CHAPTER 41: Obstetrical Hemorrhage

A profuse hemorrhage occurring prior to or shortly after the birth of the child is always dangerous and not infrequently a fatal complication.

—J. Whitridge Williams (1903)

INTRODUCTION

As in Williams' time, obstetrical hemorrhage continues along with hypertension and infection to be one part of the infamous "triad" of maternal death causes. It also is a leading reason for admission of pregnant women to intensive care units (Chantry, 2015; Crozier, 2011; De Greve, 2016; Guntupalli, 2015). Hemorrhage was a direct cause of 11.4 percent of 5367 pregnancy-related maternal deaths from 2006 to 2013 in the United States (Creanga, 2015, 2017). Similarly, 16 percent of 1102 maternal deaths recorded in the Nationwide Inpatient Sample were caused by hemorrhage (Kuriya, 2016). In developing countries, hemorrhage's contribution is even more striking, and it is the single most important cause of maternal death worldwide (Goffman, 2016; Oladapo, 2016; Thomas, 2016). Despite these numbers, a declining maternal mortality rate from hemorrhage in the United States has been a seminal achievement. But, as discussed in Chapter 1 (Maternal Mortality), it seems unlikely that deaths from hemorrhage have reached an irreducible minimum.

GENERAL CONSIDERATIONS

Mechanisms of Normal Hemostasis

A major concept in understanding the pathophysiology and management of obstetrical hemorrhage is the mechanism by which hemostasis is achieved after normal delivery. Recall that near term an incredible amount of blood—at least 600 mL/min—flows through the intervillous space (Pates, 2010). This prodigious flow circulates through the spiral arteries, which average 120 in number. Also, recall that these vessels have no muscular layer because of their remodeling by trophoblasts, which creates a low-pressure system. With placental separation, these vessels at the implantation site are avulsed, and hemostasis is achieved first by myometrial contraction, which compresses this formidable number of large vessels. Compression is followed by clotting and obliteration of vessel lumens.

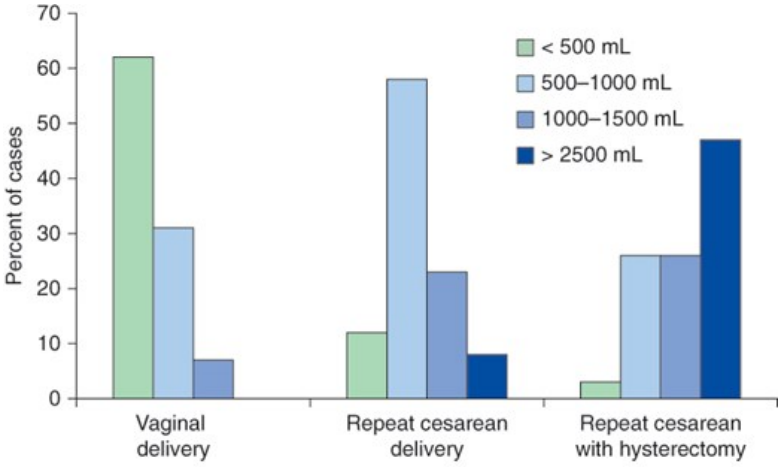
If, after delivery, the myometrium contracts vigorously, fatal hemorrhage from the placental implantation site is unlikely. *Importantly, an intact coagulation system is not necessary for postpartum hemostasis unless there are lacerations in the uterus, birth canal, or perineum.* At the same time, however, fatal postpartum hemorrhage can result from uterine atony despite normal coagulation.

Definition and Incidence

Traditionally, postpartum hemorrhage is defined as the loss of ≥500 mL of blood after completion of the third stage of labor. This is problematic because almost half of all women delivered vaginally shed that amount of blood or more when losses are carefully measured (Pritchard, 1962). These results are depicted in Figure 41-1 and show further that approximately 5 percent of women delivering vaginally lose more than 1000 mL of blood. According to the American College of Obstetricians and Gynecologists (2017d), postpartum hemorrhage is defined as cumulative blood loss >1000 mL accompanied by signs and symptoms of hypovolemia. And, almost a third of women undergoing cesarean delivery have blood loss that exceeds 1000 mL. *These studies show that estimated blood loss is commonly only approximately half the actual loss.* Because of this, estimated blood loss in excess of "average" should alert the obstetrician to possible excessive bleeding. Whether quantification of blood loss improves accuracy is controversial (Hamm, 2017; Toledo, 2007).

FIGURE 41-1

Blood loss associated with vaginal delivery, repeat cesarean delivery, and repeat cesarean delivery plus hysterectomy. (Data from Pritchard, 1962.)



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The blood volume of a pregnant woman with normal pregnancy-induced hypervolemia usually rises by half, but individual increases range from 30 to 60 percent, that is, 1500 to 2000 mL for an average-sized woman (Pritchard, 1965). The equation to calculate blood volume is shown in Table 41-1. It is axiomatic that a normal pregnant woman tolerates, without any decrease in postpartum hematocrit, blood loss at delivery that approaches the volume of blood that she added during pregnancy. Thus, if blood loss is less than the pregnancy-added volume, the hematocrit remains the same acutely and during the first several days postpartum. It then rises as nonpregnant plasma volume normalizes during the next week or so. *Whenever the postpartum hematocrit is lower than one obtained on admission for delivery, blood loss can be estimated as the sum of the calculated pregnancy-added volume plus 500 mL for each 3 volume percent decline of the hematocrit.*

TABLE 41-1

Calculation of Maternal Total Blood Volume

Nonpregnant blood volume[a]:

$$\frac{[\text{Height (inches)} \times 50] + [\text{Weight (pounds)} \times 25]}{2} = \text{Blood volume (mL)}$$

Pregnancy blood volume:

Average increase is 30 to 60 percent of calculated nonpregnant volume

Increases across gestational age and plateaus at approximately 34 weeks

Usually larger with low normal-range hematocrit (~30) and smaller with high normal-range hematocrit (~40)

Average increase is 40 to 80 percent with multifetal gestation

Average increase is less with preeclampsia—volumes vary inversely with severity

Postpartum blood volume with serious hemorrhage:

Assume acute return to nonpregnant total volume after fluid resuscitation

Pregnancy hypervolemia cannot be restored postpartum

[a]Formula arrived at by measuring blood volume and blood loss in more than 100 women using ^{51}Cr-labeled erythrocytes.

Data from Hernandez, 2012.

Excessive blood loss has been estimated by several methods. Sosa and colleagues (2009) used specially constructed drapes and reported that 10.8 percent of women had hemorrhage in excess of 500 mL with vaginal delivery, whereas 1.9 percent lost >1000 mL. Compared with the findings of Figure 41-1, these estimates likely are too low. Tita and associates (2012) used a 6-volume percent drop in the postpartum hematocrit to define clinically significant blood loss with vaginal delivery. This decline easily signifies a >1000-mL blood loss in the averaged-sized woman. They documented this amount in a fourth of women, which agrees with Figure 41-1.

Another marker used to estimate hemorrhage incidence is the transfusion rate. In the study by Tita just cited, more than 6 percent of women who delivered vaginally underwent blood transfusions. In a study of more than 66,000 women delivered at Parkland Hospital, 2.3 percent overall were given blood transfusions for hypovolemia (Hernandez, 2012). Half of these women had undergone cesarean delivery. Importantly, for those transfused, these investigators calculated blood loss to average approximately 3500 mL! Finally, Green and coworkers (2016) reported that the incidence of *massive transfusion* for postpartum hemorrhage was 23 per 100,000 births.

From the foregoing, it is apparent that significant blood loss accompanies up to a fourth of vaginal deliveries. The amounts and proportions for cesarean delivery are much greater. And, hemorrhage is underreported. For example, data from the National Hospital Discharge Summary database reported postpartum hemorrhage incidences of only 2.0 and 2.6 percent for two epochs in the United States (Berg, 2009). Similar incidences have been reported by others (Kramer, 2013; Mehrabadi, 2013; Patterson, 2014).

Risks

Numerous clinical circumstances raise the risks for obstetrical hemorrhage. The imposing list shown in Table 41-2 illustrates that hemorrhage can manifest at any time throughout pregnancy, delivery, and the puerperium. Thus, any description of obstetrical hemorrhage should include gestational age. Contributions to maternal death from some of these causes of are shown in Figure 41-2.

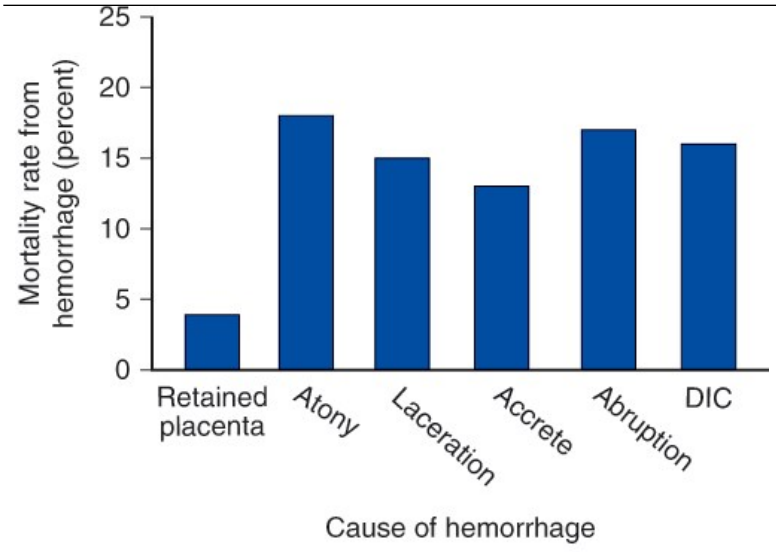
TABLE 41-2

Obstetrical Hemorrhage: Causes, Predisposing Factors, and Vulnerable Patients

Abnormal Placentation	**Uterine Atony**
Placenta previa	Uterine overdistention
Placental abruption	Large fetus
Morbidly adherent placenta	Multiple fetuses
Ectopic pregnancy	Hydramnios
Hydatidiform mole	Retained clots
Injuries to the Birth Canal	Labor induction
Episiotomy and lacerations	Anesthesia or analgesia
Forceps or vacuum delivery	Halogenated agents
Cesarean delivery or hysterectomy	Conduction analgesia with hypotension
Uterine rupture	Labor abnormalities
Previously scarred uterus	Rapid labor
High parity	Prolonged labor
Hyperstimulation	Augmented labor
Obstructed labor	Chorioamnionitis
Intrauterine manipulation	Previous uterine atony
Midforceps rotation	Parity: primiparity, high parity
Breech extraction	**Coagulation Defects—Intensify Other Causes**
Obstetrical Factors	Massive transfusions
Obesity	Placental abruption
Previous postpartum hemorrhage	Sepsis syndrome
Early preterm pregnancy	Severe preeclampsia syndrome
Sepsis syndrome	Acute fatty liver
Preeclampsia/eclampsia	Anticoagulant treatment
Vulnerable Patients	Congenital coagulopathies
Chronic renal insufficiency	Amnionic fluid embolism
Constitutionally small size	Prolonged retention of dead fetus
	Saline-induced abortion

FIGURE 41-2

Contributions to maternal death from various causes of obstetrical hemorrhage. Percentages are approximations because of different classification schemata used. DIC = disseminated intravascular coagulopathy. (Data from Al-Zirqi, 2008; Berg, 2010; Creanga, 2015; Zwart, 2008.)



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Timing

Antepartum Hemorrhage

Obstetrical hemorrhage is traditionally classified as *antepartum*—such as with placenta previa or placental abruption, or as *postpartum*—commonly caused by uterine atony or genital tract lacerations. In individual women, however, these terms are nonspecific, and it is reasonable to specify the cause and gestational age as descriptors.

Bleeding during various times in gestation may give a clue to its cause. Many aspects of bleeding during the first half of pregnancy from abortion or ectopic pregnancy are covered in Chapters 18 and 19. Discussions that follow concern pregnancies with a viable-size fetus. *In these cases, rapid assessment should always consider the deleterious fetal effects of maternal hemorrhage.*

During active labor, slight vaginal bleeding is common. This “bloody show” is the consequence of effacement and dilation of the cervix, with tearing of small vessels. Uterine bleeding above the cervix, however, is concerning. It may follow some separation of a placenta previa implanted in the immediate vicinity of the cervical canal, or it may be from a placental abruption or uterine tear. In some women, especially with a placenta previa, cervical varicosities may bleed (O’Brien, 2013). Rarely, there may be velamentous insertion of the umbilical cord, and the involved placental vessels may overlie the cervix—*vasa previa.* In this case, serious fetal hemorrhage follows laceration of these vessels at the time of membrane rupture (Swank, 2016).

Near term in many women, the source of uterine bleeding is not identified, bleeding ceases, and no apparent anatomical cause is found at delivery. In most of these cases, bleeding likely originated from a slight marginal placental separation. *Despite this, any pregnancy with antepartum bleeding remains at higher risk for an adverse outcome even though bleeding has stopped and placenta previa has been excluded sonographically.*

Bleeding after midpregnancy is associated with several adverse outcomes. The Canadian Perinatal Network described 806 women with hemorrhage between 22 and 28 weeks’ gestation (Sabourin, 2012). Placental abruption (32 percent), previa (21 percent), and cervical bleeding (6.6 percent) were the most frequent causes identified. In a third, no cause was found. Of all women, 44 percent were delivered before 29 weeks’ gestation. In more than 68,000 women in Scotland, the incidence of antepartum hemorrhage after the first trimester was 11 percent (Bhandari, 2014). These women were at significantly higher risk for preterm birth, labor induction, and postpartum hemorrhage.

Postpartum Hemorrhage

In most cases, the source of postpartum hemorrhage can and should be determined. Frequent causes are uterine atony with placental site bleeding, genital tract trauma, or both. Postpartum hemorrhage is usually obvious. Important exceptions are unrecognized intrauterine and intravaginal blood

accumulation and uterine rupture with intraperitoneal or retroperitoneal bleeding. Another consideration is an expanding vulvar or vaginal hematoma (Puerperal Hematomas). Initial evaluation attempts to differentiate uterine atony from genital tract lacerations. For this, risk factors are sought, the lower genital tract is examined, and uterine tone is assessed. Atony is identified by a boggy, soft uterus during bimanual examination and by expression of clots and hemorrhage during uterine massage.

Persistent bleeding despite a firm, well-contracted uterus suggests that hemorrhage most likely is from lacerations. Bright red blood further suggests arterial bleeding. *To confirm that lacerations are a source of bleeding, careful inspection of the vagina, cervix, and uterus is essential.* Sometimes bleeding may be caused by both atony and trauma, especially after forceps or vacuum-assisted vaginal delivery. Examination is easier if conduction analgesia was given. If there are no lower genital tract lacerations and the uterus is contracted, yet supracervical bleeding persists, then manual exploration of the uterus is done to exclude a uterine tear (Kaplanoglu, 2016). This also is completed routinely after internal podalic version, breech extraction, or successful vaginal birth after cesarean.

Late postpartum hemorrhage describes bleeding after the first 24 hours. Found in up to 1 percent of women, it may be serious and is discussed in Chapter 37 (American College of Obstetricians and Gynecologists, 2017d).

Blood Loss Estimation

As noted, visual estimates are notoriously inaccurate, especially with excessive bleeding. Instead of sudden massive hemorrhage, postpartum bleeding is frequently steady. If atony persists, bleeding may appear to be only moderate at any given instant but may continue until serious hypovolemia develops. Bleeding from an episiotomy or a vaginal laceration can also appear to be only minimal to moderate. But, constant seepage can lead to enormous blood loss relatively quickly. In some cases, after placental separation, blood may not escape vaginally but instead may collect within the uterine cavity, which can become distended by 1000 mL or more of blood. In others, postpartum uterine massage is applied to a roll of abdominal fat mistaken for the uterus.

All of these factors can lead to an underappreciation of the magnitude of hemorrhage over time. The effects of hemorrhage depend to a considerable degree on the maternal nonpregnant blood volume and the corresponding degree of pregnancy-induced hypervolemia. For this and other reasons, hypovolemia may not be recognized until very late. *A treacherous feature of postpartum hemorrhage is the failure of the pulse and blood pressure to undergo more than moderate alterations until large amounts of blood have been lost.* The normotensive woman initially may actually become somewhat hypertensive from catecholamine release in response to hemorrhage. And importantly, women with preeclampsia may become “normotensive” despite remarkable hypovolemia.

