for perimortem cesarean delivery as soon as the pregnant woman develops cardiac arrest, because rescuers should be prepared to proceed with the hysterotomy if the resuscitation is not successful within minutes.

Although pregnancy and delivery in the United States usually are safe for the mother and her newborn child, serious maternal complications, including cardiac arrest, can and do occur in the prenatal, intrapartum, and postpartum periods. The busy clinical obstetrician can expect to encounter this complication in his or her career. It is incumbent on the obstetrician to be aware of the special circumstances of resuscitation of the gravid woman to assist emergency medicine and critical care physicians in reviving the patient. Moreover, understanding the decision process leading to the performance of a perimortem cesarean and the actual performance of the cesarean delivery clearly are the responsibilities of the obstetrician.

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Angiographic and Interventional Options in Obstetric and Gynecologic Emergencies

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The role of endovascular techniques for diagnosis and treatment of obstetrical and gynecologic emergencies has evolved over last 3 decades. Obstetricians and gynecologists, using surgical techniques and medical management, can adequately manage most vascular emergencies. However, in certain situations, angiographic intervention can play a complementary role in patient management. In this article, the authors describe the technique of pelvic arterial embolization and the role of embolization and catheterization for specific kinds of postpartum hemorrhage and gynecologic vascular emergencies. In addition, the authors provide a brief review of the literature on pelvic arterial embolization in the setting of postpartum hemorrhage . Finally, the authors discuss some complications and short- and intermediate-term outcomes of embolization, particularly as they affect fertility.

Postpartum hemorrhage

Postpartum hemorrhage is among the most common causes of maternal morbidity and mortality. In the United States, postpartum hemorrhage ranks among the top three causes of maternal death [1]. Bleeding of 500

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mL or more following a vaginal delivery, or 1000 mL or more following a cesarean section, meets the definition of postpartum hemorrhage. Because objective measurement of blood loss can be difficult, a more qualitative definition includes a clinical need for a transfusion or a 10% hematocrit drop between admission and the postpartum period [2,3].

The first line of treatment for postpartum hemorrhage includes conservative measures, such as administration of uterotonic medications, laceration repair, uterine packing, and correction of underlying coagulopathies. If these measures failed, obstetricians would often attempt surgical ligation of the arterial supply to the uterus, or they would perform a hysterectomy with associated loss of fertility.

In the last 30 years, a new angiographic approach for treatment of postpartum hemorrhage has emerged. Pelvic arterial embolization, after emerging as a treatment option to control and prevent pregnancy-related hemorrhage, has been established to be safe and effective [4–8]. In appropriate circumstances, pelvic arterial embolization provides some advantages in management of postpartum hemorrhage. In addition to providing a high technical success rate, this angiographic approach, compared to other options, also offers a greater likelihood of preserving fertility.

Common causes of obstetric hemorrhage

Postpartum hemorrhage is frequently categorized as either early or delayed onset. Early postpartum hemorrhage occurs within the first 24 hours after delivery while delayed postpartum hemorrhage is commonly defined as bleeding after 24 hours but within 6 weeks after delivery. The most common cause of early postpartum hemorrhage is uterine atony (Fig. 1) [9,10], although genital tract lacerations can also cause significant bleeding in the early postpartum period [11]. Delayed postpartum hemorrhage usually occurs because of retained placental fragments.

Arteriovenous malformations, invading trophoblastic tissue, complications related to evacuation of ectopic pregnancies, and instrumentation in the peripartum period are also known causes of pregnancy-related hemorrhage. Congenital arteriovenous malformations are not a complication of pregnancy and are discussed separately later in this article. However, acquired arteriovenous malformations can be seen after uterine curettage or after removal of an intrauterine device, and are an uncommon cause of hemorrhage (Fig. 2) [12,13]. Cervical and abdominal ectopic pregnancies can also be difficult to evacuate surgically and thus are occasionally associated with significant hemorrhage.

Early postpartum hemorrhage usually occurs in the immediate postpartum period while the patient is still under supervision of the obstetric team and thus management can start immediately. The usual clinical management includes uterine packing, repair of visible lacerations,

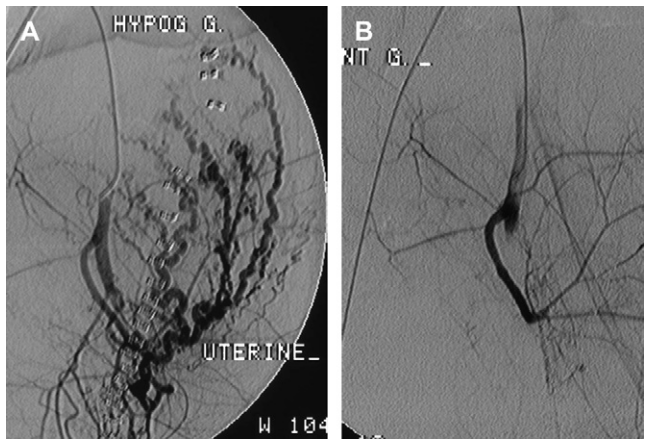

Fig. 1. Angiographic appearance of uterine atony. (*A*) Usual appearance of uterine atony without contrast extravasation. (*B*) Postembolization image with occlusion of the anterior division of the internal iliac artery. After selective embolization of the uterine artery, large gelatin sponge pledgets were placed into the anterior division of the internal iliac to control the bleeding from the lower uterine segment vaginal and cervical branches.

administration of uterotonic drugs, and correction of underlying coagulopathies. If these measures fail, more aggressive management with surgical ligation of the arterial supply to the uterus and hysterectomy can be performed. Angiographic treatments for early postpartum hemorrhage are now also gaining acceptance and are discussed in some detail in this text. Delayed postpartum hemorrhage most commonly occurs weeks after delivery and most women are not under immediate medical supervision. Initial management of delayed postpartum hemorrhage includes a clinical evaluation and the usual clinical management described above. If these measures fail, angiographic options are also available and will be discussed.

Finally, intrapartum and postpartum hemorrhage is seen in some high-risk populations with placentation abnormalities and during surgical management of ectopic pregnancies. Advanced imaging and serologic testing have greatly enhanced early detection and management of these conditions. Therefore, the incidence of life-threatening hemorrhage has been significantly reduced in last few decades. Nonetheless, clinical and surgical management of placentation abnormalities can be difficult and angiographic techniques now exist to assist the obstetric team in limiting blood loss. Likewise, during operative management of abdominal pregnancies and occasionally cervical pregnancies, interventional and angiographic management can offer additional options for decreasing the risk of massive bleeding. Some of these options are discussed here.

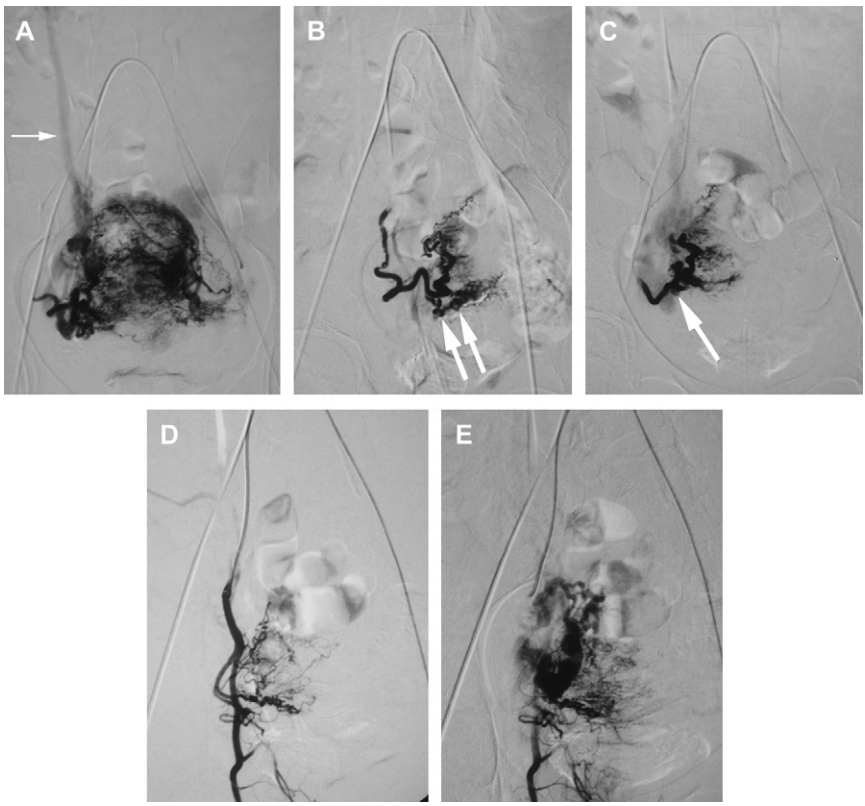

Fig. 2. Uterine and adnexal arteriovenous malformation. (*A*) Twenty-four–year–old woman with recent miscarriage, dilatation, and curettage, complicated by severe bleeding and subsequent recurrent hemorrhage. Ultrasound examination showed hypervascular lesion in right cervical area with a differential diagnosis of either cervical pregnancy or arteriovenous fistula. Bilateral simultaneous anteroposterior arteriographic image reveals increased vascularity on the right uterus with an early filling right ovarian vein (*arrow*). (*B*) Right uterine arteriogram, early arterial phase in the left anterior oblique position. An enlarged cervicovaginal branch (*arrows*) supplied a hypervascular nidus on subsequent images. The position correlated with the cervical abnormality on duplex ultrasound (not shown). (*C*) Right uterine arteriogram in the left anterior oblique position after embolization. The cervicovaginal branch is occluded (*arrow*) and the arterial flow diminished. There is faint early opacification of veins in the right adnexae for uncertain reasons. (*D*) Arteriogram of anterior division of right hypogastric artery after embolization, revealing additional branches to the adnexae from other pelvic branches. (*E*) Late phase of arteriogram showing markedly enlarged veins extending laterally from the margin of the uterus into the adnexa. The uterine bleeding was controlled by the limited embolization of the cervicovaginal branch. The larger asymptomatic portion of the vascular malformation was asymptomatic and not treated. (*From* Roth AR, Goodwin SC, Vedantham S, et al. Management of gynecologic hemorrhage. In: Spies JB, Pelage JP, editors. Uterine artery embolization. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 155; with permission).

Angiographic techniques and strategies in obstetric hemorrhage

Early postpartum hemorrhage

The traditional approach to persistent and massive postpartum hemorrhage, if initial conservative clinical measures fail, has involved emergent hysterectomy. Uterine artery ligation or internal iliac artery ligation, instead of hysterectomy, is possible in women who wish to preserve their fertility. While some investigators report very good results with bilateral internal iliac artery ligation for controlling postpartum hemorrhage [14], others found that internal iliac artery ligation for control of hemorrhage is often unsuccessful, with success rates as low as 42% [15]. This may be attributable to distal reconstitution of the internal iliac arteries in the setting of a markedly hypervascular postpartum uterus [16]. Hysterectomy after a failed ligation carries a higher morbidity than hysterectomy alone [15].

Angiographic techniques with embolization are available to contribute to the overall management of early postpartum hemorrhage. The technique was first described by Brown and colleagues [17] in 1979 and by Pais and colleagues [16] in 1980. To this day, the embolization technique has remained largely unchanged from these initial reports. The procedure is performed by interventional radiologists in the angiographic suite. Fluoroscopic guidance is used to catheterize the anterior division of internal iliac arteries with angiographic catheters and embolization is subsequently performed. Subselective embolization of the uterine arteries [10] or vaginal arteries [7] is performed whenever possible as each of these have been separately reported as the most common source of bleeding. If the exact source of bleeding cannot be identified, as sometimes occurs, empiric embolization of the anterior division of the internal iliac arteries is performed with pledgets of gelatin sponge or gelatin sponge slurry. A gelatin sponge is the agent of choice because it causes a temporary arterial occlusion with recanalization of blood flow within weeks. Microcoil embolization alone for postpartum hemorrhage is not advocated because rich distal vascular supply often reconstitutes the hypervascular gravid uterus [16,18]. Collateral branches, such as the medial circumflex artery from the profunda femoris and branches from the inferior epigastric artery, often reconstitute the distal supply and bleeding often continues. For similar reasons, bilateral embolization is often performed because bleeding can continue through transpelvic vascular supply after unilateral embolization [19]. No prospective studies are available comparing unilateral and bilateral embolization, but bilateral embolization is typically performed.