Some gravidas may be particularly susceptible to hemorrhage because their blood volume expansion is less than expected. This situation is most commonly encountered in small women—even those with normal pregnancy-induced hypervolemia. Women with severe preeclampsia or eclampsia are also more vulnerable to hemorrhage because they frequently do not have a normal blood volume accrual. Specifically, Zeeman and associates (2009) documented a mean increase above nonpregnant volume of only 10 percent in *eclamptic* women (Chap. 40, Blood Volume). A third example is the moderate-to-severe curtailing of pregnancy-induced volume expansion in women with chronic renal insufficiency (Chap. 53, Chronic Kidney Disease). *When excessive hemorrhage is suspected in these high-risk women, crystalloid and blood are promptly administered for suspected hypovolemia.*

UTERINE ATONY

Third-Stage Labor Management

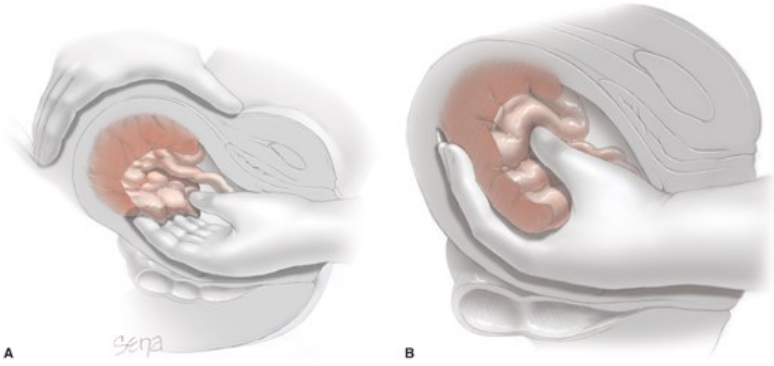
The most frequent cause of obstetrical hemorrhage is failure of the uterus to contract sufficiently after delivery and to arrest bleeding from vessels at the placental implantation site (General Considerations). That said, some bleeding is inevitable during third-stage labor as the placenta begins to separate. Blood from the implantation site may escape into the vagina immediately—the *Duncan mechanism* of placental separation, or it remains concealed behind the placenta and membranes until the placenta is delivered—the *Schultze mechanism.* After signs of placental separation, the uterus should be massaged if it is not contracted firmly, and placental descent is indicated by a slack umbilical cord. *Importantly, separation and delivery of the placenta by cord traction, especially when the uterus is atonic, may cause uterine inversion.*

If heavy bleeding persists after delivery of the newborn and while the placenta remains partially or totally attached, then manual placental removal is

indicated (Cummings, 2016; Frolova, 2016). For this, adequate analgesia is mandatory, and aseptic surgical technique should be used. As illustrated in Figure 41-3, the fingertips of one hand, with fingers approximated, are insinuated between the uterine wall and placenta. A sweeping forward motion in this plane will peel the placenta off its uterine attachment. After its removal, trailing membranes are carefully teased free from the decidua using ring forceps as needed. Another method to clear membranes is to wipe out the uterine cavity with a gauze-wrapped hand. Most recommend ampicillin or cefazolin antimicrobial prophylaxis after manual removal (World Health Organization, 2015).

FIGURE 41-3

Manual removal of placenta. **A.** One hand grasps the fundus. The other hand is inserted into the uterine cavity, and the fingers are swept from side to side as they are advanced. **B.** When the placenta has become detached, it is grasped and removed.



The fundus is always palpated following placental delivery to confirm that the uterus is well contracted. If it is not firm, then vigorous fundal massage usually prevents postpartum hemorrhage from atony (Hofmeyr, 2013). Simultaneously, 20 units of oxytocin in 1000 mL of crystalloid solution will often be effective given intravenously at 10 mL/min for a dose of 200 mU/min. Higher concentrations are minimally more effective (Tita, 2012). *Oxytocin is never given as an undiluted bolus dose because serious hypotension or cardiac arrhythmias can develop.*

Risk Factors

In many women with known risks, uterine atony can at least be anticipated well in advance of delivery. In one study, however, up to half of women with atony after cesarean delivery had no risk factors (Rouse, 2006). The magnitude of risk for atony imposed by each of the factors shown in Table 41-2 varies considerably between reports. *Primiparity* and *high parity* are risk factors (Driessen, 2011). In one study, the incidence of postpartum hemorrhage rose from 0.3 percent in women of low parity to 1.9 percent with parity of four or greater. It was 2.7 percent with parity of seven or greater (Babinszki, 1999). The *overdistended uterus* is prone to hypotonia after delivery, and thus women with a large fetus, multiple fetuses, or hydramnios are at greater risk. *Labor abnormalities* predispose to atony and include hyper- or hypotonic labor. Similarly, *labor induction* or *augmentation* with either prostaglandins or oxytocin is more likely to be followed by atony (Driessen, 2011). The frequency of hemorrhage increases with prolongation of the third stage (Frolova, 2016). Finally, the woman who has had a *prior postpartum hemorrhage* is at risk for recurrence.

Evaluation and Management

With immediate postpartum hemorrhage, careful inspection is done to exclude birth canal laceration. Because bleeding can be caused by retained placental fragments, inspection of the placenta after delivery should be routine. If a defect is seen, the uterus should be manually explored and the fragment removed. Occasionally, retention of a *succenturiate lobe* may cause postpartum hemorrhage (Chap. 6, Shape and Size Variants). During examination for lacerations and causes of atony, the uterus is massaged and uterotonic agents are administered.

Uterotonic Agents

Several compounds can prompt the postpartum uterus to contract (Chap. 27, Immediate Postpartum Care). One of these is routinely selected and given to *prevent* postpartum bleeding by ensuring uterine contractions. Most of these same agents are also used to *treat* uterine atony with bleeding. Moreover, because many trials combine results from atony prophylaxis and treatment, their evaluation is problematic. For example, o*xytocin* has been used for more than 70 years, and in most cases, it is infused intravenously or given intramuscularly after placental delivery. Neither route has been

shown to be superior (Dagdeviren, 2016). This or other uterotonics given prophylactically will prevent most cases of uterine atony.

To treat uterine atony, ergot alkaloids have been used for centuries. If atony persists despite oxytocin and other preventive measures, ergot derivatives can be used for second-line treatment. Ergot preparations include methylergonovine (Methergine) and ergonovine, however, only methylergonovine is currently manufactured in the United States. Given parenterally, these drugs rapidly stimulate tetanic uterine contractions and act for approximately 45 minutes (Schimmer, 2011). A common regimen is 0.2 mg of either drug given intramuscularly. Methergine can be repeated at 2- to 4-hour intervals as needed. *A caveat is that ergot agents, especially given intravenously, may cause dangerous hypertension, especially in women with preeclampsia.* Severe hypertension is also seen with concomitant use of protease inhibitors given for human immunodeficiency viral (HIV) infection. These adverse effects notwithstanding, it is speculative whether ergot derivatives offer superior therapeutic effects compared with oxytocin.

In cases of atony refractory to one agent, an agent from a different group can be added. At least two randomized studies have addressed combined ergot-oxytocin regimens. In one, ergometrine plus oxytocin was compared with ergometrine alone to prevent postpartum hemorrhage (Koen, 2016). The overall need for transfusion was significantly lower with the combination regimen. Another comparable study reaffirmed these findings (Şentürk, 2016).

During the past 40 years, other second-line agents for atony have included the E- and F-series prostaglandins. Carboprost tromethamine (Hemabate) is the 15-methyl derivative of prostaglandin $F_{2\alpha}$. It is approved for uterine atony treatment in a dose of 250 µg (0.25 mg) given intramuscularly. This dose can be repeated if necessary at 15- to 90-minute intervals up to a maximum of eight doses. Observational data indicate an 88-percent success rate (Oleen, 1990). Carboprost causes side effects in approximately 20 percent of women. These include, in descending order of frequency, diarrhea, hypertension, vomiting, fever, flushing, and tachycardia. Another pharmacological effect is pulmonary airway and vascular constriction. Thus, carboprost should not be used for asthmatic women and those with suspected amnionic fluid embolism (General Management). We have occasionally encountered severe hypertension with carboprost given to women with preeclampsia. It has also been reported to cause arterial oxygen desaturation that averaged 10 percent (Hankins, 1988). Relative contraindications to carboprost include renal, liver, and cardiac disease (American College of Obstetricians and Gynecologists, 2017d).

E-series prostaglandins can also prevent or treat atony. Dinoprostone—prostaglandin E_2—may be used off label and is given as a 20-mg suppository per rectum or per vaginum every 2 hours. It typically causes diarrhea, which is problematic for the rectal route, whereas vigorous vaginal bleeding may preclude its use per vaginum. Hypotension, which is commonly encountered with hemorrhage, is considered a contraindication by some. Intravenous prostaglandin E_2—*sulprostone*—is used in Europe, but it is not available in the United States (Schmitz, 2011).

Misoprostol—*Cytotec*—is a synthetic prostaglandin E_1 analogue that is used for prevention and treatment of atony (Abdel-Aleem, 2001; Ugwu, 2016). Most studies have addressed prevention and have conflicting conclusions. In a Cochrane review, Mousa and associates (2014) reported no added benefits for misoprostol use compared with oxytocin or ergonovine for treatment. Derman and coworkers (2006) compared a 600-µg oral dose given preventively at delivery against placebo. They found that the drug lowered the incidence of hemorrhage from 12 to 6 percent and that of severe hemorrhage from 1.2 to 0.2 percent. In another study, Gerstenfeld and Wing (2001) concluded that 400 µg misoprostol administered rectally was not superior to intravenous oxytocin given to prevent postpartum hemorrhage. From a systematic review, Villar (2002) found that oxytocin and ergot preparations administered after delivery were more effective than misoprostol for prevention of postpartum hemorrhage (Chap. 27, Immediate Postpartum Care). If misoprostol is used to treat atony, the American College of Obstetricians and Gynecologists (2017d) recommends a dose of 600 to 1000 µg rectally, orally, or sublingually.

Bleeding Unresponsive to Uterotonic Agents

If bleeding persists after initial measures for atony have been implemented, then the following management steps are performed immediately and simultaneously:

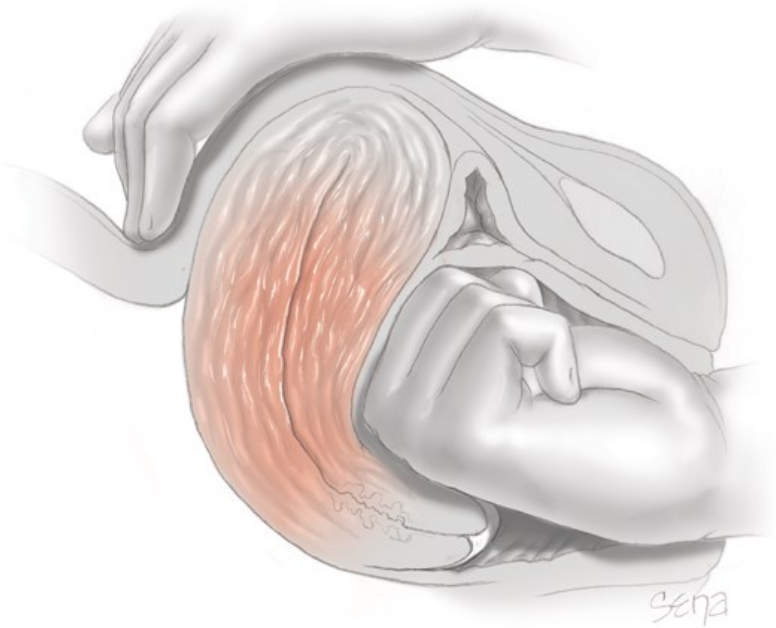
1. Begin bimanual uterine compression, which is easily done and controls most cases of continuing hemorrhage (Fig. 41-4). This technique is not simply fundal massage. The posterior uterine wall is massaged by one hand on the abdomen, while the other hand is made into a fist and placed into the vagina. This fist kneads the anterior uterine wall through the anterior vaginal wall and the uterus is also compressed between the two hands.

2. Immediately mobilize the emergent-care obstetrical team to the delivery room and call for whole blood or packed red cells.

3. Request urgent help from the anesthesia team.
4. Secure at least two large-bore intravenous catheters so that crystalloid with oxytocin can be continued simultaneously with blood products. Insert an indwelling Foley catheter for continuous urine output monitoring.
5. Begin volume resuscitation with rapid intravenous infusion of crystalloid (Hypovolemic Shock).
6. With sedation, analgesia, or anesthesia established and now with optimal exposure, once again manually explore the uterine cavity for retained placental fragments and for uterine abnormalities, including lacerations or rupture.
7. Thoroughly inspect the cervix and vagina again for lacerations that may have escaped attention.
8. If the woman is still unstable or if there is persistent hemorrhage, then blood transfusions are given (Hypovolemic Shock).

FIGURE 41-4

Bimanual compression for uterine atony. The uterus is positioned with the fist of one hand in the anterior fornix pushing against the anterior wall, which is held in place by the other hand on the abdomen. The abdominal hand is also used for uterine massage.



At this juncture, after causes other than atony have been excluded and after hypovolemia is reversed, several other measures are considered if bleeding continues. Their use depends on several factors such as parity, desire for sterilization, and experience with each method.

Balloon Tamponade

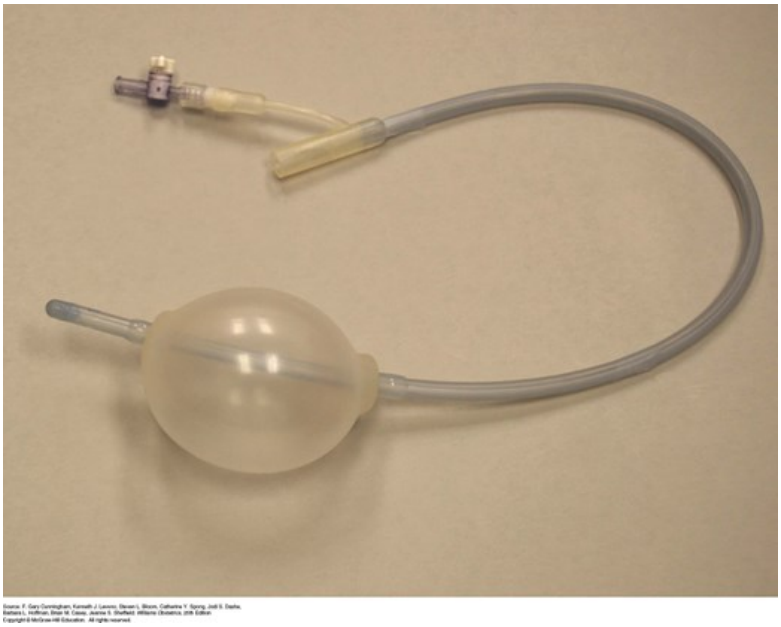
Uterine packing to treat refractory uterine atony fell from favor because of concerns regarding concealed bleeding and infection (Gilstrap, 2017). Newer techniques of balloon tamponade help alleviate some of these concerns (Sentilhes, 2016; Zelop, 2011). In one technique, the tip of a 24F to 30F Foley catheter with a 30-mL balloon is guided into the uterine cavity and filled with 60 to 80 mL of saline. The open tip permits continuous drainage of blood from the uterus. We have experienced balloon rupture when more than 50 mL was instilled into the balloon, thus a 34F Foley with a 60-ml balloon can be used. If bleeding subsides, the catheter is typically removed after 12 to 24 hours. Similar devices for tamponade include Segstaken-Blakemore, Rusch, and ebb balloons and condom catheters (Antony, 2017; Georgiou, 2009).

Enthusiasm has developed for specially constructed intrauterine balloons to treat hemorrhage from uterine atony and other causes. A *Bakri Postpartum Balloon* or *BT-Cath* may be inserted and inflated to tamponade the endometrial cavity and stop bleeding (Fig. 41-5). Insertion requires two

or three team members. The first performs abdominal sonography during the procedure. The second places the deflated balloon into the uterus and stabilizes it. The third member instills fluid to inflate the balloon, rapidly infusing at least 150 mL followed by further instillation over a few minutes for a total of 300 to 500 mL to arrest hemorrhage. It is reasonable to remove the balloon after approximately 12 hours (Einerson, 2017).

FIGURE 41-5

Intrauterine Bakri balloon for postpartum hemorrhage.



In prospective studies, nearly 150 women have been managed for postpartum hemorrhage with these uterine balloons (Grönvall, 2013; Kaya, 2016; Vintejoux, 2015). Perhaps a fourth of cases were caused by uterine atony. For all causes, the success rate was noted to be approximately 85 percent. Combinations of balloon tamponade and uterine compression sutures have also been described (Diemert, 2012; Yoong, 2012). Failures for all of these require various surgical methods including hysterectomy.

Surgical Procedures

These include uterine compression sutures, pelvic vessel ligation, angiographic embolization, and hysterectomy. These are discussed in Adjunctive Surgical Procedures.

UTERINE INVERSION

Puerperal inversion of the uterus is one of the classic hemorrhagic disasters encountered in obstetrics. Unless promptly recognized and managed appropriately, associated bleeding often is massive. Risk factors include alone or in combination: (1) fundal placental implantation, (2) uterine atony, (3) cord traction applied *before* placental separation, and (4) abnormally adhered placentation such as with the accrete syndromes (Morbidly Adherent Placenta).

Depending on which of these factors are contributory, the incidence and severity of uterine inversion varies. There is progressive severity of inversion as shown in Figure 41-6. The worst scenario is complete inversion with the uterus protruding from the birth canal (Fig. 41-7).

FIGURE 41-6

Progressive degrees of uterine inversion.