Delayed postpartum hemorrhage

From the technical standpoint, embolization for late or delayed postpartum hemorrhage is the same as for early postpartum hemorrhage. Delayed postpartum hemorrhage is often attributable to retained placental fragments

with or without endometritis and occasionally genital tract lacerations. If the bleeding persists after primary repair of the lacerations or curettage, embolization is an alternative to surgical ligation or hysterectomy [20,21]. Again, reported embolization techniques vary (Fig. 3). Most investigators used gelatin sponge pledgets for embolization. Pelage and colleagues [21] selectively catheterized and embolized the uterine arteries in most cases,

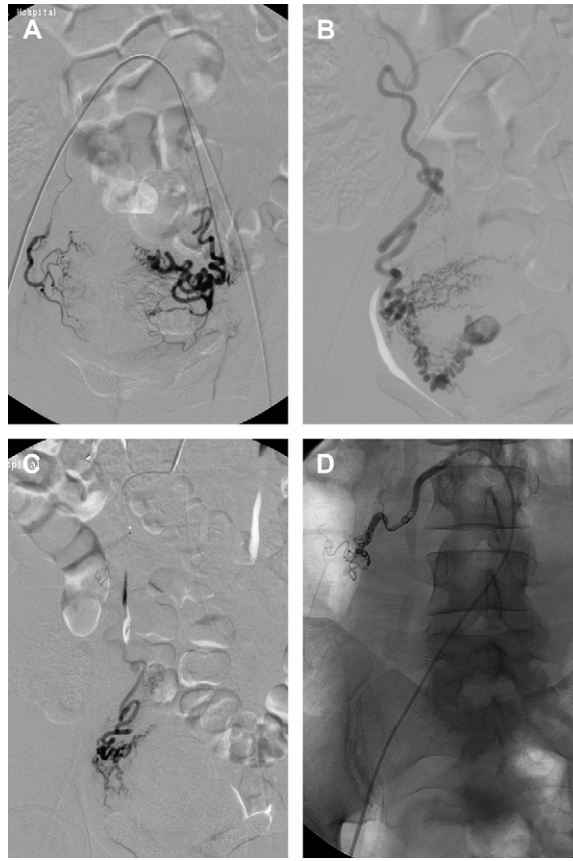

Fig. 3. Thirty-three–year–old woman 3 weeks postpartum with intermittent vaginal bleeding. (*A*) Selective uterine artery arteriograms using simultaneous injections through catheters placed via left and right common femoral approach fail to demonstrate any active extravasation. (*B*) A more thorough search for the source of bleeding resulted in a selective arteriogram of the right ovarian artery, which demonstrated a pseudoaneurysm. (*C*) Gelatin slurry embolization of the right ovarian artery through a coaxially placed microcatheter successfully amputated the flow to the distal branches that were supplying the pseudoaneurysm. (*D*) Shortly after the procedure, the hemorrhage continued and patient was brought back to the interventional radiology suite for microcoil embolization. Coils were deposited into the right ovarian artery, effectively arresting antegrade flow. (*From* Baum S, Pentecost M. Abrams' angiography: interventional radiology. Philadelphia: Lippincott Williams and Wilkins;. 2005. p. 823; with permission).

while Feinberg and colleagues [22] reported nonselective gelatin sponge and coil embolization of internal iliac arteries.

Embolization options for ectopic pregnancies

Embolization plays a very limited role in management of ectopic pregnancies. The diagnosis of ectopic pregnancy based on ultrasound findings, elevated levels of the beta subunit of human chorionic gonadotrphin (beta-HCG), and clinical presentation most often results in prompt medical or operative treatment. Clinically significant hemorrhage is mostly avoided. However, successful embolization has been reported in the context of overall management for abdominal [4,5,23–25] and cervical [26,27] ectopic pregnancies, mostly to reduce the operative blood loss. Using standard angiographic techniques, vascular supply to the pregnancy is determined and selective gelatin sponge embolization is performed before operative management. Badawy and colleagues [12] reviewed 11 reports totaling 21 cases of arterial embolization for abdominal and cervical pregnancies and reported a 100% success rate in controlling the hemorrhage. In the setting of hemorrhage after the operative removal of the cervical ectopic pregnancy, successful selective embolization of the placental fragment has been reported [28]. Although the role of angiography and embolization in the setting of abdominal and cervical pregnancies is limited, consultation for perioperative embolization can be considered in certain cases.

Embolization for placentation abnormalities

Placentation abnormalities can present a formidable clinical challenge. Among them, placenta percreta is the most problematic because uterine rupture and ensuing hemorrhage can occur. However placenta accreta and increta also carry an increased risk of bleeding (Fig. 4). Miller and colleagues [29] quantified the amount of blood loss during cesarean hysterectomy associated with placenta accreta in a group of 62 patients. Estimated blood loss exceeded 2000 mL in 41 patients, 5000 mL in 9 patients, 10,000 mL in 4 patients, and 20,000 mL in 2 patients.

Interventional radiologists have two principal management algorithms in this setting. First, embolization either before or immediately after the cesarean delivery can be performed. Arterial access can be obtained via the axillary artery [5], thus limiting the exposure of the fetus to ionizing radiation. Embolization can be performed quickly if significant hemorrhage occurs. Alternatively, femoral artery catheterization can be obtained emergently after delivery.

Second, temporary occlusion of both internal iliac arteries with angioplasty balloons or compliant occlusion balloons can be done after initial catheterization via either femoral or axillary approach [30,31]. This portion of the procedure is done in the angiographic suite before delivery. During operative delivery, the balloons are left deflated. Then, while the patient is

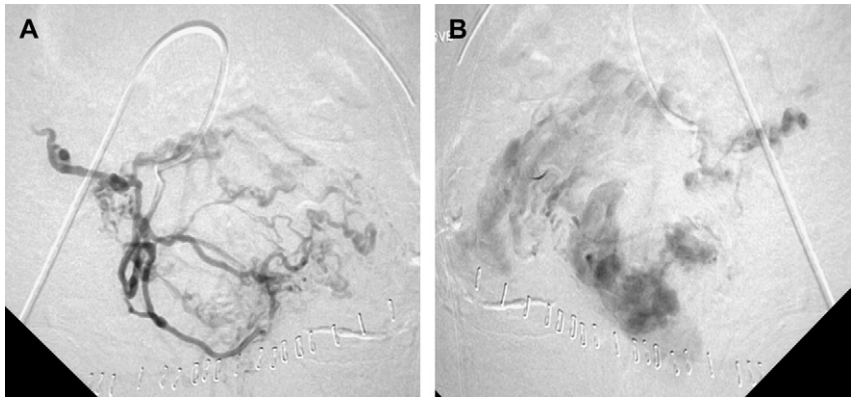

Fig. 4. Angiographic appearance of placenta accreta. (*A*) Early arterial phase. (*B*) Late arterial phase. A typical pseudotumoral multifocal blush is seen.

in the operating room, balloons are inflated to occlude the blood flow. This technique allows additional time to try to control the hemorrhage surgically. Alternatively, with the catheters still in place, the patient can be transferred to the interventional radiology suite for embolization. Either selective gelatin sponge embolization of the uterine arteries can be performed by inserting a microcatheter coaxially [32], or nonselective gelatin sponge embolization can be performed through the end hole of the balloon catheter [30,31]. Although most investigators advocate balloon placement before delivery, the technique is somewhat controversial because a small prospective cohort study [33] and a retrospective review [34] failed to demonstrate a benefit. Therefore, the value of this technique is yet to be proven. Nonetheless, embolization in the setting of placentation abnormalities has a role and has been used in minimizing the operative blood loss during hysterectomy. As described by Greenberg and colleagues [35], embolization can also be used as an adjunct to hysteroscopic morcellation of placenta accreta. In a separate report, embolization in the setting of placenta accreta has even been shown to control the hemorrhage and preserve the uterus and fertility [36].

Fertility outcomes after embolization

Embolization for postpartum hemorrhage, placentation abnormalities, or arteriovenous malformations (or as an adjunct in treatment of ectopic pregnancies) invariably causes some degree of ischemia to the uterus. However, clinically significant ischemic injury to the uterus is extremely rare. Fertility after embolization has not been thoroughly studied, although a number of reports in both gynecologic and radiological literature suggests favorable outcomes. Normal resumption of menses [8,11,24,37] and normal pregnancies have been reported by a number of investigators [8,20,24, 38–41]. In a small group follow-up study (1–6 years), Stancato-Pasik and

colleagues [24] found that 92% of the patients resumed normal menses within 2 to 5 months after embolization, without complications related to embolotherapy. All three patients who wished to conceive gave birth to full-term, healthy newborns. Similar results were reported by Ornan and colleagues [42] who found that, after embolization for postpartum hemorrhage, all patients who wished to become pregnant were successful. Shim and colleagues [41] followed 37 patients after embolization for postpartum hemorrhage and found that 36 resumed normal menses and 9 became pregnant.

The effects of prior embolization on potential complications during the ensuing pregnancies have not been studied thoroughly; however, some groups reported an increased rate of postpartum hemorrhage in those patients who had a prior embolization. Additionally, the effects on fetal development are only sporadically reported. Although most investigators report normal pregnancies after embolization, in utero death and preeclampsia have been reported [43], without speculation on the attributable cause.

Pelvic embolization in gynecologic hemorrhage

Perhaps because hemmorhage in gynecologic conditions is so rare, the use of embolotherapy in such cases has been studied less than the use of embolotherapy for obstetric-related hemmorhage. However, the same general techniques and principles apply, and these appear to be effective in most cases. Most reports have been in the setting of gynecologic malignancy, but case reports suggest similar results would be achieved for arteriovenous malformation and other benign pathology, such as pelvic hemorrhage due to trauma [44]. This section reviews applications of embolotherapy to control hemorrhage from gynecologic conditions, as opposed to obstetric-related hemorrhage.

Causes of gynecologic hemorrhage

Malignancy

Among malignant causes of vaginal hemorrhage, carcinoma of the cervix, endometrium, and choriocarcinoma are the most common causative tumors [45]. Vaginal bleeding related to pelvic neoplasms is typically slow and intermittent but persistent and poorly responsive to surgical intervention or radiation therapy. The bleeding may be the result of invasion of small vessels by tumor or the result of ulceration or necrosis of the tumors. More massive bleeding may occur as tumors invade large vessels (Fig. 5).

Uterine vascular abnormalities

Uterine vascular abnormalities may be congenital or acquired. Congenital arteriovenous malformations are quite rare and may have a complex set of feeding arteries and draining veins. They may cause massive hemorrhage or intermittent bleeding. Acquired lesions are more common and often are the

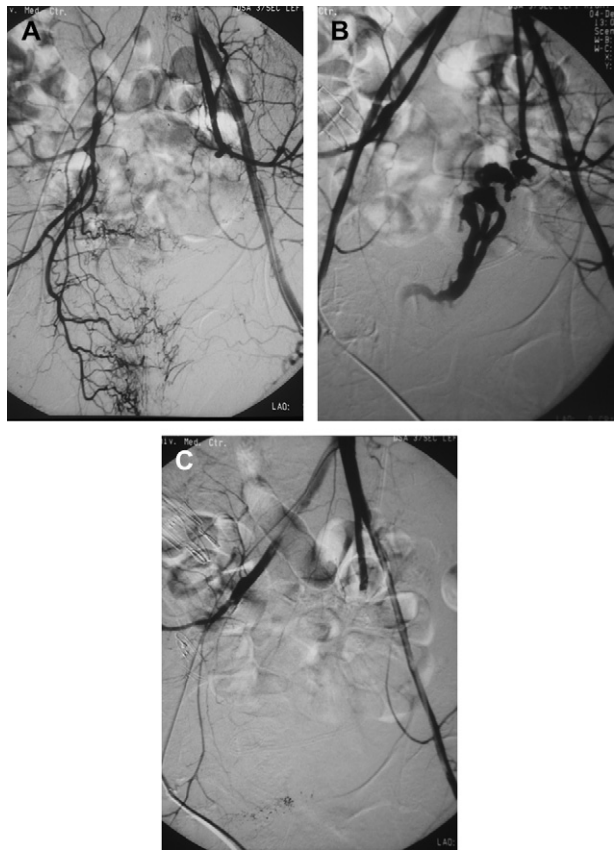

Fig. 5. Massive hemorrhage from neoplastic erosion or radiation injury to left hypogastric artery. (*A*) Initial bilateral hypogastric arteriogram revealing postoperative changes in the left hypogastric artery, intact vessels on the right, without a clear site of bleeding. It was decided to proceed with embolization on the right, using polyvinyl alcohol particles. After the embolization on the right, the patient suddenly became tachycardic. The blood pressure was maintained and the cause of the tachycardia was not immediately clear. It was decided to consider termination of the procedure after a repeat arteriogram. (*B*) Repeat arteriogram reveals massive bleeding from the left hypogastric artery stump. The anterior division of the right hypogastric artery was occluded. (*C*) After embolization of the left bleeding site with gelatin sponge and coils, with control of the bleeding. (*From* Roth AR, Goodwin SC, Vedantham S, et al. Management of gynecologic hemorrhage. In: Spies JB, Pelage JP, editors. Uterine artery embolization. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 152; with permission).

result of uterine surgery, curettage, a retained placenta, or obstetrical trauma. Delayed postpartum hemorrhage that does not resolve spontaneously may be due to arterial injury. In one small series of 14 patients, those 3 patients treated for delayed postpartum hemorrhage had uterine vascular abnormalities as the underlying cause [21]. Similar findings have been noted in patients with hemorrhage following uterine curettage or surgery [46]. These vascular

abnormalities include pseudoaneurysms, arteriovenous fistulas, and direct vessel rupture.

The diagnosis of vascular malformations of the uterus is usually made with color and duplex Doppler ultrasound revealing a blood-filled cystic structure with swirling arterial flow (pseudoaneurysm); rapid arterial-to-venous shunting, such as that seen in arteriovenous fistulas; or an intense vascular tangle of vessels or arteriovenous malformations [47]. On duplex Doppler ultrasound, arteriovenous fistulas and arteriovenous malformations demonstrate low-resistance, high-velocity arterial flow.