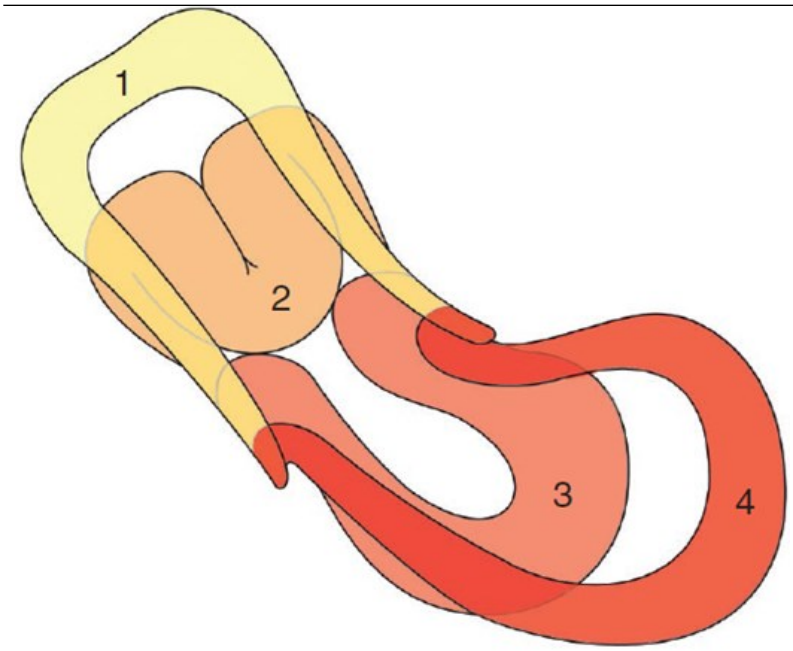
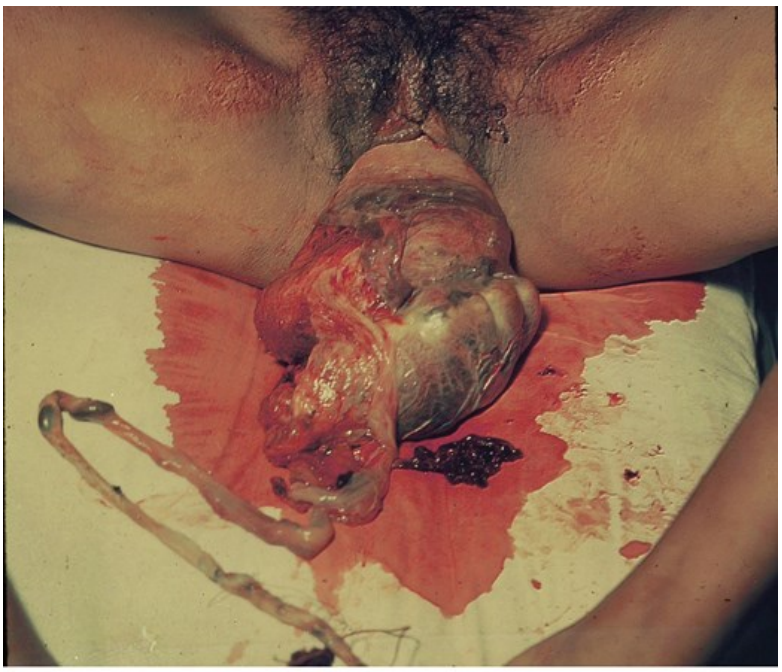


FIGURE 41-7

Maternal death during home delivery caused by exsanguination from uterine inversion and a fundally implanted placenta accreta.



The incidence of uterine inversion ranges from 1 in 2000 to 1 in 20,000 vaginal deliveries (Coad, 2017; Ogah, 2011; Rana, 2009; Witteveen, 2013). Our experiences at Parkland Hospital comport with the higher 1:2000 incidence. This is despite our policy of discouraging placental delivery by cord traction alone, and before certainty of its separation. It is unknown if *active management of third-stage labor* with cord traction applied ostensibly *after* signs of placental separation raises the likelihood of uterine inversion (Deneux-Tharaux, 2013; Gülmezoglu, 2012; Prick, 2013).

Recognition and Management

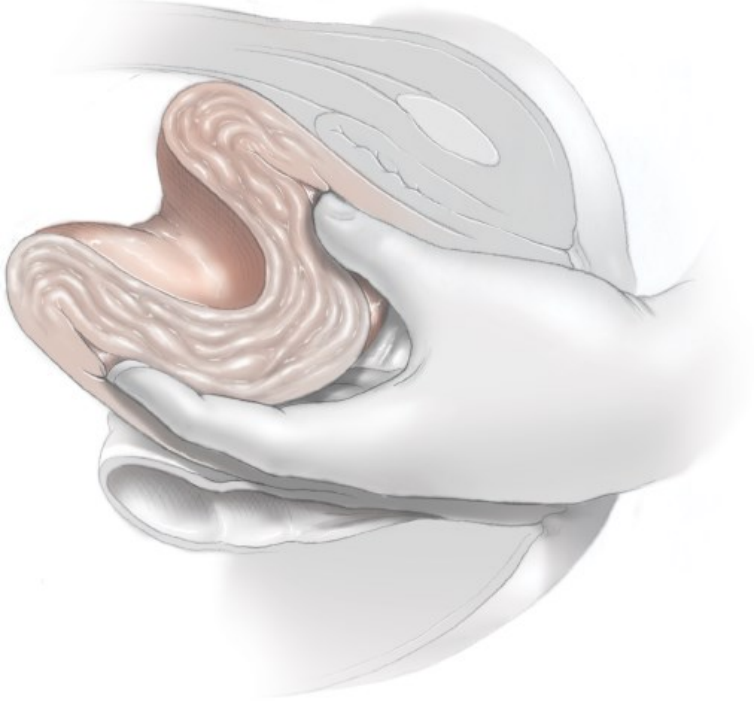
Immediate recognition of uterine inversion improves the chances of a quick resolution and good outcome (Furukawa, 2015b). If initially unrecognized, continued hemorrhage likely will prompt closer examination of the birth canal. Although complete inversion is usually evident, the partially inverted uterus can be mistaken for a uterine myoma, and sonography can aid differentiation (Pan, 2015; Smulian, 2013). Many cases are associated with immediate life-threatening hemorrhage, and a fourth require blood replacement (Coad, 2017).

Once any degree of uterine inversion is recognized, several steps must be implemented urgently and simultaneously:

1. Immediate assistance is summoned, including obstetrical and anesthesia personnel.
2. Blood is brought to the delivery suite for potential use.
3. The woman is evaluated for emergency general anesthesia. Large-bore intravenous infusion systems are secured to begin rapid crystalloid infusion to treat hypovolemia while awaiting arrival of blood products.
4. If the recently inverted uterus has not contracted and retracted completely and if the placenta has already separated, then the uterus may often be replaced simply by pushing up on the inverted fundus with the palm of the hand and fingers in the direction of the long axis of the vagina (Fig. 41-8). Some use two fingers rigidly extended to push the center of the fundus upward. *Care is taken not to apply so much pressure as to perforate the uterus with the fingertips.*
5. If the placenta is still attached, then attempts are made to reposition the uterus with the placenta in situ. Many recommend a trial of an intravenously administered tocolytic drug such as terbutaline, magnesium sulfate, or nitroglycerin for uterine relaxation and repositioning (You, 2006). If these fail to provide sufficient relaxation, then a rapidly acting halogenated inhalational agent is administered. After the uterus is replaced, the placenta is carefully manually removed.
6. If uterine repositioning fails with the placenta attached, then it is peeled off and steady pressure with the fist, palm, or fingers is applied to the inverted fundus in an attempt to push it up into and through the dilated cervix as described in Step 4.
7. Once the uterus is restored to its normal configuration, tocolysis is stopped. Oxytocin is then infused, and other uterotonics may be given as described for atony (Risk Factors). Meanwhile, the operator maintains the fundus in its normal anatomical position while applying bimanual compression to control further hemorrhage until the uterus is well contracted (see Fig. 41-4). The operator continues to monitor the uterus transvaginally for evidence of subsequent inversion. A Bakri balloon has been used to maintain the repositioned uterus (Haeri, 2015; Ida, 2015).

FIGURE 41-8

Incomplete uterine inversion repositioned by using the abdominal hand for palpation of the crater-like depression while simultaneously gently pushing the inverted fundus upward.



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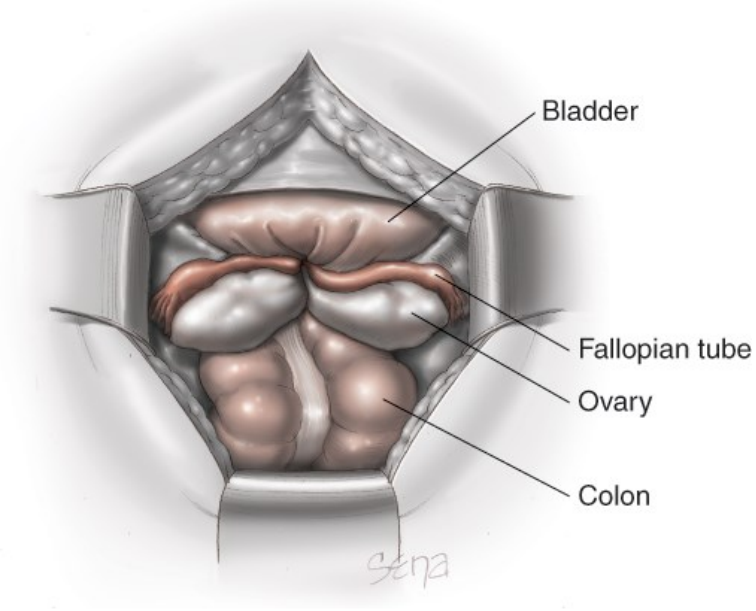
Surgical Intervention

In most cases, the inverted uterus can be restored to its normal position by the techniques just described. Occasionally, manual replacement fails. One cause is a dense myometrial constriction ring. At this point, laparotomy is imperative. The anatomical configuration found at surgery can be confusing as shown in Figure 41-9. With agents given for tocolysis, a combined effort is made to reposition the uterus by simultaneously pushing upward from below and pulling upward from above. Application of atraumatic clamps to each round ligament and upward traction may be helpful—the *Huntington procedure*. In some cases, placing a deep traction suture in the inverted fundus or grasping it with tissue forceps may be of aid. Either or both of these may be technically difficult. If a constriction ring still prohibits repositioning, a sagittal surgical cut—*Haultain incision*—is made posteriorly through the muscular ring to release it. The exposed fundus can then be reinverted (Sangwan, 2009). After uterine replacement, tocolytics are stopped, oxytocin and other uterotonics are given, and the uterine incision is repaired. Risks of separation of this posterior hysterotomy incision during subsequent pregnancy, labor, and delivery are unknown. Further illustration and discussion is found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Zahn, 2017).

FIGURE 41-9

Surgical anatomy of a completely inverted uterus viewed from above at laparotomy.



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In some cases, the uterus will again invert almost immediately after repositioning. With this problem, uterine compression sutures can be used to prevent another inversion (Matsubara, 2009; Mondal, 2012). Occasionally, chronic puerperal uterine inversion may become apparent weeks after delivery.

INJURIES TO THE BIRTH CANAL

Childbirth is invariably associated with trauma to the birth canal, which includes the uterus and cervix, vagina, and perineum. Injuries sustained during labor and delivery range from minor mucosal tears to lacerations that create life-threatening hemorrhage or hematomas.

Vulvovaginal Lacerations

According to the American College of Obstetricians and Gynecologists (2016b), up to 80 percent of women sustain some type of laceration at vaginal delivery. These may lie proximally or distally along the lower genital tract.

First, small tears of the anterior vaginal wall near the urethra are relatively common. They are often superficial with little to no bleeding, but they occasionally require sutures for hemostasis. Those large enough to require extensive repair are typically associated with short-term voiding difficulty, and an indwelling bladder catheter will obviate this.

Deeper perineal lacerations are usually accompanied by varying degrees of injury to the outer third of the vaginal vault. Some extend to involve the anal sphincter or varying depths of the vaginal walls. Repair of these perineal lacerations is detailed in Chapter 27 (Laceration and Episiotomy Repairs).

Lacerations involving the middle or upper third of the vaginal vault usually are comorbid with injuries of the perineum or cervix. These sometimes are missed unless inspection is thorough. Those that extend upward usually are longitudinal. They may follow spontaneous delivery but frequently result from injuries sustained during operative vaginal delivery. Most involve deeper underlying tissues and thus usually cause significant hemorrhage, which is controlled by suture repair. For this, effective analgesia or anesthesia, clear visualization, capable assistance, and sufficient resuscitation of hypovolemia are mandatory.

Extensive vaginal or cervical tears should prompt a careful search for evidence of retroperitoneal hemorrhage or of peritoneal perforation with hemorrhage. Also, intrauterine exploration is considered to exclude uterine tears or rupture (Conrad, 2015). If peritoneal perforation or uterine rupture is strongly suspected, laparotomy is considered (Rafi, 2010). As discussed later (Angiographic Embolization), imaging and potential embolization may be suitable for large retroperitoneal hematomas.

Cervical Lacerations

Superficial lacerations of the cervix can be seen on close inspection in more than half of all vaginal deliveries. Most of these measure <0.5 cm and seldom require repair. Deeper lacerations are less frequent, but even these may be unnoticed. Due to ascertainment bias, variable incidences are described. For example, with close inspection, the incidence of cervical lacerations in the Consortium on Safe Labor database was 1 percent in nulliparas and 0.5 percent in multiparas (Landy, 2011). But, the overall incidence in a study of more than 81,000 Israeli women was only 0.16 percent (Melamed, 2009). Such lacerations are more likely to be associated with vacuum- or forceps-assisted vaginal delivery (Fong, 2014).

Cervical lacerations are not usually problematic unless they cause hemorrhage or extend to the vagina. Rarely, the cervix may be entirely or partially avulsed from the vagina in the anterior, posterior, or lateral fornices, an injury termed co*lporrhexis*. Another rare injury is when the entire vaginal portion of the cervix is avulsed—*annular* or *circular detachment*. These injuries sometimes follow forceps deliveries performed through an incompletely dilated cervix with the blades applied over the cervix. In some women, cervical tears reach into the lower uterine segment and involve the uterine artery and its major branches. They occasionally extend into the peritoneal cavity. More severe lacerations usually manifest as external hemorrhage or as a hematoma, however, they may occasionally be unsuspected. In the Israeli study just cited, almost 11 percent of women with a cervical laceration required blood transfusions (Melamed, 2009).

At times, the edematous anterior cervical lip is compressed between the fetal head and maternal symphysis pubis. This usually is of little consequence and resolves spontaneously. Rarely, this causes severe ischemia, and the anterior lip may undergo necrosis and subsequently separate from the rest of the cervix.

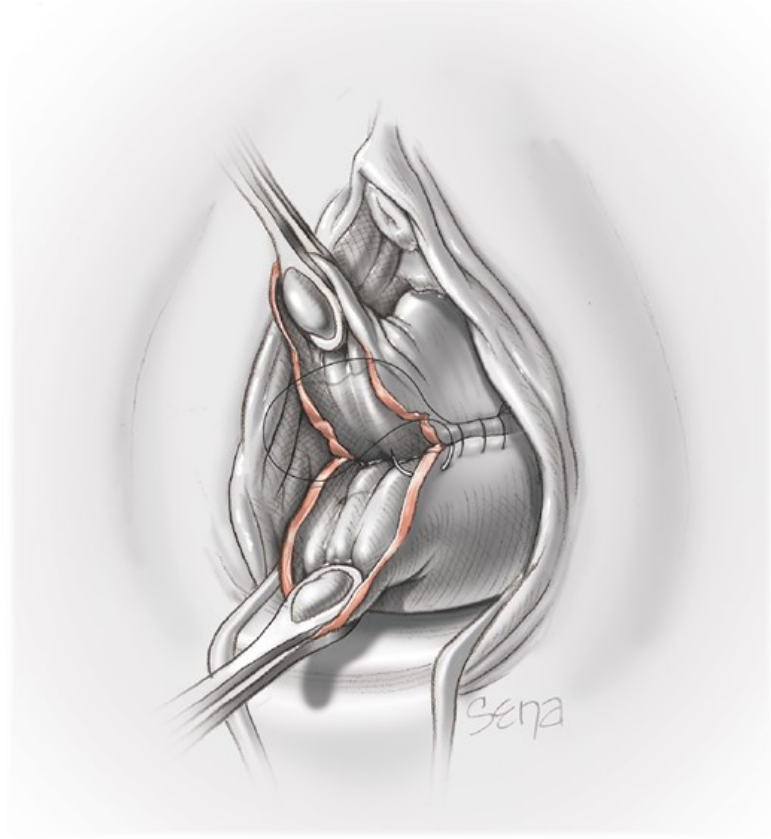
As with vulvovaginal lacerations, cervical tears can be more fully appreciated with adequate exposure, which may be best attained with transfer to an operating room. An assistant applies firm downward pressure on the uterus, while the operator exerts gentle traction on the lips of the cervix with ring forceps. A second assistant can provide even better exposure with right-angle vaginal wall retractors or Breisky vaginal retractors. Use of suction devices can also aid viewing.

In general, cervical lacerations of 1 and even 2 cm are not repaired unless they are bleeding. Such tears heal rapidly and ultimately create an irregular, sometimes stellate appearing, external cervical os that indicates previous delivery.