Embolization technique for gynecologic hemorrhage

The exact source of the bleeding is often not known before the embolization procedure and survey arteriography is often needed before catheterizing individual vessels. A pelvic arteriogram with injection of contrast in the lower abdominal aorta is usually the first study performed. This may be supplemented by injection into ovarian and inferior mesenteric vessels if no bleeding site is identified. Using these initial studies as a guide, further selective arteriograms are performed to isolate the site of bleeding. If the patient has not had a hysterectomy, then the uterine vessels are likely the source. In the postoperative patient, other pelvic visceral vessels are often involved.

Although a variety of technical approaches have been used, there is a consensus on the general approach to pelvic embolization [44,48]. An angiographic catheter is advanced selectively into the branch in question, using fluoroscopic guidance with a digital roadmap or image as a guide. This is often done using a coaxial technique, in which a microcatheter is advanced through an outer 5F catheter. The use of a microcatheter allows smaller branches to be entered, which provides for a more targeted embolization. Embolic material, usually polyvinyl alcohol particles, microspheres, or coils, are injected in the bleeding vessel. The material is injected into the target vessel until stasis of flow is confirmed angiographically. These materials are best applied when bleeding is identified from small arterial branches of less than a few millimeters in diameter.

Gelatin sponge is often used in larger vessels, often in conjunction with coils. In general, particulate emboli penetrate farther into vessels than gelatin sponge and will occlude at or within the tumor. Gelatin sponge and coils provide a more proximal occlusion of larger feeding vessels than that provided by the particulate materials. Also, gelatin sponge and coils allow a more rapid occlusion of large vessels when bleeding is severe. Coils are often also used as a trap for the gelatin sponge and a ''plug'' in the vessels can be created. This is particularly useful when the feeding vessels to the bleeding site arise from a larger branch and the feeding vessels themselves cannot be catheterized. Rather than extensively embolizing the large vessel and possibly endangering the perfusion of other important structures, a plug can be created that crosses the origins of the vessels and seals them, while filling the

lumen of the large vessel distal to the plug. This preserves the potential for collateral vessel flow to the normal tissue below the site of occlusion.

The technique for vascular malformation embolization varies with the size and extent of the abnormalities. Congenital malformations often are complex and may be treated in some cases with the embolic materials mentioned above. However, these often must be supplemented with permanent tissue adhesive or other liquid embolics [49,50]. For simple arteriovenous fistulas and pseudoaneurysms, various combinations of embolic materials have been employed, the choice depending the anatomic considerations in each case [51].

The embolization process is monitored using video fluoroscopy. Ipsilateral internal iliac angiography is repeated to exclude the possibility of additional feeding arteries, which occasionally become visible only after the primary feeding artery is occluded. Embolization of the contralateral hypogastric artery or its branches may be performed to decrease the likelihood of cross-filling. This type of ''prophylactic'' embolization is usually only done in patients with pelvic malignancy and often is more limited in extent to minimize the chance of ischemic injury to the pelvic organs. If the patient's clinical condition suggests that the bleeding has not stopped, then additional angiographic exploration is necessary to identify other potential sources of blood.

The technique of embolization can be more complicated in gynecologic bleeding than in the postpartum setting, particularly when the patient has already had surgery, radiotherapy, or both. Normal anatomic relationships are distorted and there may be atypical sources of blood supply to the bleeding site. Thus, to be effective, the embolization may need to be more extensive than is normally required for a typical postpartum embolization.

Outcome from embolotherapy for gynecologic hemorrhage

The limited published data on embolotherapy of pelvic malignancy suggest that embolization can be both safe and effective in controlling hemorrhage secondary to pelvic malignancy. Early case reports from the 1970s demonstrated the feasibility of the technique [52,53]. Several case series were published in the 1980s. In 1981, Lang [54] reported the results of embolization of 23 patients who had pelvic neoplasms. There was 100% immediate cessation of bleeding. In a larger series, Pisco and colleagues [55] reported the results of a series of 108 patients with hemorrhage from pelvic malignancy, including 55 with gynecologic malignancy. They achieved complete hemorrhage control in 74 patients, partial control in 23, and no control in 11.

In 1993, Yamshita and colleagues [56] reported on 17 patients with cervical cancer who developed malignancy-related massive hemorrhage. Active extravasation from the uterine artery was found in only 2 patients, but neovascularity was demonstrated in 12. Immediate control of bleeding was achieved in 100%. However 7 patients (41.1%) had recurrent bleeding after

2 weeks, and 3 of those patients required repeat embolization. All patients continued with planned therapy after control of hemorrhage. Other smaller series have noted similar results [57]. There is also evidence that these procedures prolong survival in patients with advanced malignancy, with median survival extended 4 to 6 months [58,59]. Long-term follow-up in patients with hemorrhage from benign causes suggests long-term symptom control, with one 7.5-year follow-up study [60].

Therapeutic outcomes from treatment of vascular malformations are also quite good. Among 17 patients treated, Maleux and colleagues [51] noted recurrence in only 1, with a mean follow-up of 18.8 months. Similar results were noted by Ghai and colleagues [61]. In the long-term, this therapy appears durable. Jacobowitz and colleagues [62] treated 35 patients, each having an average of 2.4 procedures. More than one procedure was often needed to completely treat these complex lesions. With an average of 84 months follow-up, 83% of patients remained asymptomatic or significantly improved.

Complications of embolization for peripartum and gynecologic hemorrhage

Complications of angiography and embolization in the setting of peripartum bleeding after angiographic intervention for gynecologic emergencies are rare. From a technical standpoint, catheterization is straightforward for a trained interventional radiologist because most women in this group are young and free of atherosclerotic vascular disease. In the early evolution of embolization in this setting, a concern about end-organ ischemia was raised. Therefore in 1980, Pais and colleagues [16] histologically evaluated a hysterectomy specimen after embolization and failed to find any ischemic changes. Over time, it was found that generalized uterine ischemia is indeed a very rare complication. However, uterine ischemic necrosis was reported when very small (150–250 μm) polyvinyl alcohol particles were used along with gelatin sponge pledgets [63]. Small particles can cause very distal embolization and have potential to cause ischemic injury. When using gelatin sponge alone, only one report of severe ischemic injury and uterine necrosis has been reported [64].

While trying to elicit the effects and outcomes of embolization for postpartum hemorrhage, Badawy and colleagues [12] reviewed 22 publications from 1979 to 1999. In their review of 138 cases of postpartum hemorrhage treated with embolization, they report a high technical success rate of 95% for controlling the bleeding in the short term. Seven cases required an eventual hysterectomy. Other reported complications related to embolization for either postpartum hemorrhage or gynecologic hemorrhage included transient fevers [11,65], transient buttock ischemia and lower extremity parasthesia [8], external iliac artery perforation [4], groin hematoma, pelvic abscess formation [66], transient foot ischemia, bladder gangrene [12], and

Table 1
Embolization for treatment of postpartum hemorrhage

Investigators	Number of patients	Embolic material	Complications
Abbas et al [43]	1	Gelatin sponge, coil, PVA	Readmission, fever, vaginal bleeding, abdominal hematoma, septic shock
Bakri and Linjawi [57]	3	Gelatin sponge, coil	Femoral hematoma
Brown et al [17]	1	Gelatin sponge	none
Chin et al [65]	2	Gelatin sponge, coil	fever
Dubois et al [30]	2	Gelatin sponge	None
Feinberg et al [22]	1	Gelatin sponge, coil	none
Gilbert et al [6]	6	Gelatin sponge	none
Greenwood et al [4]	6	Gelatin sponge, coil	Transient buttock ischemia, external iliac perforation
Hansch et al [32]	5	Gelatin sponge, coil, PVA	none
Heffner et al [68]	3	Gelatin sponge	None
Hsu and Wan [69]	2	Gelatin sponge	None
Joseph et al [70]	2	Gelatin sponge, coil	None
Merland et al [71]	16	Gelatin sponge, PVA	None
Mitty et al [5]	7	Gelatin sponge, coil	None
Pais et al [16]	1	Gelatin sponge, coil	Uterine perforation, fever
Pelage et al [10]	27	Gelatin sponge, PVA	Repeat embolization, hysterectomy
Pelage et al [21]	14	Gelatin sponge, n-butyl-2-cyanoacrylate	none
Rosenthal and Colapinto [19]	2	Coil	Failed embolization, wound infection
Shweni et al [72]	4	Gelatin sponge	None
Soncini et al [73]	14	Gelatin sponge, coil	Hysterectomy, fever
Stancato-Pasik et al [24]	12	Gelatin sponge	None
Vegas et al [74]	27	Coil, PVA	Hysterectomy, repeat embolization, hysterectomy, vaginal fistula
Yamashita et al [11]	6	Gelatin sponge	Fever
Yamashita et al [56]	15	Gelatin sponge, coil	None
Yong and Cheung [75]	29	Not specified	Cardiac arrest, hysterectomy, claudication, fever

Abbreviation: PVA, polyvinyl alcohol particles.

vesicovaginal fistula formation [67]. Primary embolization has also been reported to technically fail with need for a hysterectomy [10]. A summary of selected reports describing the technique and complications of embolization in the setting of postpartum hemorrhage is presented in Table 1 [68–75].

Summary

Arterial embolization can play an important role in overall management of obstetric and gynecologic vascular emergencies. A substantial body of literature from obstetric–gynecologic and radiological sources describes the embolization techniques as safe and effective in achieving control of hemorrhagic complications for postpartum hemorrhage and gynecologic emergencies.

Embolization avoids operative morbidity in patients who are usually poor surgical candidates due to anemia and coagulopathies. Embolization does not preclude surgical ligation or hysterectomy should embolization fail and surgical approaches become necessary [76]. Additionally, new angiographic techniques can serve as an important adjunct in the management of ectopic pregnancies and placentation abnormalities. Obstetricians, gynecologists, and interventional radiologists alike should be familiar with these options to provide the most comprehensive care to patients.

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Liability in High-Risk Obstetrics

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Liability issues have changed the obstetrical landscape. The 2006 American College of Obstetricians and Gynecologists (ACOG) survey on professional liability revealed significant practice changes as a result of insurance availability or affordability. According to the survey, 25.6% of surveyed physicians decreased their number of high-risk obstetrical patients, while 7.2% quit practicing obstetrics altogether. Furthermore, 28.5% of those who continue to deliver patients reported increasing the number of cesarean sections, with 26.4% not performing vaginal births after cesarean sections (VBACs). Reducing liability risk requires an understanding of the prime reasons physicians are sued and are limiting exposure in the main areas affecting obstetrics [1].

Reasons physicians are sued

A recent plaintiff's attorney's article highlighted the major reasons physicians get sued. The most common reason for suit is, predictably, that a medical error injured a patient. Although frivolous lawsuits do occur, credible plaintiff firms avoid such suits, as the cost of prosecuting a medical malpractice suit ranges from $40,000 to over $200,000 [2]. In general, plaintiff firms turn down over 90% of cases, either because expert review supports the physician actions or because damages are insufficient to cover the costs of litigation. It is for this latter reason that obstetrics, with its high exposure, is a focus of many plaintiff firms. The average damages in a successful suit with a neurologically impaired infant in $1,150,687 [1].

New paradigms in delivering obstetrical care, such as laborists and large group practices, may actually expose physicians to greater liability. Patients may be attended and delivered by physicians they have never seen. If problems occur during labor and delivery, the lack of a trusting relationship

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raises questions of competency, and thus the specter of malpractice. This problem is compounded if there is a lack of communication between the primary obstetrician and the covering physician. Thus, the covering obstetrician may be unaware of risk factors that might lower the threshold for cesarean section.

A common source of malpractice suit is injuries associated with delayed cesarean sections and difficult operative vaginal deliveries. Pritchard [2] termed this "wishful obstetrics." This refers to futile attempts at vaginal delivery by allowing another 0.5 to 1 hour of pushing, or making one or two more pulls with the vacuum.

Some hospitals are not equipped or staffed to respond to acute emergencies. Thus, if a delivery delay from emergencies, such as a prolapsed cord, placental abruption, or uterine rupture results in an adverse fetal outcome, hospitals, as well as physicians, are exposed to significant liability. The patient should be informed of the facility's capabilities and, if appropriate, offered delivery at a hospital better equipped for the patient's condition.

Physicians who treat indigent patients are sued more frequently. Inner city hospitals may be staffed with poorly trained physicians, thus placing those patients at greater risk for harm. Residency training commonly entails treating indigent patients. In combination with recognized communication concerns and numerous "hand-offs," there is greater chance for medical error. Numerous suits result from a lack of appropriate communication skills. Families often seek legal advice to learn what happened, rather than because of a primary interest in money. When adverse outcomes occur, physicians must discuss this with the patient and her family, addressing her concerns and questions in a frank and open manner. A 1995 Journal of the American Medical Association article reported that in many cases, while no technical errors occurred, the practitioner generated enough misunderstanding and anger to provoke a malpractice claim [3]. Furthermore, 85% of suits were filed against 3% to 6% of doctors. The authors concluded that doctors who are hurried, uninterested, or unwilling to listen to and answer questions are at risk of suit, even if they practice quality medicine. Conversely, those who are perceived as concerned, accessible, and willing to communicate are sued far less.