Deep cervical tears usually require surgical repair. When the laceration is limited to the cervix or even when it extends somewhat into the vaginal fornix, satisfactory results are obtained by suturing the cervix after bringing it into view as depicted in Figure 41-10. While cervical lacerations are repaired, any associated vaginal lacerations or an episiotomy may be tamponaded with gauze packs to arrest their bleeding. Because hemorrhage usually comes from the upper angle of the wound, the first suture using 2–0 chromic or polyglactin is placed in tissue above the angle. Subsequently, either interrupted or continuous locking sutures are serially placed outward toward the operator. If the uterus is involved and hemorrhage persists, some of the methods described later (Adjunctive Surgical Procedures) may be necessary to obtain hemostasis.

FIGURE 41-10

Repair of cervical laceration with appropriate surgical exposure. Continuous absorbable sutures are placed beginning at the upper angle of the laceration.



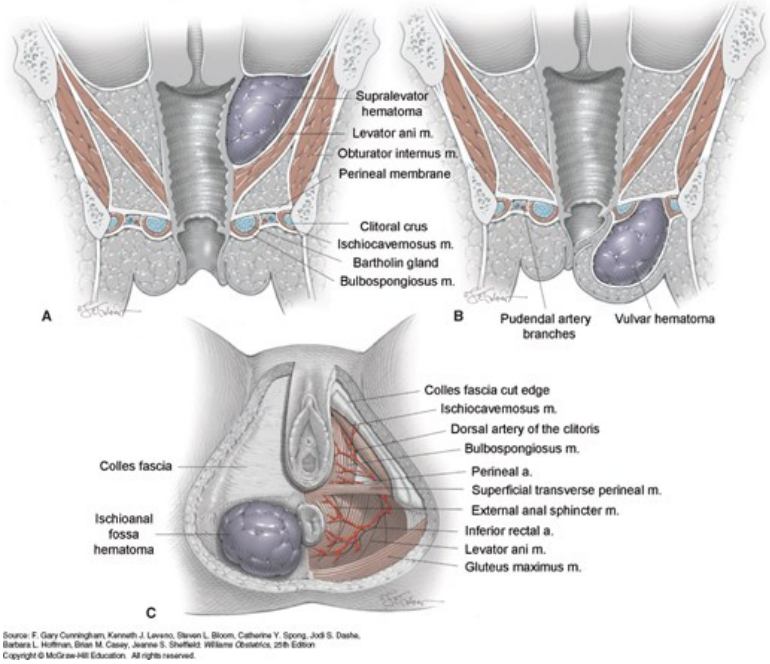
Puerperal Hematomas

Classification and Risks

Pelvic hematomas can have several anatomical manifestations following childbirth. One classification is anatomical and describes vulvar, vulvovaginal, paravaginal, and retroperitoneal hematomas. Vulvar hematomas may involve the vestibular bulb or branches of the pudendal artery, which are the inferior rectal, perineal, and clitoral arteries (Fig. 41-11). Paravaginal hematomas may involve the descending branch of the uterine artery. In some cases, a torn vessel lies above the pelvic fascia, and a supralevator hematoma develops. These can extend into the upper portion of the vaginal canal and may almost occlude its lumen. Continued bleeding may dissect retroperitoneally to form a mass palpable above the inguinal ligament. In some cases, it may even dissect up behind the ascending colon to the hepatic flexure (Rafi, 2010).

FIGURE 41-11

Schematic drawing showing types of puerperal hematomas. **A.** Coronal view showing a supralevator hematoma. **B.** Coronal view showing an anterior perineal triangle hematoma. **C.** Perineal view showing posterior perineal triangle anatomy and an ischioanal fossa hematoma. (Reproduced with permission from Cunningham FG: Genital tract lacerations and hematomas. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017a.)



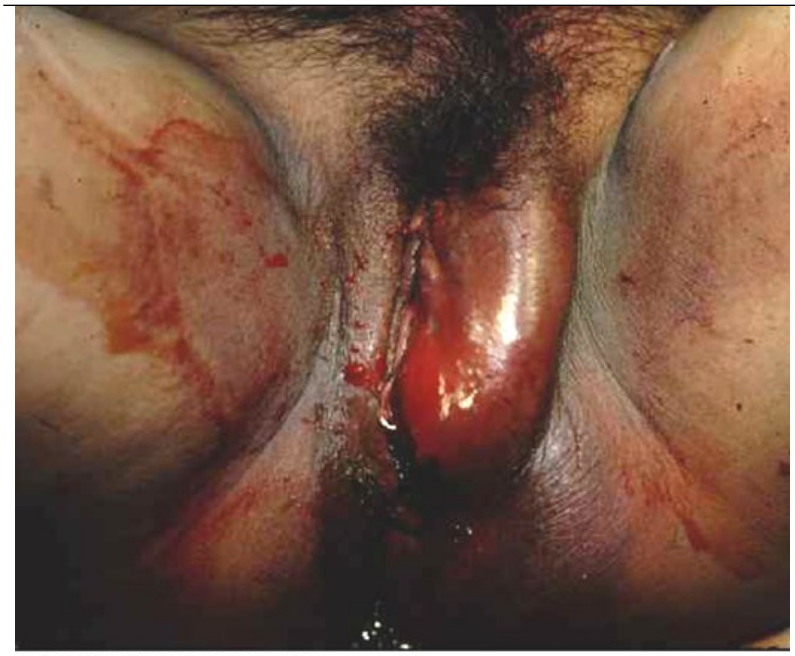
Risks for puerperal hematomas include vaginal or perineal laceration, episiotomy, or an operative delivery (Iskender, 2016). Any hematoma can also develop following stretch and rupture of a blood vessel without an associated laceration (Nelson, 2012). This may be especially true with forceps delivery. Occasionally, they are associated with an underlying coagulopathy (Obstetrical Coagulopathies).

Diagnosis

Perineal, vulvar, and paravaginal hematomas can develop rapidly and frequently cause excruciating pain (Fig. 41-12). A tense, tender swelling of varying size rapidly develops, encroaches on the vaginal lumen, and causes overlying skin or epithelium to become ecchymotic. A paravaginal hematoma may escape detection initially. However, symptoms of pelvic pressure, pain, or inability to void should prompt evaluation. Others may go undetected until other measures of hypovolemia become evident. When there is a supralevator extension, the hematoma extends upward in the paravaginal space and between the leaves of the broad ligament. The hematoma may escape detection until it can be felt on abdominal palpation or until hypovolemia develops. Imaging with sonography or computed tomographic scanning may be useful (Cichowski, 2017; Kawamura, 2014; Takeda, 2014).

FIGURE 41-12

Left-sided anterior perineal triangle hematoma associated with a vaginal laceration following spontaneous delivery in a woman with consumptive coagulopathy from acute fatty liver of pregnancy.



Clinical Course and Management

Small hematomas often remained contained and show minimal expansion. In others, the tissues overlying an expanding hematoma may rupture from pressure necrosis. In some, profuse hemorrhage may follow, but in other cases, the hematoma drains in the form of large clots and old blood. In those that involve the paravaginal space and extend above the levator sling, retroperitoneal bleeding may be massive and occasionally fatal. Finally, we have encountered a few that rebled up to 2 weeks postpartum (Cunningham, 2017a).

Vulvovaginal hematomas are managed according to their size, location, duration since delivery, and expansion. If bleeding ceases, then small- to moderate-sized hematomas may be treated expectantly until absorbed. But, if pain is severe or if the hematoma continues to enlarge, surgical exploration is preferable. *Blood loss with large puerperal hematomas is nearly always considerably more than the clinical estimate.* Hypovolemia is common, and transfusions are frequently required when surgical repair is necessary.

For repair, an incision is made at the point of maximal distention, blood and clots are evacuated, and bleeding points ligated. The cavity may then be obliterated with absorbable sutures. Often, no sites of bleeding are identified. Nonetheless, the evacuated hematoma cavity is surgically closed, and the vagina is packed for 12 to 24 hours. Supralevator hematomas are more difficult to treat. Although some can be evacuated by vulvar or vaginal incisions, laparotomy or interventional embolization, described next, is a consideration if bleeding continues.

Angiographic embolization has become popular for management of some puerperal hematomas. This is especially true for supralevator or retroperitoneal hematomas. Embolization can be used primarily, or more likely secondarily, if surgical attempts at hemostasis have failed or if the hematoma is difficult to access surgically (Distefano, 2013; Lee, 2012; Poujade, 2012). The use of a Bakri balloon for a paracervical hematoma has also been described (Gizzo, 2013; Grönvall, 2013). Finally, ultrasound-guided drainage of a recurrent supralevator hematoma has been reported (Mukhopadhyay, 2015).

Uterine Rupture

Predisposing Factors

Uterine rupture frequently is catastrophic. It may be *primary*, defined as occurring in a previously intact or unscarred uterus, or may be *secondary* and associated with a preexisting incision, injury, or anomaly of the myometrium. Some of the etiologies associated with uterine rupture are presented in Table 41-3. Importantly, the contribution of each of these underlying causes has changed remarkably during the past 50 years. Specifically, before 1960, when the cesarean delivery rate was much lower and women of great parity were numerous, primary uterine rupture predominated. As the

incidence of cesarean delivery rose and especially as a subsequent trial of labor in these women became prevalent through the 1990s, uterine rupture through the cesarean hysterotomy scar became the preeminent cause (Gibbins, 2015; Mone, 2016). However, concurrent with the diminished enthusiasm for a trial of labor in women with a prior cesarean delivery, incidence trends for the two types of rupture have again changed. In a study of 3942 cases of uterine rupture in more than 15 million women, approximately half were in women with a prior cesarean delivery (Yao, 2017). In 40 cases of rupture at Parkland Hospital from 2009 to 2016, 15 events (37 percent) were primary, and 25 (63 percent) were secondary (Happe, 2017).

TABLE 41-3

Some Causes of Uterine Rupture

Preexisting Uterine Injury or Anomaly	Uterine Injury or Abnormality Incurred in Current Pregnancy
Surgery involving the myometrium:	**Before delivery:**
Cesarean delivery or hysterotomy	Persistent, intense, spontaneous contractions
Previously repaired uterine rupture	Labor stimulation—oxytocin or prostaglandins
Myomectomy incision through or to the endometrium	Intraamnionic instillation—saline or prostaglandins
Deep cornual resection of interstitial fallopian tube	Perforation by internal uterine pressure catheter
Metroplasty	External trauma—sharp or blunt
Coincidental uterine trauma:	External version
Abortion with instrumentation—sharp or suction curette, sounds	Uterine overdistention—hydramnios, multifetal pregnancy
Sharp or blunt trauma—assaults, vehicular accidents, bullets, knives	**During delivery:**
Silent rupture in previous pregnancy	Internal version second twin
Congenital:	Difficult forceps delivery
Pregnancy in undeveloped uterine horn	Rapid tumultuous labor and delivery
Defective connective tissue—Marfan or Ehlers-Danlos syndrome	Breech extraction
	Fetal anomaly distending lower segment
	Vigorous uterine pressure during delivery
	Difficult manual removal of placenta
	Acquired:
	Placental accrete syndromes
	Gestational trophoblastic neoplasia
	Adenomyosis
	Sacculation of entrapped retroverted uterus

Additional risks for rupture include other previous operations or manipulations that traumatize the myometrium. Examples are uterine curettage or perforation, endometrial ablation, myomectomy, or operative hysteroscopy (Kieser, 2002; Pelosi, 1997). In a study by Porreco and colleagues (2009), seven of 21 women without a prior cesarean delivery had undergone prior uterine surgery.

In developed countries, the incidence of rupture is 1 in 4800 deliveries (Getahun, 2012). During a 40-year period in Norway, the uterine rupture rate rose significantly to about 1 in 1560 deliveries (Al-Zirqi, 2016). The frequency of primary rupture, however, approximates 1 in 10,000 to 15,000 births (Porreco, 2009). As discussed, one reason is a decreased incidence of women of great parity. Another is that excessive or inappropriate uterine stimulation with oxytocin—previously a frequent cause—has mostly disappeared. Maggio and associates (2014) found no association between the number of Montevideo units and secondary uterine rupture. In addition, in a recent analysis of three trials comparing high- versus low-dose oxytocin regimens, the rate of uterine rupture did not differ between groups (Budden, 2014). The rate of rupture is elevated with sequential induction of labor with prostaglandins and oxytocin (Al-Zirqi, 2017). At Parkland Hospital, we too have encountered primary uterine rupture in a disparate number of women in whom labor was induced with prostaglandin E_1.

Blunt abdominal trauma can precipitate uterine rupture. Although the distended pregnant uterus is surprisingly resistant, pregnant women sustaining such trauma should be watched carefully for signs of a ruptured uterus (Chap. 47, Other Blunt Trauma). In one study of 13 cases of primary uterine rupture, trauma accounted for three cases (Miller, 1996). Other causes of traumatic rupture that are uncommon today are those due to internal podalic

version and extraction, difficult forceps delivery, breech extraction, and unusual fetal enlargement such as with hydrocephaly.

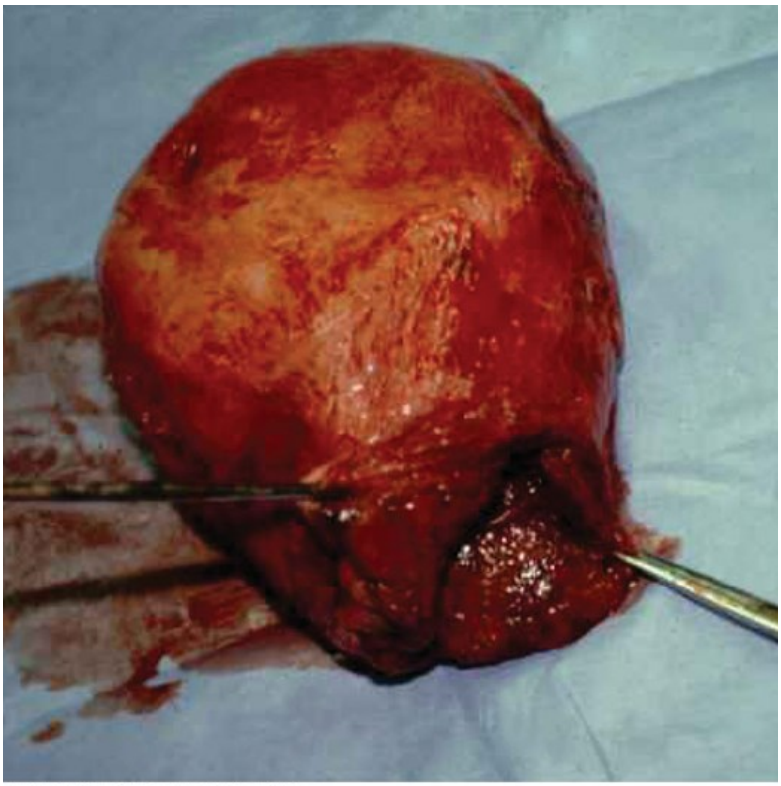
Uncommon associations of rupture are uterine anomalies or multifetal pregnancy (Bankada, 2015; Tarney, 2013; Tola, 2014). Occasionally, focal inherent weakness in the myometrium predisposes to rupture. Examples include anatomical anomalies, leiomyomas, adenomyosis, choriocarcinoma, and connective-tissue defects such as Ehlers-Danlos syndrome (Arici, 2013; Nikolaou, 2013; Noh, 2013; Ramskill, 2014; Sun, 2016).

Pathogenesis

Rupture of the previously intact uterus during labor most often involves the thinned-out lower uterine segment. When the rent is in the immediate vicinity of the cervix, it frequently extends transversely or obliquely. When the rent forms in the portion of the uterus adjacent to the broad ligament, the tear is usually longitudinal. Although these tears develop primarily in the lower uterine segment, they can extend upward into the active segment or downward through the cervix and into the vagina (Fig. 41-13). In some cases, the bladder may also be lacerated. If the rupture is of sufficient size, the uterine contents will usually escape into the peritoneal cavity. If the presenting fetal part is firmly engaged, however, then only a portion of the fetus may be extruded from the uterus. Fetal prognosis is largely dependent on the degree of placental separation and magnitude of maternal hemorrhage and hypovolemia. In some cases, the overlying peritoneum remains intact, and this usually is accompanied by hemorrhage that extends into the broad ligament to cause a large retroperitoneal hematoma.

FIGURE 41-13

Supracervical hysterectomy specimen showing uterine rupture during spontaneous labor with a vertical tear at the left lateral edge of lower uterine segment.



Following vaginal delivery in an unscarred uterus, we and others have occasionally encountered cases of an incomplete tear on the inside of the uterus that extends vertically into the active segment and is a source of profuse hemorrhage (Conrad, 2015). These tears are usually not visible from below but are found at the time of hysterectomy for intractable bleeding despite a contracted uterus. Hemorrhage with this type of tear can be torrential, and bleeding is usually not slowed until the uterine artery pedicles are clamped bilaterally.

Management and Outcomes

The varied clinical presentations of uterine rupture and its management are discussed in detail in Chapter 31 (Uterine Scar Rupture). In the most recent maternal mortality statistics from the Centers for Disease Control and Prevention, uterine rupture accounted for almost 10 percent of deaths caused by hemorrhage (Creanga, 2015, 2017). Maternal morbidity includes hysterectomy that may be necessary to control hemorrhage. Rates of perinatal mortality and morbidity, which may include severe neurological impairment, are also high (Gibbins, 2015; Porreco, 2009). Maternal obesity comorbid with uterine rupture is associated with increased rates of adverse neonatal outcomes (Yao, 2017).