Innovative early-intervention programs, such as the COPIC Insurance Company of Colorado's 3R's, have demonstrated the effectiveness of such programs in averting malpractice suits [4]. The 3R's stand for "Recognize-Respond-Resolve." COPIC insurance may pay disability payments up to $5,000, with additional reimbursement for out-of-pocket expenses up to $25,000. In essence, the physician-patient relationship is preserved through clear, candid communication regarding a treatment-related injury. The patient retains her right to pursue further legal action if she desires. The physician's participation in the program does not limit their professional coverage or raise their premiums. This program resulted in remarkably lower payouts than traditional methods, where the average cost of paid claims was

over $250,000. As of December 2003, no cases had gone to litigation. Thus, in effective programs, early and clear communication can reduce litigation exposure.

Areas of litigation in obstetrics

Litigation centers on errors of omission or commission. Thus prime areas for obstetrical litigation comprise the following:

1. Errors or omission in antenatal screening and diagnosis
2. Errors in ultrasound diagnosis
3. The neurologically impaired infant
4. Neonatal encephalopathy
5. Stillborn or neonatal death
6. Shoulder dystocia, with either brachial plexus injury or hypoxic injury
7. Vaginal birth after cesarean section
8. Operative vaginal delivery
9. Training programs (Resident supervision markedly impacts litigation exposure. Increased used of nurse midwives and nurse practitioners may increase ones liability exposure.)

Antenatal screening and diagnosis

Errors in antenatal screening and diagnosis are an increasing focus for litigation. Such errors can lead to claims for wrongful birth, wrongful life, and wrongful death. Although these specific claims may be prohibited by law in some states, they serve as the basis for most suits relating to antenatal diagnosis.

Wrongful birth is a claim for relief by the parents, who allege they would have avoided conception or would have terminated a pregnancy if they had been advised of the likelihood of giving birth to an impaired child [5]. Classic examples are Tay-Sachs disease or cystic fibrosis. A wrongful life claim is a cause of action by a special needs child, who claims damages because he was conceived or not aborted because of the physician's negligence [6]. This cause of action is barred in most states. Wrongful death is a cause of action arising when an otherwise normal pregnancy, which has reached viability, is terminated because of a misdiagnosis [7]. An example would be a misdiagnosis of renal agenesis resulting in pregnancy termination.

ACOG now recommends offering antenatal screening for chromosomal abnormalities to all pregnancy patients regardless of age [8]. In addition, the broader availability of nuchal translucency screening establishes a standard of care in which most patients should be offered the opportunity for first trimester screening. A physician failing to offer patients such diagnostic testing is at risk for suit.

Ultrasound is routine in caring for obstetrical patients. Missed diagnosis of fetal anomalies accounts for over a one-fourth of obstetrical malpractice cases. Guidelines for proper performance of obstetric ultrasound examinations have been established [9]. As such, this represents the standard of care for obstetrical ultrasound. The best approach for obstetrical ultrasound is to have properly trained or certified ultrasonographers performing comprehensive studies on contemporary, well-maintained equipment, with image interpretation by a qualified sonologist. Referral for consultation is appropriate in confusing circumstances or when the acuity of the clinical situation warrants enhanced evaluation and knowledge.

Failure to recommend further testing or procedures is an area of increasing concern, particularly when evaluating possible genetic syndromes or chromosomal abnormalities. For example, isolated findings suggesting Down's syndrome, such as an intracardiac echogenic focus or minimal pyelectasis, may be of no consequence. However, when multiple subtle findings are present, the patient's risk for chromosomal abnormalities should be recalculated and, if appropriate, further testing recommended [10]. Prenatal screening for genetic disease is also indicated in certain populations [11]. Failure to communicate these findings to the referring physician, however subtle, can place the consultant at risk of suit.

Antepartum fetal assessment

High-risk pregnancies require antepartum fetal surveilalance [12]. Fetal heart rate monitoring, ultrasound surveillance, amniotic fluid volumes, Doppler studies, and cordocentesis are appropriate in pregnancies complicated by conditions such as intrauterine growth restriction, twins, diabetes, hypertension, severe preeclampsia, and sensitization, among others [13–15]. Guidelines for appropriate use establish an accepted standard of care. Deviating from these guidelines requires substantiated decision making; otherwise, physicians are at risk of a malpractice suit in the event of an adverse outcome.

Intrapartum liability

Obvious liability lies with an adverse fetal or neonatal outcome. Intrapartum management undergoes close scrutiny. The most devastating outcomes, and thus costly awards, center on neurologically impaired infants and babies with permanent neurologic deficits after shoulder dystocia.

Neurologically impaired infants

Almost 70% of neonatal encephalopathy is attributable to antepartum events. However, 19% of newborns meet criteria for intrapartum hypoxia, with 10% having a significant intrapartum event that may be associated with intrapartum hypoxia. The ACOG Task Force on Neonatal

Encephalopathy and Cerebral Palsy determined four essential criteria that must be met for a diagnosis of hypoxic encephalopathy [16]. These are:

1. Metabolic acidosis evidenced by an umbilical cord artery pH lower than 7 and a base deficit greater than 12 mmol/L;
2. Early onset neonatal encephalopathy in infants at more than 34 weeks of gestation;
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type; and
4. Exclusion of other etiologies.

This group also outlined criteria suggesting intrapartum timing including:

1. A sentinel hypoxic event;
2. Sudden and sustained bradycardia or absence of variability with persistent, late, or variable decelerations after a sentinel hypoxic event;
3. Apgar scores of 0 to 3 beyond 5 minutes;
4. Multisystem involvement under 72 hours of age; or
5. Imaging with acute nonfatal cerebral abnormality.

These criteria are offered as mandatory findings to establish an intrapartum hypoxic event leading to neonatal encephalopathy and, ultimately, cerebral palsy. However, at least five jurisdictions have held that the criteria are not dispositive, that is, not a final determination. The report can be admitted into evidence; however, all proffered opinions are subject to scrutiny and cross-examination.

It is clear that careful attention to labor progress and fetal status, including adequate documentation, enhances defensibility. Intrapartum fetal heart rate changes must be recognized and responded to appropriately [17]. Prompt intervention and operative delivery, if indicated, minimize allegations of negligence.