PLACENTAL ABRUPTION

Etiopathogenesis

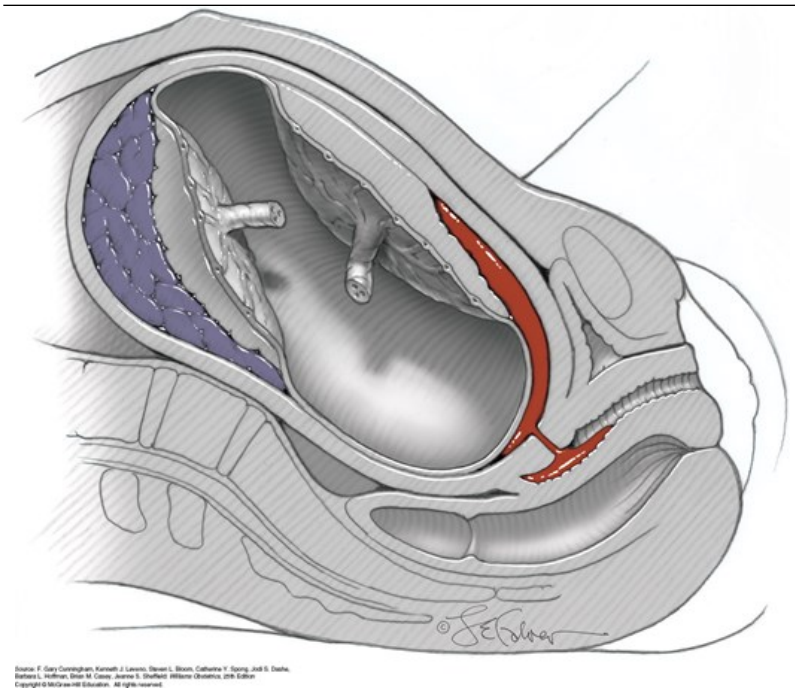
Separation of the placenta—either partially or totally—from its implantation site before delivery is described by the Latin term *abruptio placentae*. Literally translated, this refers to "rending asunder of the placenta," which denotes a sudden accident that is a clinical characteristic of most cases. In the purest sense, the cumbersome—and thus seldom used—term *premature separation of the normally implanted placenta* is most descriptive because it excludes separation of a placenta previa.

Placental abruption is initiated by hemorrhage into the decidua basalis. The decidua then splits, leaving a thin layer adhered to the myometrium. Consequently, the process begins as a decidual hematoma and expands to cause separation and compression of the adjacent placenta. Inciting causes of many cases have been posited. The phenomenon of impaired trophoblastic invasion with subsequent atherosis is related in some cases of preeclampsia complicated by abruption (Brosens, 2011). Inflammation or infection may be contributory (Mhatre, 2016; Nath, 2007). Histological findings cannot be used to determine timing of the abruption (Chen, 2017).

Abruption likely begins with rupture of a decidual spiral artery and then an expanding retroplacental hematoma. In the early stages of placental abruption, clinical symptoms may be absent. Even with continued bleeding and placental separation, placental abruption can still be either *total* or *partial* (Fig. 41-14). With either, bleeding typically insinuates itself between the membranes and uterus, ultimately escaping through the cervix to cause *external hemorrhage*. Less often, the blood is retained between the detached placenta and the uterus, leading to *concealed hemorrhage* and delayed diagnosis. The delay translates into greater maternal and fetal hazards. Also with concealed hemorrhage, the likelihood of consumptive coagulopathy is elevated. This is because increased pressure within the intervillous space, caused by the expanding retroplacental clot, forces more placental thromboplastin into the maternal circulation (Diagnosis).

FIGURE 41-14

Schematic of placental abruption. Shown to left is a total placental abruption with concealed hemorrhage. To the right is a partial abruption with blood and clots dissecting between membranes and decidua to the internal cervical os and then externally into the vagina.

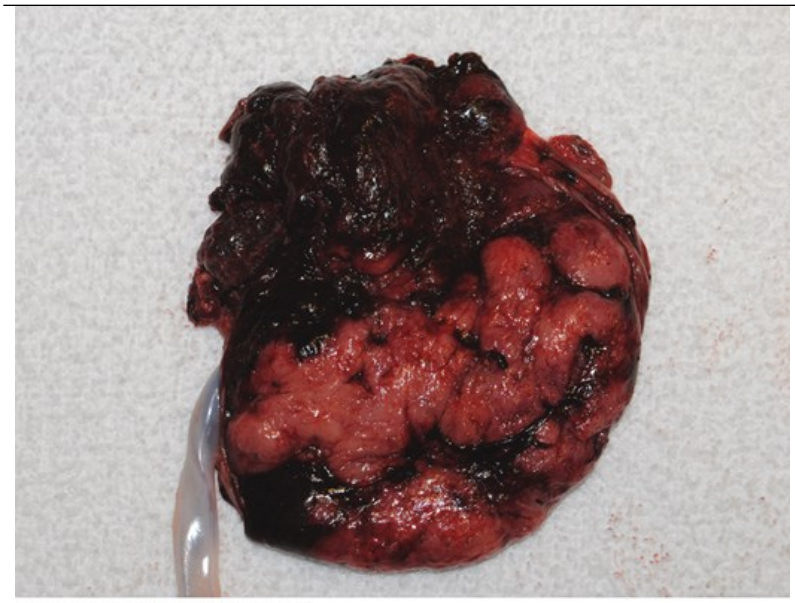


Most blood in the retroplacental hematoma in a nontraumatic placental abruption is maternal. This is because hemorrhage derives from separation within the maternal decidua, and placental villi are usually initially intact. In 78 women at Parkland Hospital with a nontraumatic placental abruption, fetal-to-maternal hemorrhage was documented in only 20 percent—and all of these had <10 mL fetal blood loss (Stettler, 1992). Atkinson and colleagues (2015) identified fetal cells in peripheral blood in only 4 percent of 68 women with a placental abruption.

When clinically suspected, an abruption is seen on a freshly delivered placenta as a circumscribed depression on the maternal surface. These usually measure a few centimeters in diameter and are covered by dark, clotted blood. Because several minutes are required for these anatomical changes to materialize, a very recently separated placenta may appear totally normal at delivery. Our experiences are like those of Benirschke and associates (2012) in that the "age" of the retroplacental clot cannot be determined exactly. In the example shown in Figure 41-15, a large dark clot is well formed, it has depressed the placental bulk, and it likely is at least several hours old.

FIGURE 41-15

Partial placental abruption with a dark adherent clot.



Defining severity of placental abruption is problematic. We have considered abruption severe when the fetus dies, however, maternal and fetal complications can be serious even with a liveborn fetus. Ananth and coworkers (2016) have defined *severe abruption* as displaying one or more of the following: (1) maternal sequelae that include disseminated intravascular coagulation, shock, transfusion, hysterectomy, renal failure, or death; (2) fetal complications such as nonreassuring fetal status, growth restriction, or death; or (3) neonatal outcomes that include death, preterm delivery, or growth restriction.

Traumatic Abruption

External trauma—usually from motor vehicle accidents or aggravated assault—can cause placental separation. The frequency of abruption originating from trauma varies. Kettel (1988) and Stafford (1988) and their associates have appropriately stressed that abruption can stem from relatively minor trauma. The clinical presentation and consequences of these abruptions differ somewhat from spontaneous cases. For example, associated fetomaternal hemorrhage, while seldom clinically significant with most spontaneous abruptions, is more common with trauma because of concomitant placental tears or "fractures" (Chap. 47, Placental Injuries). Fetal bleeding that averaged 12 mL was noted in a third of women with a traumatic abruption reported by Pearlman (1990). In eight women cared for at Parkland Hospital, we found fetal-to-maternal hemorrhage of 80 to 100 mL in three of eight cases of traumatic placental abruption (Stettler, 1992). Importantly, in some cases of trauma, a nonreassuring fetal heart rate tracing may not be accompanied by other evidence of placental separation. A sinusoidal tracing is one example. Traumatic abruption is considered in more detail in Chapter 47 (Placental Injuries).

Chronic Abruption

Some cases of chronic placental separation begin early in pregnancy. Dugoff and coworkers (2004) observed an association between some abnormally elevated maternal serum aneuploidy markers and subsequent abruption. Other have correlated first- and second-trimester bleeding with third-trimester placental abruption (Ananth, 2006; Weiss, 2004). In some cases of a chronic abruption, subsequent oligohydramnios develops—*chronic abruption-oligohydramnios sequence—CAOS* (Elliott, 1998). Even later in pregnancy, hemorrhage with retroplacental hematoma formation is occasionally arrested completely without delivery. These women may have abnormally elevated serum levels of alpha-fetoprotein or placenta-specific RNAs as markers of the event (Miura, 2016; Ngai, 2012).

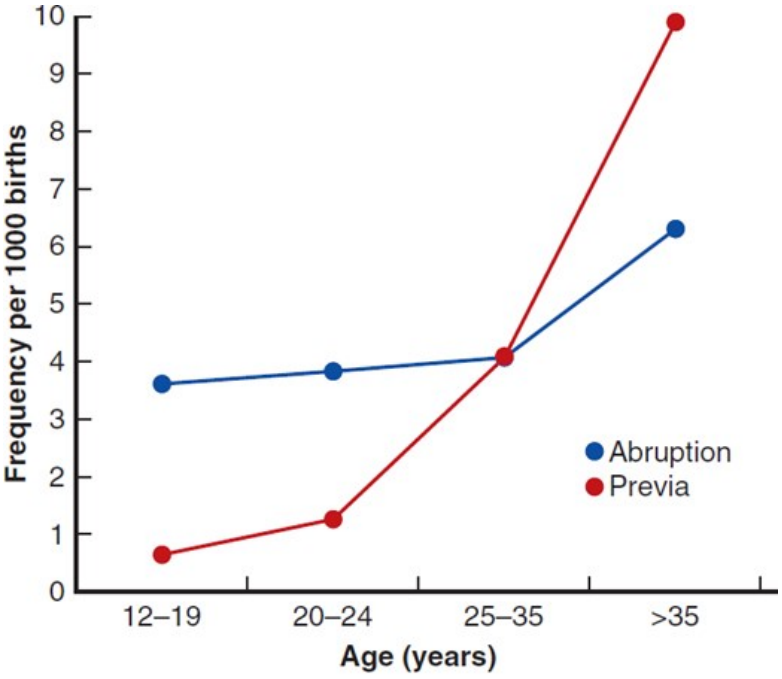
Frequency

The reported incidence of placental abruption varies because of different criteria used for diagnosis. That said, its frequency averages 0.5 percent or 1 in 200 deliveries. From one database of almost 28 million births from 2006 through 2012, the incidence of placental abruption was nearly 1 percent (Ananth, 2016). From a cohort of more than 1.57 million births in the Netherlands, Ruiter and coworkers (2015) found the frequency was 0.22 percent—1 in 450. In more than 250,000 deliveries at Parkland Hospital from 2000 through 2015, the incidence of placental abruption averaged 0.35 percent or 1

in 290 (Fig. 41-16).

FIGURE 41-16

Frequency of placental abruption and placenta previa by maternal age at Parkland Hospital from 2000 through 2015.



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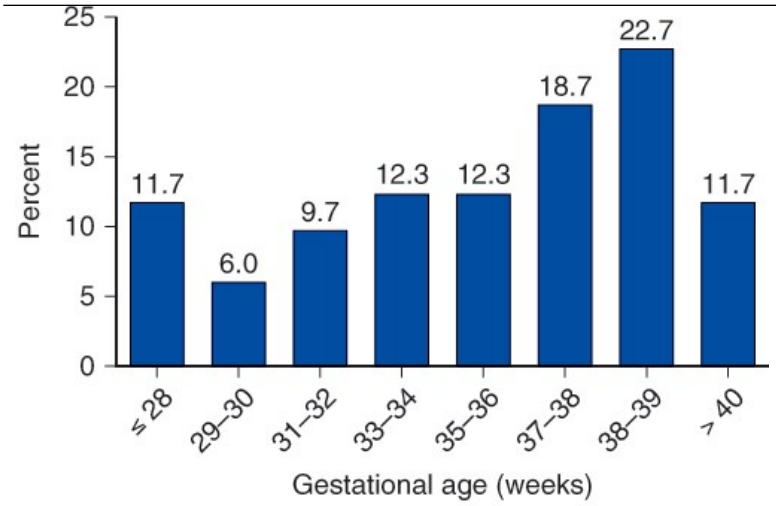
The frequency of placental abruption has *risen* in this country, and most of this increase is in black women (Ananth, 2005, 2016). At Parkland Hospital, however, the frequency of severe abruption has declined. This discrepancy may be explained in part by the variations in management of early-onset preeclampsia (Chap. 40, Preeclampsia). Specifically, with placental abruption *so extensive as to kill the fetus*, the incidence was 0.24 percent or 1 in 420 births from 1956 through 1967 (Pritchard, 1967). As the number of high-parity women giving birth declined along with improved availability of prenatal care and emergency transportation, the frequency of abruption causing fetal death dropped to 0.12 percent through 1989 in our obstetrical population. And, most recently through 2015, it declined to 0.05 percent or 1 in 2060.

Perinatal Morbidity and Mortality

Overall, perinatal outcomes are influenced by gestational age, and the frequency of placental abruption rises across the third trimester. As seen in Figure 41-17, more than half of the placental abruptions at Parkland Hospital developed at gestational ages ≥37 weeks. Perinatal mortality and morbidity, however, are more common with earlier abruptions (Furukawa, 2015a). Of other related factors, major fetal congenital anomalies have greater association with placental abruption (Riihimäki, 2013).

FIGURE 41-17

Frequency of placental abruption by gestational age at Parkland Hospital.



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Although the rates of fetal death have declined, the contribution of abruption as a cause of stillbirth remains prominent because other causes have also decreased. For example, since the early 1990s, 10 to 12 percent of all third-trimester stillbirths at Parkland Hospital have been the consequence of placental abruption. Others have documented high perinatal mortality rates caused by placental abruption. Salihu and colleagues (2005) analyzed more than 15 million singleton births between 1995 and 1998. The perinatal mortality rate associated with placental abruption was 119 per 1000 births compared with 8 per 1000 for the general obstetrical population.

Neonatal deaths are common following placental abruption. At Parkland Hospital, 15 percent of liveborn neonates died. Perinatal morbidity—often severe—is also common in surviving newborns (Abdella, 1984). Studies by Matsuda and coworkers (2003, 2013) reported that 20 percent of survivors developed cerebral palsy. These observations are similar to ours from Parkland Hospital. Notably, 20 percent of liveborn neonates of women with an abruption had severe acidemia, defined by a cord arterial blood pH <7.0 or base deficit of ≥12 mmol/L. One review confirmed the associated risk for cerebral palsy (Downes, 2017). Even so, Ananth and coworkers (2017) attribute adverse neurodevelopmental outcomes to be largely attributable to preterm delivery.

Predisposing Factors

Demographic Factors

Several predisposing factors raise the risk for placental abruption, and some are listed in Table 41-4. *Advancing maternal age* is one, although data are conflicting regarding women of *great parity* (Okby, 2017; Pritchard, 1991). *Race* or ethnicity also appears to be important. In almost 366,000 deliveries at Parkland Hospital, abruption severe enough to kill the fetus was most common in black and white women—1 in 200, less so in Asian women—1 in 300, and least common in Latin-American women—1 in 350 (Pritchard, 1991). A *familial association* was found in an analysis of a Norwegian population-based registry (Rasmussen, 2009). If a woman had a severe abruption, the risk for her sister was doubled.

TABLE 41-4

Risk Factors for Placental Abruption

Risk Factor	Relative Risk
Prior abruption	10–188
Increased age and parity	1.3–2.3
Preeclampsia	2.1–4.0
Chronic hypertension	1.8–3.0
Chorioamnionitis	3.0
Preterm ruptured membranes	2.4–4.9
Multifetal gestation	2–8
Low birthweight	14.0
Hydramnios	2–8
Cigarette smoking	1.4–1.9
Single umbilical artery	3.4
Cocaine use	NA
Uterine leiomyoma	NA

NA = not available.

Data from Ananth, 1999a,b, 2004, 2007; Aviram, 2015; Gutvirtz, 2016; Morgan, 2016; Nath, 2007, 2008; Ruiter, 2015.

Pregnancy-Associated Hypertension

Some form of hypertension is the most frequent condition associated with placental abruption. This includes gestational hypertension, preeclampsia, chronic hypertension, or a combination thereof. In a report by Pritchard and colleagues (1991) that described 408 women with placental abruption and fetal demise, hypertension was apparent in half once hypovolemia was corrected. Half of these latter women—a fourth of all 408—had chronic hypertension. Looked at another way, one Maternal–Fetal Medicine Units (MFMU) Network study found that 1.5 percent of pregnant women with chronic hypertension suffered placental abruption (Sibai, 1998). As discussed in Chapter 50 (Adverse Pregnancy Effects), at Parkland Hospital, the frequency of placental abruption in treated chronically hypertensive women was almost 1 percent, which was threefold higher than the 0.3-percent baseline (Morgan, 2016).