Shoulder dystocia with permanent palsy

Shoulder dystocia is an infrequent, and often unpredictable, nightmare for the obstetrician [18]. However, the law evaluates whether the complication was foreseeable and, if not, whether appropriate maneuvers performed. Recognized risk factors include a prior pregnancy complicated by shoulder dystocia and resultant Erb's palsy, macrosomia, and a midpelvic operative delivery in fetuses with an estimated weight over 4000 grams [19]. An estimated fetal weight over 5000 grams in nondiabetic pregnancies and over 4500 grams in diabetic pregnancies has been offered as justification for a primary cesarean section. Thus, a physician who overlooks the prior obstetrical history, does not estimate the fetal weight in labor, or who pursues a midpelvic operative delivery in larger infants subjects him or herself to a claim of negligence.

Controversy exists regarding the impact of active phase abnormalities or second stage abnormalities on shoulder dystocia [20]. Although not reaching significance, the incidence of shoulder dystocia is twice as frequent with

operative delivery in both diabetic (23.8% versus 12.0%) and nondiabetic (13.3% versus 6.5%) patients. Thus, an operative delivery should be approached with care. Documentation of indications, fetal status, fetal position, pelvic adequacy, number of pulls or pop-offs, and the immediate neonatal status are critical to defense. A dictated operative note is also recommended, including all pertinent information, such as infant birth weight, Apgar scores, cord gases, anesthesia, and estimated blood loss.

Several maneuvers are appropriate in the event of a shoulder dystocia [21,22]. There is no required sequence of maneuvers, only that they be applied in an orderly and timely fashion [23]. Two specific maneuvers should always be avoided: fundal pressure, which serves to further impact the anterior shoulder, and extreme lateral flexion of the spinal column and neck, the presumed cause of stretch or avulsion injuries. A dictated or thoroughly documented delivery note includes the aforementioned items, plus other critical information [24]:

1. All providers present at the delivery
2. Note of the anterior shoulder
3. The time from recognition of the shoulder dystocia and delivery
4. All maneuvers used and in what order
5. Note if the infant moves all extremities after delivery

Documenting such information enhances defensibility of a shoulder dystocia case.

Vaginal birth after cesarean section

Vaginal birth after cesarean section has come under great scrutiny. It is a safe alternative in well-selected patients delivering in hospitals with appropriate resources [25]. However, recognized risks and the dire consequences have prompted some states to impose practice guidelines for VBAC [26]. Physicians should document discussions of the risks and benefits of VBAC and the hospital's capabilities, with signed patient consent. Immediate physician availability and operative capabilities are required. If this cannot be offered, then the patient should be transferred to a facility with these capabilities.

Supervision of residents and advanced-care providers

Guidelines have been established for resident supervision, propagated by the Centers for Medicare and Medicaid Services [27]. Attending supervision requires an understanding of the resident's skill, training, and knowledge. Thus, appropriate delegation of responsibility can occur while keeping patient safety paramount. In most jurisdictions, the attending is held responsible for actions of a resident under their supervision. Clear and specific direction of expectations, communication, and documentation

are required. Documentation review and confirmation are attending responsibilities that must comply with billing rules for supervised care by residents.

Certified nurse midwives often have independent practice authority. However, collaborative agreements may be required to independently prescribe medications [28]. Written protocols, including scope of practice and referral guidelines should be in place and carefully followed. Hospital protocols and guidelines often dictate the level of supervision and consultation required. A physician employing a midwife is liable for any acts under the doctrine of respondent superior. Vicarious liability occurs as it would for an employer liable for the wrong of an employee if it was committed within the scope of employment [29]. Thus, guidelines and protocols must be followed to maintain defensibility of a case.

A primer in medical malpractice

A plaintiff must prove the following elements of negligence for a successful malpractice suit:

1. A duty was owed to the patient by the health care provider,
2. There was a breach of that duty,
3. This breach was the proximate cause of the injury, and
4. The injury that resulted is compensable.

The duty to care for a patient is clear with an established physician-patient relationship. However, such a relationship may exist if phone advice is rendered or communication and advice is given via electronic communications [30]. The Emergency Medical Treatment and Active Labor Act creates a physician-patient relationship in emergency situations. As such, the physician is obligated to care for the patient until they are stable for discharge or transfer to a better-suited facility.

Breach of the duty is breach of the standard of care. The standard of care is how a similarly qualified practitioner would have managed the patient's care under the same or similar circumstances. Breach of duty is typically proven by expert testimony. Testimony must be based on reliable and accepted scientific principles [31]. ACOG recommends that expert testimony should withstand peer review [32]. Breach of hospital protocols may be introduced to demonstrate a deviation from the established standard of care. Thus, a physician's knowledge of such protocols is imperative in caring for patients and preparing for successful case defense. Occasionally a breach of duty falls under the doctrine of res ipsa loquitur, which holds but for the failure to exercise due care the injury would not have occurred [29]. An example would be a retained surgical instrument or operating on the wrong limb.

The breach must also be the proximate cause of the damages suffered by the patient. In civil cases, such as medical malpractice, the level of proof required is by a preponderance of the evidence, that is, greater than or equal

to 51%. This is different from criminal cases requiring proof beyond a reasonable doubt. Thus, if the breach resulted in at least a 51% likelihood of the injury or outcome, then proximate cause can be proven.

Finally, the injury must be compensable, commonly called damages. Damages are of three types: economic, noneconomic, and punitive. Economic damages, also called "special damages," compensate for the medical costs of an injury, such as medical bills, rehabilitation, and loss of income. Noneconomic damages, termed "general damages," compensate for losses that are not monetary, such as loss of consortium, loss of future fertility, or pain and suffering. Punitive damages, termed "exemplary damages," are awarded to punish a defendant for willful and wanton conduct, such as sexual misconduct. The latter two categories are limited, or capped, in many jurisdictions.

If a plaintiff's case is successful and damages are awarded, each state or jurisdiction has specific rules regarding responsibility for payment. If a state follows joint and several liability, then each defendant is individually liable for the entire award. Ultimately, they can seek reimbursement from the nonpaying parties, the right of subrogation. Proportional liability, also called comparative negligence, can be pure or partial in nature. Proportional liability allocates a portion of the blame to each defendant and, in certain cases, the plaintiff. In pure comparative negligence, a plaintiff may receive recovery even if their contribution to the injury is more than the defendant's. However, the award is reduced by that percent contribution. In some states, the plaintiff is barred from recovery if their contribution is more that 50%. With partial comparative negligence, each defendant is responsible for the portion of the damage award based on the allocated proportion of their fault.

Summary

This article has outlined the major causes of malpractice suits, focusing on those in obstetrical practice. It has reviewed the prime areas in antepartum and intrapartum care. Finally, understanding the basic elements of medical malpractice allows a provider to better understand the nature of a suit for medical negligence. The threat of a medical malpractice is ever present in obstetrics. However, practicing contemporary, evidence-based medicine, with compassion and excellent communication is the best way to avoid alleged negligence. If a suit occurs, the best defense entails comprehensive documentation, particularly in recognized areas of risk.

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