Chronic hypertension with superimposed preeclampsia or with fetal-growth restriction confers an even greater risk (Ananth, 2007). Even so, the severity of hypertension does not necessarily correlate with abruption incidence (Morgan, 2016; Zetterstrom, 2005). The long-term effects of these associations are apparent from the significantly elevated cardiovascular mortality risk in women with prior abruption, with or without chronic hypertension (DeRoo, 2016; Pariente, 2013). Observations from the Magpie Trial Collaborative Group suggest that women with preeclampsia, with or without chronic hypertension, given magnesium sulfate may have a reduced risk for abruption (Altman, 2002).

Preterm Prematurely Ruptured Membranes

The abruption risk substantially rises when placental membranes rupture before term (American College of Obstetricians and Gynecologists, 2016a; Hackney, 2016). Major and colleagues (1995) reported that 5 percent of 756 women with ruptured membranes between 20 and 36 weeks' gestation developed an abruption. It was 17 percent with previable prematurely ruptured membranes (Kibel, 2016). The risk for abruption with preterm rupture is further increased with comorbid infection (Ananth, 2004). In these cases, inflammation and infection as well as preterm delivery may be primary causes leading to abruption (Nath, 2007, 2008).

Somewhat related, Aviram and coworkers (2015) found an eightfold higher abruption risk in pregnancies ≥34 weeks if hydramnios was comorbid. Abrupt uterine decompression during membrane rupture may be an inciting factor.

Prior Abruption

Many of the predisposing factors are chronic, and in these cases, placental abruption has a high recurrence rate. Pritchard and associates (1970) identified a recurrence rate of 12 percent—and half of these caused another fetal death. Furuhashi and colleagues (2002) reported a 22-percent recurrence rate—half recurred at a gestational age 1 to 3 weeks earlier than the first abruption. In the Dutch study mentioned previously, Ruiter and coworkers (2015) cited a recurrence risk of 5.8 percent. Looked at a second way, Tikkanen and associates (2006) found that of 114 parous women who experienced an abruption, 9 percent had a prior abruption. A third perspective is provided by a population-based study of 767,000 pregnancies reported by Rasmussen and Irgens (2009). They found a 6.5-fold higher risk for recurrence of a "mild" abruption and 11.5-fold risk for a "severe" abruption. For women who had two severe abruptions, the risk for a third was increased 50-fold.

Management of a pregnancy subsequent to an abruption is difficult because another separation may suddenly occur, even remote from term. In many of these recurrences, fetal well-being is almost always reassuring beforehand. Thus, antepartum fetal testing is usually not predictive. Because term abruptions tend to be recurrent, Ruiter and coworkers (2015) recommend labor induction at 37 weeks. Our practice at Parkland Hospital is to induce labor at 38 weeks if other complications do not develop beforehand.

Other Associations

Cigarette smoking is linked to an elevated risk for abruption (Misra, 1999; Naeye, 1980). Results of a metaanalysis of 1.6 million pregnancies included a twofold risk for abruption in smokers (Ananth, 1999b). This risk was five- to eightfold if smokers had chronic hypertension, severe preeclampsia, or both. Similar findings are reported by others (Hogberg, 2007; Kaminsky, 2007). Antepartum Vitamin C and E were reported to be protective for abruption in smokers (Abramovici, 2015).

Cocaine abuse is linked with an alarming frequency of placental abruption (Addis, 2001; Cressman, 2014). Bingol and colleagues (1987) described 50 women who abused cocaine during pregnancy—eight had a stillbirth caused by placental abruption.

Uterine leiomyomas, especially if located near the mucosal surface behind the placental implantation site, can predispose to placental abruption. This was reviewed recently by Ezzedine and Norwitz (2016).

Isolated single umbilical artery is associated with a 3.4-fold increased risk for placental abruption (Gutvirtz, 2016). Twins resulting from infertility treatments also carry greater risk (Okby, 2017). Subclinical hypothyroidism or high levels of antithyroid antibodies have been associated with a two- to threefold higher risk for abruption (Abbassi-Ghanavati, 2010; Casey, 2014; Maraka, 2016).

Women affected by some of the thrombophilias have higher associated rates of thromboembolic disorders during pregnancy. However, the link with placental abruption is less clear (American College of Obstetricians and Gynecologists, 2017a,b). Lupus anticoagulant is associated with maternal floor infarction of the placenta but is less so with typical abruptions. No convincing evidence supports a role for thrombophilias and placental abruption.

Clinical Findings and Diagnosis

Most women with a placental abruption have sudden-onset abdominal pain, vaginal bleeding, and uterine tenderness. In a prospective study, Hurd and colleagues (1983) reported that 78 percent with placental abruption had vaginal bleeding, 66 percent had uterine tenderness or back pain, and 60 percent had a nonreassuring fetal status. Other findings included frequent contractions and persistent hypertonus. In a fifth of these women, preterm

labor was diagnosed, and abruption was not suspected until fetal distress or death followed.

Importantly, the signs and symptoms of placental abruption can vary considerably. In some women, external bleeding can be profuse, yet placental separation may not be so extensive as to compromise the fetus. In others, there may be no external bleeding, but the placenta is sufficiently sheared off that the fetus is dead—a concealed abruption. In one unusual case, a multiparous woman cared for at Parkland Hospital presented with a nosebleed. She had no abdominal or uterine pain, tenderness, or vaginal bleeding. Her fetus was dead, however, and her blood did not clot. The plasma fibrinogen level was 25 mg/dL. Labor was induced, and a total abruption was confirmed at delivery.

Differential Diagnosis

With severe placental abruption, the diagnosis generally is obvious. From the previous discussion, it follows that less severe, more common forms of abruption cannot always be recognized with certainty. Thus, the diagnosis is one of exclusion. Unfortunately, no laboratory tests or other diagnostic methods accurately confirm lesser degrees of placental separation. Sonography has limited use because the placenta and fresh clots may have similar imaging characteristics. Glantz and Purnell (2002) reported only 24-percent sensitivity for sonography in 149 consecutive women with a suspected placental abruption. *Importantly, negative findings with sonographic examination do not exclude placental abruption.* Conversely, magnetic resonance (MR) imaging is highly sensitive for placental abruption and should be considered if the diagnostic information would change management (Masselli, 2011).

With abruption, some degree of intravascular coagulation is almost universal. Thus, elevated serum levels of d-dimers may be suggestive, but this has not been adequately tested. Preliminary data show that serum alpha-fetoprotein levels >280 µg/L have a positive-predictive value of 97 percent (Ngai, 2012).

Thus, in the woman with vaginal bleeding and a live fetus, it is often necessary to exclude placenta previa and other causes of bleeding by clinical and sonographic evaluation. It has long been taught—perhaps with some justification—that *painful* uterine bleeding signifies placental abruption, whereas *painless* uterine bleeding is indicative of placenta previa. The differential diagnosis is usually not this straightforward, and labor accompanying previa may cause pain suggestive of placental abruption. On the other hand, pain from abruption may mimic normal labor, or it may be painless, especially with a posterior placenta. At times, the cause of the vaginal bleeding remains obscure even after delivery.

Hypovolemic Shock

Placental abruption is one of several notable obstetrical entities that may be complicated by massive and sometimes torrential hemorrhage. Hypovolemic shock is caused by maternal blood loss. In an earlier report from Parkland Hospital, Pritchard and Brekken (1967) described 141 women with abruption so severe as to kill the fetus. Blood loss in these women often amounted to at least half of their pregnant blood volume. Importantly, massive blood loss and shock can develop with a concealed abruption. Prompt treatment of hypotension with crystalloid and blood infusion is essential, and resuscitation steps are described later (Hypovolemic Shock).

Consumptive Coagulopathy

Obstetrical events—mainly placental abruption and amnionic fluid embolism—led to the initial recognition of *defibrination syndrome.* This syndrome is currently referred to as *consumptive coagulopathy* or *disseminated intravascular coagulation,* which later is described more broadly in Obstetrical Coagulopathies. The major mechanism causing procoagulant consumption is intravascular activation of clotting. Abruption is the most common cause of clinically profound consumptive coagulopathy in obstetrics—and indeed, probably in all of medicine (Cunningham, 2015).

An important consequence of intravascular coagulation is the activation of plasminogen to plasmin, which lyses fibrin microemboli to maintain microcirculatory patency. With placental abruption severe enough to kill the fetus, there are always pathological levels of fibrinogen–fibrin degradation products and d-dimers in maternal serum (Erez, 2015). Their quantification is not clinically useful. In a third of women with an abruption severe enough to kill the fetus, the plasma fibrinogen level will be <150 mg/dL. These levels are dependent on the maternal preabruption fibrinogen level, and thus higher levels are “protective” (Cunningham, 2015; Wang, 2016). Clinically significant low levels may cause troublesome surgical bleeding. Levels of several other coagulation factors are also variably decreased. In addition, thrombocytopenia, sometimes profound, may accompany severe hypofibrinogenemia initially and becomes common after repeated blood transfusions.

Consumptive coagulopathy is more likely with a concealed abruption because intrauterine pressure is higher. This forces more thromboplastin into

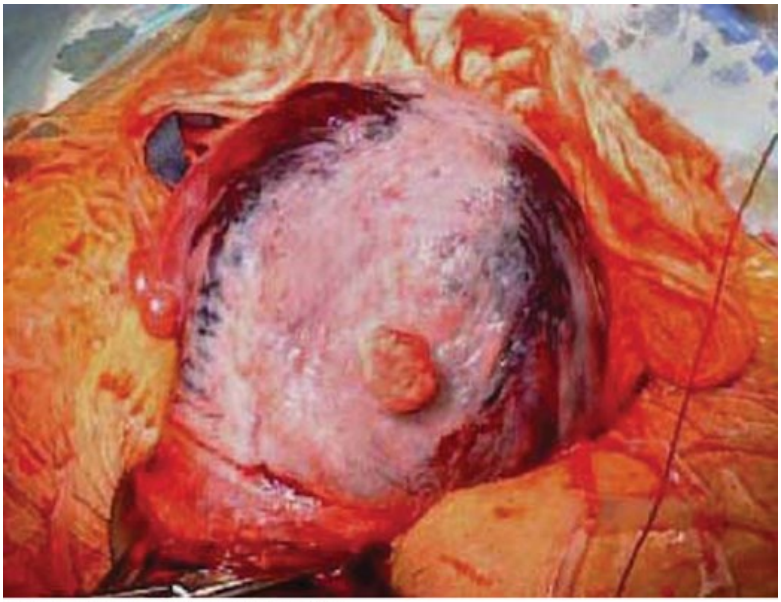
the large veins draining the implantation site. With a partial abruption and a live fetus, severe coagulation defects are less common. Our experience has been that if serious coagulopathy develops, it is usually evident by the time abruption symptoms appear.

Couvelaire Uterus

At the time of cesarean delivery, it is not uncommon to find widespread extravasation of blood into the uterine musculature and beneath the serosa (Fig. 41-18). It is named after Couvelaire, who in the early 1900s termed it *uteroplacental apoplexy*. These myometrial hemorrhages seldom cause uterine atony, and alone they are not an indication for hysterectomy. Effusions of blood are also seen beneath the tubal serosa, between the leaves of the broad ligaments, in the substance of the ovaries, and free in the peritoneal cavity.

FIGURE 41-18

Couvelaire uterus from total placental abruption after cesarean delivery. Blood markedly infiltrates the myometrium to reach the serosa, especially at the cornua. The small serosal leiomyoma seen on the lower anterior uterine surface is an incidental finding. (Used with permission from Dr. Angela Fields Walker.)



End-Organ Injury

Acute kidney injury (AKI) is a general term describing renal dysfunction from many causes (Chap. 53, Acute Kidney Injury). Delayed or incomplete treatment of hypovolemia with severe placental abruption can be one. However, even with abruption complicated by severe disseminated intravascular coagulation, prompt and vigorous treatment of hemorrhage with blood and crystalloid solution usually prevents clinically significant renal dysfunction. The risk for renal injury with abruption is magnified when preeclampsia coexists (Alexander, 2015; Drakeley, 2002). Most cases of AKI are reversible and not so severe as to require dialysis. Generally, long-term outcomes are good (Arazi, 2015). That said, irreversible *acute cortical necrosis* encountered in pregnancy can be associated with abruption (Gopalakrishnan, 2015).

Rarely, pituitary failure—*Sheehan syndrome*—follows severe intrapartum or early postpartum hemorrhage. Described in Chapter 58 (Acromegaly), the exact pathogenesis is not well understood, especially because endocrine abnormalities are infrequent even in women who suffer catastrophic hemorrhage (Matsuwaki, 2014; Robalo, 2012).

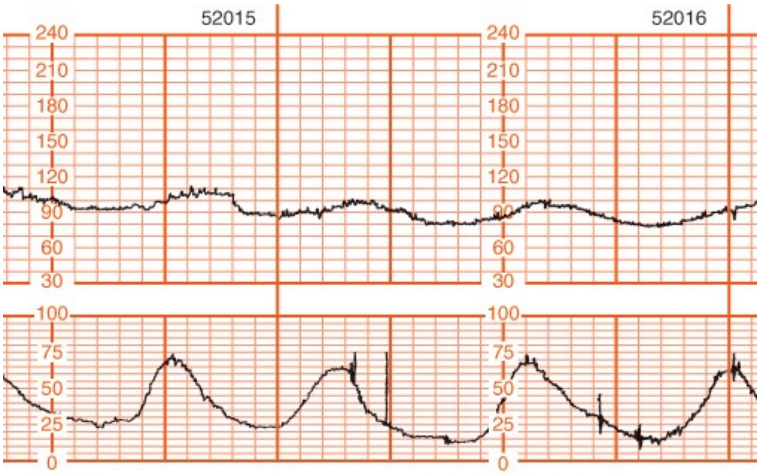
Management

Treatment of the woman with a placental abruption varies depending on her clinical condition, gestational age, and the amount of associated hemorrhage. With a living viable-aged fetus, and with vaginal delivery not imminent, emergency cesarean delivery is chosen by most. In some women,

fetal compromise will be evident as shown in Figure 41-19. When evaluating fetal status, sonographic confirmation of fetal heart activity may be necessary because sometimes an electrode applied directly to a dead fetus will provide misleading information by recording the maternal heart rate. If the fetus has died or if it is not considered sufficiently mature to live outside the uterus, then vaginal delivery is preferable. In either case, prompt and intensive resuscitation with blood plus crystalloid is begun to replace blood lost from retroplacental and external hemorrhage. These measures are lifesaving for the mother and hopefully for her fetus. If the diagnosis of abruption is uncertain and the fetus is alive and without evidence of compromise, then close observation may be warranted provided that immediate intervention is available. Colón and coworkers (2016) performed a randomized trial and found no benefits to magnesium sulfate tocolysis given to women with a preterm "nonsevere" abruption at 24 to 34 weeks' gestation.

FIGURE 41-19

Placental abruption with fetal compromise. Lower panel: Uterine hypertonus with a baseline pressure of 20 to 25 mm Hg and frequent contractions peaking at approximately 75 mm Hg. Upper panel: The fetal heart rate demonstrates baseline bradycardia with repetitive late decelerations.



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Cesarean Delivery

The compromised fetus is usually best served by cesarean delivery, and the speed of response is an important factor in perinatal outcomes. Kayani and coworkers (2003) studied this relationship in 33 singleton pregnancies with a clinically overt placental abruption and fetal bradycardia. Of the 22 neurologically intact survivors, 15 were delivered within a 20-minute decision-to-delivery interval. However, eight of 11 infants who died or developed cerebral palsy were delivered with intervals >20 minutes.

A major hazard to cesarean delivery is imposed by clinically significant consumptive coagulopathy. Preparations include plans for blood and component replacement and assessment of coagulation—especially fibrinogen levels.

Vaginal Delivery

If the fetus has died, then vaginal delivery is usually preferred. As reviewed earlier, hemostasis at the placental implantation site depends primarily on myometrial contraction and not blood coagulability. Thus, after vaginal delivery, uterotonic agents and uterine massage are used to stimulate myometrial contractions. Uterine muscle fibers compress placental site vessels and prompt hemostasis even if coagulation is defective.

In some instances, vaginal delivery may not be preferable, even with a dead fetus. One example is brisk hemorrhage that cannot be successfully managed by vigorous blood replacement. Others are the myriad obstetrical complications that prohibit vaginal delivery in general. These are listed in Table 30-1.

In some women with extensive placental abruption, labor tends to be rapid because the uterus is usually persistently hypertonic. This can magnify fetal

compromise. In some cases, *baseline* intraamnionic pressures reach 50 mm Hg or higher, and with contractions, pressures may attain levels exceeding 100 mm Hg. Overall, however, first-and second-stage labor do not appear to be shortened (Downes, 2016).

Early amniotomy has long been championed in the management of placental abruption. This ostensibly achieves better spiral artery compression to diminish implantation site bleeding and reduce thromboplastin infusion into the maternal vascular system. Although evidence supporting this theory is lacking, membrane rupture may hasten delivery. However, if the fetus is small, the intact sac may be more efficient in promoting cervical dilation. If rhythmic uterine contractions are not superimposed on baseline hypertonus, then oxytocin is given in standard doses. No data indicate that oxytocin augments thromboplastin escape into the maternal circulation to worsen coagulopathy (Clark, 1995; Pritchard, 1967). In light of hypertonus associated with abruption, misoprostol may be a less favored induction agent due to its association with uterine tachysystole.

In the past, some had set arbitrary time limits to permit vaginal delivery. Instead, experiences illustrate that maternal outcome depends on the diligence with which adequate fluid and blood replacement therapy are pursued rather than on the interval to delivery. Observations from Parkland Hospital described by Pritchard and Brekken (1967) are similar to those from the University of Virginia reported by Brame and associates (1968). Specifically, women with severe abruption who were transfused during 18 hours or more before delivery had similar outcomes to those in whom delivery was accomplished sooner.

Expectant Management with a Preterm Fetus

If possible, delaying delivery may benefit an immature fetus. Bond and colleagues (1989) expectantly managed 43 women with placental abruption before 35 weeks' gestation, and 31 of them were given tocolytic therapy. The mean interval-to-delivery for all 43 was approximately 12 days. Cesarean delivery was performed in 75 percent, and there were no stillbirths. As discussed earlier, women with a very early abruption may develop *chronic abruption-oligohydramnios sequence.* In one report, Elliott and coworkers (1998) described four women with an abruption at a mean gestational age of 20 weeks who developed oligohydramnios and delivered at an average gestational age of 28 weeks. In a description of 256 women with an abruption at <28 weeks' gestation, Sabourin and colleagues (2012) reported that a mean of 1.6 weeks was gained. Of the group, 65 percent were delivered <29 weeks, and half of all women underwent emergent cesarean delivery.

Unfortunately, even continuous fetal heart rate monitoring does not guarantee universally good outcomes. For example, a normal tracing may precede sudden further separation with instant fetal compromise. In some of these, if the separation is sufficient, the fetus will die before it can be delivered. Tocolysis is advocated by some for suspected abruption if the fetus does not display compromise. Some investigators have observed that tocolysis improved outcomes in a highly selected cohort of women with preterm pregnancies (Bond, 1989; Combs, 1992; Sholl, 1987). In another study, Towers and coworkers (1999) administered magnesium sulfate, terbutaline, or both to 95 of 131 women with abruption diagnosed before 36 weeks. The perinatal mortality rate was 5 percent in both groups with or without tocolysis. Similar results were reported from a randomized trial (Colón, 2016). We are of the opinion that suspected placental abruption contraindicates use of tocolytic agents.

PLACENTA PREVIA

The Latin *previa* means *going before*—and in this sense, the placenta goes before the fetus into the birth canal. In obstetrics, placenta previa describes a placenta that is implanted somewhere in the lower uterine segment, either over or very near the internal cervical os. Because these anatomical relationships cannot always be precisely defined, and because they frequently change across pregnancy, terminology can sometimes be confusing.

Placental Migration

Beginning with the use of sonography in obstetrics, the term *placental migration* was coined to describe the apparent movement of the placenta away from the internal os (King, 1973). Obviously, the placenta does not move per se, and the mechanism of *apparent* movement is not completely understood. To begin with, *migration* is clearly a misnomer, because decidual invasion anchors chorionic villi at the cervical os.

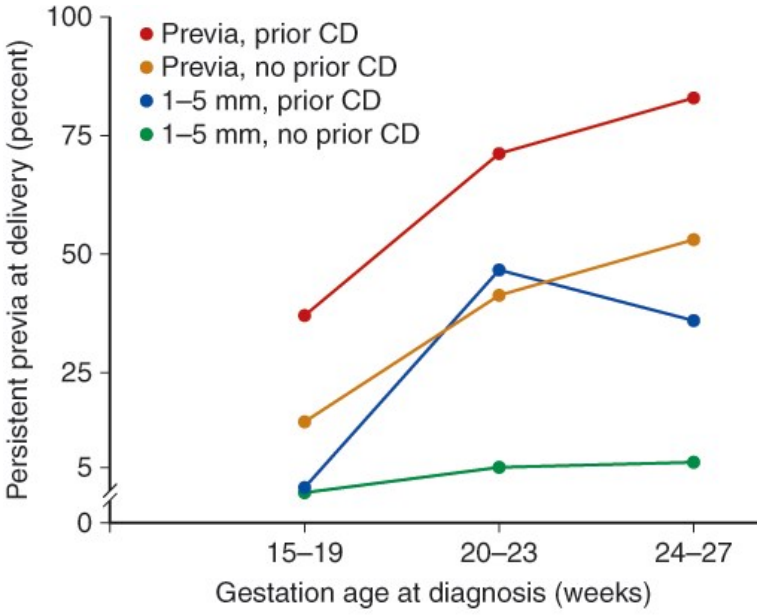
Explanations of placental migration are likely additive. First, apparent movement of the low-lying placenta relative to the internal os is related to the imprecision of two-dimensional sonography. Second, as pregnancy progresses, growth of the lower and upper uterine segments differs. With greater blood flow in the upper uterus, placental growth is more likely directed toward the fundus—*trophotropism.* Many of those placentas that "migrate" most likely never were circumferentially implanted with true villous invasion that reached the internal cervical os. *Importantly, a low-lying placenta or placenta previa is less likely to "migrate" if there is a prior cesarean delivery scar.*

The frequency of placental migration has been quantified. Sanderson and Milton (1991) studied 4300 women at midpregnancy and found that 12 percent had a low-lying placenta. Of placentas not covering the internal os, previa did not persist, and none subsequently had placental hemorrhage. Conversely, approximately 40 percent of placentas that covered the os at midpregnancy continued to do so until delivery. Thus, placentas that lie close to but not over the internal os up to the early third trimester are unlikely to persist as a previa by term (Heller, 2014; Parrott, 2015). However, other evidence from Bohrer and associates (2012) showed that a second-trimester low-lying placenta was associated with antepartum admission for hemorrhage and increased blood loss at delivery.

The likelihood that placenta previa persists after being identified sonographically at given epochs before 28 weeks' gestation is shown in Figure 41-20. For twin pregnancies, similar findings are reported until 23 weeks, after which the previa persistence rate is much higher (Kohari, 2012). Stafford and coworkers (2010), but not Trudell and colleagues (2013), found that a previa and a third-trimester cervical length <30 mm elevated the risks for hemorrhage, uterine activity, and preterm birth. Friszer and associates (2013) showed that women admitted for bleeding had a greater chance of delivery in the subsequent 7 days when the cervical length was <25 mm, although Trudell (2013) again did not confirm this.

FIGURE 41-20

Likelihood of persistence of placenta previa or low-lying placenta 1 to 5 mm from the internal os at delivery. These are shown as a function of sonographic diagnosis at three pregnancy epochs. CD = cesarean delivery. (Data from Oyelese, 2006.)



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Classification

Terminology for placenta previa has evolved, and from a Fetal Imaging Workshop sponsored by the National Institutes of Health (NIH), the following classification was recommended:

- *Placenta previa*—the internal os is covered partially or completely by placenta (Figs. 41-21 and 41-22). In the past, these were further classified as either total or partial previa.
- *Low-lying placenta*—implantation in the lower uterine segment is such that the placental edge does not cover the internal os but lies within a 2-cm wide perimeter around the os. A previously used term, *marginal previa,* described a placenta that was at the edge of the internal os but did not overlie it (Reddy, 2014).

FIGURE 41-21

Placenta previa showing that copious hemorrhage could be anticipated with any cervical dilatation.

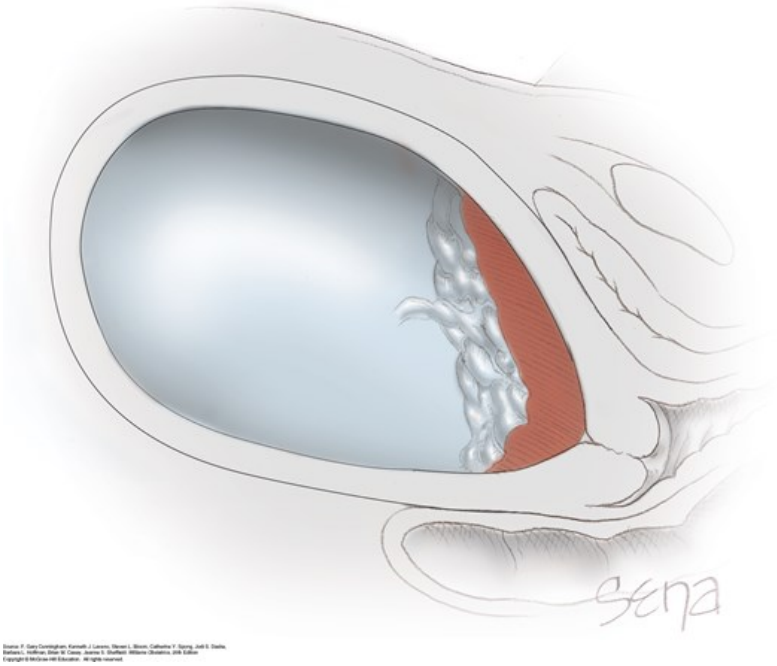
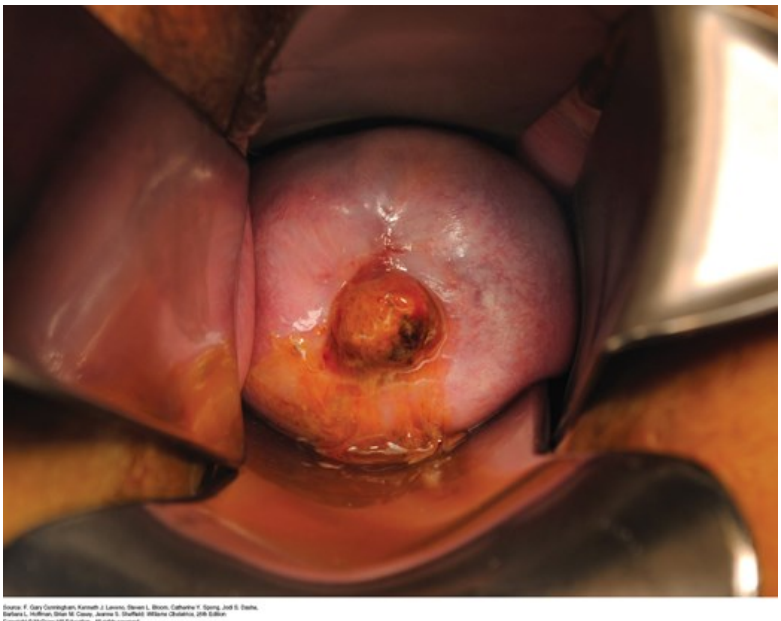


FIGURE 41-22

On speculum examination, placenta is visible protruding through the cervical os. (Used with permission from Dr. Maureen E. Flowers.)



Clearly, the classification of some cases of previa will depend on cervical dilation at the time of assessment (Dashe, 2013; Reddy, 2014). For example, a low-lying placenta at 2-cm dilation may become a partial placenta previa at 4-cm dilation because the cervix has opened to expose the placental edge. Conversely, a placenta previa that appears to be total before cervical dilation may become partial at 4-cm dilation because the cervical opening now extends beyond the edge of the placenta. *Digital palpation in an attempt to ascertain these changing relations between the placental edge and internal os as the cervix dilates usually causes severe hemorrhage!*

With any degree of placenta previa, a certain amount of spontaneous placental separation is inevitable during lower uterine segment remodeling and

cervical dilation. Although this frequently causes bleeding, and thus technically constitutes a placental abruption, this term is usually not applied in these instances.

Somewhat but not always related is *vasa previa,* in which fetal vessels course through membranes and present at the cervical os (Catanzarite, 2016). Vasa previa was recently reviewed by the Society for Maternal-Fetal Medicine (2015) and is discussed in Chapter 6 (Remnants and Cysts).

Incidence and Associated Factors

Demographic Factors

The incidence of placenta previa has risen during past 30 years. Reported incidences average 0.3 percent or 1 case per 300 to 400 deliveries. The frequency at Parkland Hospital from 1988 through 2003 for nearly 250,000 births was 2.6 per 1000. For the 2004 to 2015 epoch, it rose to 3.8 per 1000. Similar frequencies have been reported from Austria, Finland, and Israel (Kollmann, 2016; Räisänen, 2014; Rosenberg, 2011).

Several demographic factors may contribute to this higher risk for placenta previa. First, *maternal age* raises the frequency of placenta previa (Biro, 2012; Roberts, 2012). In the First- and Second-Trimester Evaluation of Risk (FASTER) trial, which included more than 36,000 women, the frequency of previa was 0.5 percent for women <35 years compared with 1.1 percent in those ≥35 years (Cleary-Goldman, 2005). At Parkland Hospital, this incidence differed from a low rate of approximately 0.65 per 1000 births for women ≤19 years to almost 10 per 1000 births for women older than 35 (see Fig. 41-16).

Multiparity also elevates the risk for previa (Räisänen, 2014). Obviously, the effects of advancing maternal age and parity are confounding. Still, Babinszki and colleagues (1999) reported that the 2.2-percent incidence in women with parity of five or greater was significantly higher than that of women with lower parity. The interpregnancy interval does not affect this rate (Fox, 2015).

Cigarette smoking increases the relative risk of placenta previa at least twofold (Usta, 2005). It has been postulated that carbon monoxide hypoxemia causes compensatory placental hypertrophy and more surface area. Smoking may also be related to decidual vasculopathy. Last, *uterine leiomyomas* are a risk factor for previa (Jenabi, 2017).

Clinical Factors

Several clinical characteristics also raise previa risks. Foremost, women with one or more *prior cesarean deliveries* are at greater risk for subsequent placental disorders that include placenta previa, abruption, or morbidly adherent placenta (Gibbins, 2018; Klar, 2014). The cumulative risks for placenta previa that accrue with the increasing number of cesarean deliveries are extraordinary. The risk rises even further if there was a prior prelabor cesarean delivery (Downes, 2015). In one MFMU Network study of 30,132 women undergoing cesarean delivery, the incidence was 1.3 percent for those with only one prior cesarean delivery, but it was 3.4 percent if there were six or more prior cesareans (Silver, 2006). In a retrospective cohort of nearly 400,000 women who were delivered of two consecutive singletons, those with a cesarean delivery for the first pregnancy had a 1.6-fold greater risk for previa in the second pregnancy (Gurol-Urganci, 2011). These same investigators reported a 1.5-fold higher risk from six similar population-based cohort studies. The likelihood of previa is increased more than eightfold in women with parity greater than four and who have more than four prior cesarean deliveries (Gesteland, 2004; Gilliam, 2002).

Importantly, women with a prior uterine incision and placenta previa have an elevated likelihood that cesarean hysterectomy will be necessary because of an associated morbidly adherent placenta (Wei, 2014). In one study, 6 percent of women with a primary cesarean delivery for previa required a hysterectomy. This rate was 25 percent for women with a previa undergoing repeat cesarean delivery (Frederiksen, 1999).

Maternal serum alpha-fetoprotein (MSAFP) levels, if abnormally elevated for otherwise unexplained reasons during prenatal screening, raise the risk for previa and a host of other abnormalities. Moreover, women with a previa and comorbid MSAFP level ≥2.0 multiples of the median (MoM) at 16 weeks' gestation were at greater risk for late-pregnancy bleeding and preterm birth (Chap. 14, Maternal Serum AFP Elevation: Neural-Tube Defect Screening).

Last, *assisted reproductive technology (ART)* used for conception elevates previa risks. Some of this association may derive from overlapping effects. For example, older women comprise a significant portion of ART patients (Luke, 2017). In addition, multifetal gestation is a well-known risk of both in vitro fertilization and previa. However, even adjusting for these overlapping elements, ART is still associated with higher previa rates (Romundstad,

2006).

Clinical Features

Painless bleeding is the most characteristic event with placenta previa. Bleeding usually does not develop until near the end of the second trimester or later, but it can begin even before midpregnancy. And undoubtedly, some late abortions are caused by an abnormally located placenta. Bleeding from a previa usually begins without warning and without pain or contractions in a woman who has had an uneventful prenatal course. This so-called *sentinel bleed* is rarely so profuse as to prove fatal. Usually it ceases, only to recur. However, in perhaps 10 percent of women, particularly those with a placenta implanted near but not over the cervical os, there is no bleeding until labor onset. Bleeding at this time varies from slight to profuse, and it may clinically mimic placental abruption.

A specific sequence of events leads to bleeding in cases in which the placenta is located over the internal os. First, the uterine body remodels to form the lower uterine segment. With this, the internal os dilates, and some of the implanted placenta inevitably separates. Bleeding that ensues is augmented by the inherent inability of myometrial fibers in the lower uterine segment to contract and thereby constrict torn vessels. Similarly, bleeding from this lower segment implantation site also frequently continues after placental delivery. Last, there may be lacerations in the friable cervix and lower segment. These may be especially problematic following manual removal of a somewhat adhered placenta.

Morbidly adherent placentas are a frequent and serious complication associated with placenta previa. Described later (Morbidly Adherent Placenta), this abnormally firm placental attachment derives in part from poorly developed decidua that lines the lower uterine segment. Biswas and coworkers (1999) performed placental bed biopsies in 50 women with a previa and in 50 control women. Trophoblastic giant-cell infiltration of spiral arterioles—rather than endovascular trophoblast cells—was found in half of previa specimens. In contrast, only 20 percent of biopsies from normally implanted placentas had these changes. In another study of 514 cases of previa, abnormal placental attachment was identified in 7 percent (Frederiksen, 1999). As discussed, previa overlying a prior cesarean incision conveys a particularly high risk for morbidly adherent placenta.

Coagulation defects are rare complications of placenta previa, even when implantation site separation is extensive (Cunningham, 2015). Placental thromboplastin, which incites the intravascular coagulation seen with placental abruption, is presumed to readily escape through the cervical canal rather than be forced into the maternal circulation. The paucity of large myometrial veins in this area may also be protective.

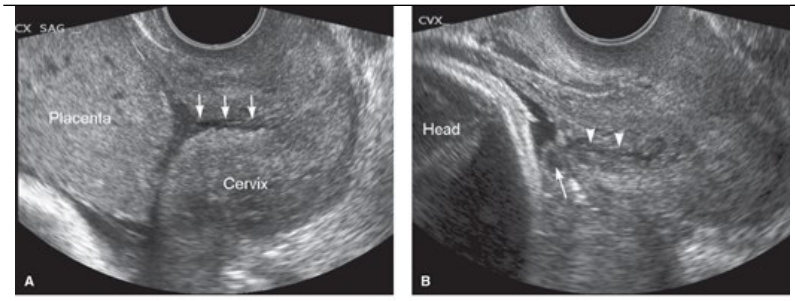
Diagnosis

Whenever there is uterine bleeding after midpregnancy, placenta previa or abruption are always considered. In the Canadian Perinatal Network study discussed earlier (Uterine Atony), placenta previa accounted for 21 percent of women admitted from 22 to 28 weeks' gestation with vaginal bleeding (Sabourin, 2012). Previa should not be excluded until sonographic evaluation has clearly proved its absence. If sonography is not readily available, diagnosis by clinical examination is done using the *double set-up* technique because it requires that a finger be passed through the cervix and the placenta palpated. A digital examination should not be performed unless delivery is planned. *A cervical digital examination is done with the woman in an operating room and with preparations for immediate cesarean delivery. Even the gentlest examination can cause torrential hemorrhage.* Fortunately, double set-up examination is rarely necessary because placental location can almost always be ascertained sonographically.

Quick and accurate localization can be accomplished using standard sonographic techniques (American Institute of Ultrasound in Medicine, 2013). This is usually done with transabdominal sonography. If the placenta clearly overlies the cervix or if it lies away from the lower uterine segment, the examination has excellent sensitivity and negative-predictive value (Olive, 2006; Quant, 2014). Obese women may have limitations of visualization of the lower uterine segment. Also, a full bladder may artificially elongate the cervix and compress the lower uterine segment to give the impression that the placenta overlies the cervix. If placental location remains in question, then transvaginal sonography is the most accurate method of assessment (Fig. 41-23). It is safe, even when there is bleeding.

FIGURE 41-23

Placenta previa. **A.** In this transvaginal image at 34 weeks' gestation, the anterior placenta completely covers the internal cervical os outlined by arrows. **B.** This transvaginal image at 34 weeks' gestation depicts a posterior placenta (*arrow*) that just reaches the level of the internal cervical os. (Reproduced with permission from Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)



Accuracy depends on the sonographic technique used. In a comprehensive study, the internal os was visualized in all cases with transvaginal sonography but in only 30 percent with transabdominal sonography (Farine, 1988). As discussed, according to the Fetal Imaging Workshop, if the placental edge is <2 cm from the internal os, but not covering it, the placenta is considered low lying (Reddy, 2014). In the absence of any other indication, sonography need not be frequently repeated simply to document placental position. At Parkland, women with a placenta previa identified at 18 to 22 weeks' gestation with a prior cesarean delivery are evaluated again at 28 weeks and those without at 32 weeks. Restriction of activity is not necessary unless a previa persists beyond 28 weeks or if clinical findings such as bleeding or contractions develop before this time. At 32 weeks' gestation, if the placental edge is still <2 cm from the os, then transvaginal sonography is repeated at 36 weeks.

Using MR imaging, several investigators have reported excellent results in visualizing placental abnormalities. That said, it is unlikely that this technique will replace sonography for routine evaluation anytime soon. However, MR imaging has proved useful for evaluation of morbidly adherent placenta (Clinical Presentation and Diagnosis).

Management

Women with a placenta previa are managed based on their individual clinical circumstances. Three prominent factors include fetal age and maturity, labor, and bleeding severity. In one study of 214 women with a previa, 43 percent had an emergency delivery, and half of these were preterm (Ruiter, 2015). But, if the fetus is immature and active bleeding subsides, close observation in an obstetrical unit is indicated. Data are sparse regarding tocolytic administration for uterine contractions. Although robust randomized trials are lacking, Bose and colleagues (2011) recommend that if tocolytics are given, they be limited to 48 hours of administration. We categorically recommend against their use in this setting.

After bleeding has ceased for approximately 2 days and the fetus is judged to be healthy, a woman can usually be discharged home with instructions for "pelvic rest." Importantly, the woman and her family must fully appreciate the possibility of recurrent bleeding and be prepared for immediate transport back to the hospital. In other cases, prolonged hospitalization may be ideal.

The frequency of emergency delivery in women with placenta previa ranges from 25 to 40 percent (Gibbins, 2018; Kassir, 2017). But, in properly selected patients, long-term inpatient care does not appear to add benefits compared with outpatient management (Neilson, 2003). In one randomized study of 53 women who had a bleeding previa at 24 to 36 weeks' gestation, maternal or fetal morbidity rates did not differ between management method (Wing, 1996). Of all study women, 60 percent had recurrent bleeding, and half eventually required expeditious cesarean delivery.

For women who are near term and who are not bleeding, plans are made for scheduled cesarean delivery. Timing balances fetal immaturity risks against antepartum hemorrhage. One NIH workshop suggested elective delivery at 36 to 37 completed weeks' gestation (Spong, 2011). The Society for Maternal-Fetal Medicine (2017) recommends delivery between 34 and 37 weeks. At Parkland Hospital, we usually perform elective cesarean delivery at 38 weeks. With a suspected morbidly adherent placenta, delivery is recommended at 34 to 35 completed weeks by the NIH workshop (Management). Our practice is to schedule delivery at 36 completed weeks.

Delivery

Practically all women with placenta previa undergo cesarean delivery. Many surgeons recommend a vertical laparotomy incision to provide rapid entry in cases with torrential bleeding or operating space if hysterectomy is required. As discussed, cesarean delivery is emergently performed in more than half because of hemorrhage, for which about a fourth require blood transfusion (Boyle, 2009; Sabourin, 2012). Although a low transverse hysterotomy is usually possible, this may cause fetal bleeding if the placenta is implanted anteriorly and the placenta is incised. In such cases, fetal delivery should be expeditious (Silver, 2015a). A vertical uterine incision may be preferable in some instances. In either case, even when the incision extends through

the placenta, maternal or fetal outcomes are rarely compromised.

Following placental removal, the placenta site may bleed uncontrollably due to poorly contracted smooth muscle, which is characteristic of the lower uterine segment. If hemostasis at the placental implantation site cannot be obtained by adequate uterotonic administration and pressure, it can be oversewn with 0-chromic sutures. Cho and associates (1991) described interrupted 0-chromic sutures at 1-cm intervals to form a circle around the bleeding portion of the lower segment to control hemorrhage. Others have reported success with compression sutures that traversed and compressed the anterior and posterior uterine wall (Kayem, 2011; Penotti, 2012).

Of other methods, Bakri or Foley balloon tamponade used alone or coupled with compression sutures has been described (Albayrak, 2011; Diemert, 2012; Kumru, 2013). Law and coworkers (2010) successfully used a hemostatic gel. Other surgical options are bilateral uterine or internal iliac artery ligation, illustrated later (Adjunctive Surgical Procedures). Finally, pelvic artery embolization has also gained acceptance.

Hysterectomy

If these more conservative methods fail and bleeding is brisk, hysterectomy is necessary. Placenta previa—especially with an abnormally adherent placenta—currently is the most frequent indication for peripartum hysterectomy at Parkland Hospital and other institutions (Jakobsson, 2015; Wong, 2011). When there is no associated accrete syndrome, the reported incidence of hysterectomy is 2 percent (Gibbins, 2018).

Thus, it is not possible to accurately estimate the effect on the hysterectomy rate from previa alone without considering the associated accrete syndromes. *Again, for women whose placenta previa is implanted anteriorly at the site of a prior uterine incision, the likelihood of an associated morbidly adherent placenta and need for hysterectomy is increased.* In a study of 318 peripartum hysterectomies performed in the United Kingdom, 40 percent were done for abnormal placentation (Knight, 2007). Similar results were reported for 211 hysterectomies from the Nordic Obstetric Surveillance Study (Jakobsson, 2015). At Parkland Hospital, 44 percent of cesarean hysterectomies were done for bleeding placenta previa or for a morbidly adherent placenta (Wortman, 2015). The technique for peripartum hysterectomy is described in Chapter 30 (Peripartum Hysterectomy).

Maternal and Perinatal Outcomes

Placenta previa and coexistent accrete syndromes both contribute substantively to maternal morbidity and mortality rates. The maternal mortality ratio is increased approximately threefold for women with a placenta previa (Gibbins, 2018; Oyelese, 2006). In another report of 5367 maternal deaths in the United States from 2006 to 2013, placenta previa alone accounted for nearly 3 percent of deaths from hemorrhage (Creanga, 2015, 2017).

The report from the Consortium on Safe Labor emphasizes the ongoing perinatal morbidity with placenta previa (Lai, 2012). Preterm delivery continues to be a major cause of perinatal death (Nørgaard, 2012). In deliveries with placenta previa in the United States in 1997, the neonatal mortality rate was threefold higher than that in unaffected pregnancies and stemmed primarily from preterm delivery (Salihu, 2003). Ananth and colleagues (2003) reported a comparably elevated risk of neonatal death even for fetuses who delivered at term. This is at least partially related to the fetal anomaly rate, which is two- to threefold higher in pregnancies with placenta previa (Crane, 1999).

The association of fetal-growth restriction with placenta previa is likely minimal after controlling for gestational age. In a population-based cohort of more than 500,000 singleton births, Ananth and associates (2001) found that most low-birthweight newborns associated with placenta previa resulted from preterm birth. Harper and coworkers (2010) reported similar findings from a cohort of nearly 58,000 women. In contrast, at least two studies reported a greater risk for fetal-growth restriction (Räisänen, 2014; Weiner, 2016).

MORBIDLY ADHERENT PLACENTA

Etiopathogenesis

The term *morbidly adherent placenta* describes aberrant placentation characterized by abnormally implanted, invasive, or adhered placenta. We also refer to these disorders collectively as *accrete syndromes* and use these terms interchangeably. Derivation of accrete comes from the Latin *ac-* + *crescere*—to adhere or become attached to (Benirschke, 2012).

In the accrete syndromes, abnormal placental adherence to the myometrium stems in part from partial or total absence of the decidua basalis and imperfect development of the fibrinoid or Nitabuch layer, described in Chapter 5 (Decidual Histology). If the decidual spongy layer is lacking either

partially or totally, then the physiological line of cleavage is absent, and some or all cotyledons are densely anchored. Microscopically, placental villi attach to smooth muscle fibers rather than to decidual cells. This decidual deficiency then prevents normal placental separation after delivery. The surface area of the implantation site involved and the depth of trophoblastic tissue ingrowth are variable between women, but all affected placentas can potentially cause significant hemorrhage.

Substantiated data now suggest that accrete syndromes are not solely caused by this anatomical layer deficiency (Duzyj, 2017; Tantbirojn, 2008). Indeed, the cytotrophoblasts may control decidual invasion through factors such as angiogenesis (Duzyj, 2015; Goh, 2016; Wehrum, 2011). Also, accrete syndrome tissue specimens show "hyperinvasiveness" (Pri-Paz, 2012). Myometrial fibers attached to the basal plate in an antecedent pregnancy are predictive markers for a subsequent placenta accreta (Linn, 2015; Miller, 2016). This implies an antecedent "constitutional endometrial defect" in most cases. The greater risk conveyed by previous surgical uterine trauma may be partially explained by an enhanced vulnerability to trophoblast invasion (Garmi, 2012; Gill, 2015; Jauniaux, 2017).

This association with prior trauma is reinforced by the close relationship between *cesarean-scar pregnancy (CSP)* and later development of placenta accreta in the same pregnancy. Indeed, accruing evidence suggests that CSP and accrete syndromes lie on a spectrum and that CSP is a precursor, as both share the same histopathology (Happe, 2018; Timor-Tritsch, 2014). CSP frequency has been reported to approximate 1 in 2000 pregnancies (Berhie, 2015; Rotas, 2006). Described in Chapter 19 (Cesarean Scar Pregnancy), early rupture and hemorrhage are not uncommon with CSP, and women often elect pregnancy-terminating interventions to avoid these (Michaels, 2015; Timor-Tritsch, 2015).

Classification

Variants of the morbidly adherent placenta are classified by the depth of trophoblastic growth (Figs. 41-24 and 41-25). *Placenta accreta* indicates that villi are attached to the myometrium. With *placenta increta*, villi actually invade the myometrium, and *placenta percreta* defines villi that penetrate through the myometrium and to or through the serosa (Bailit, 2015; Silver, 2015a). In clinical practice, these three variants are encountered in an approximate ratio of 80:15:5, respectively (Wong, 2008). In all three varieties, abnormal adherence may involve all lobules—*total placenta accreta*. If all or part of a single lobule is abnormally attached, it is described as a *focal placenta accreta*. Histological diagnosis cannot be made from the placenta alone, and myometrial samples are necessary for confirmation (Benirschke, 2012).

FIGURE 41-24

Morbidly adherent placentas: **A.** Placenta accreta. **B.** Placenta increta. **C.** Placenta percreta.

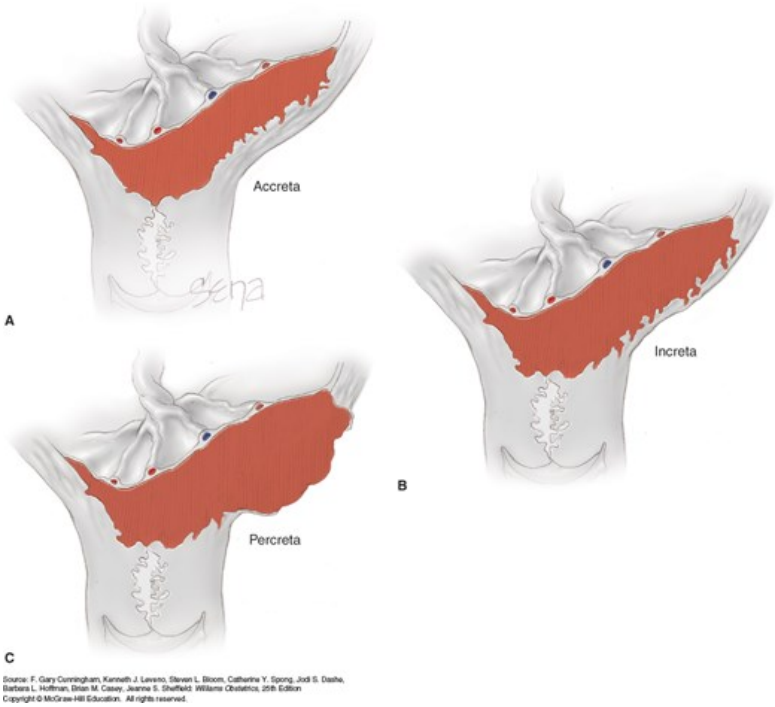
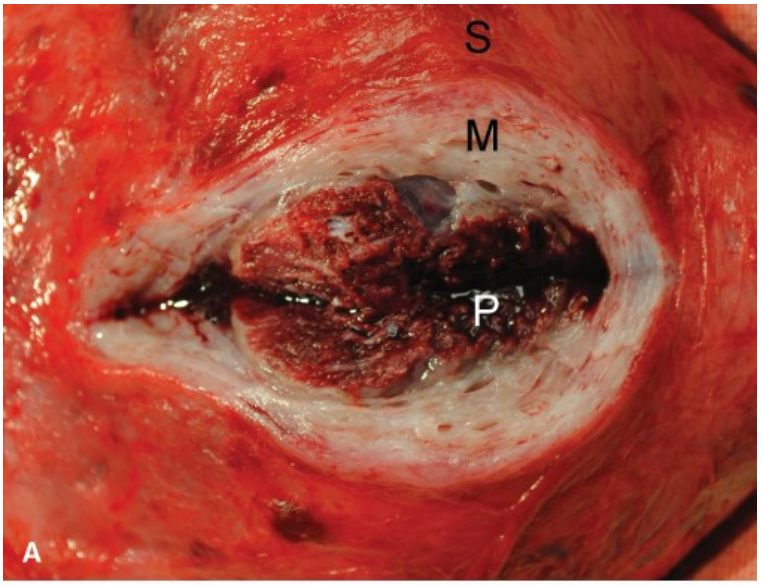
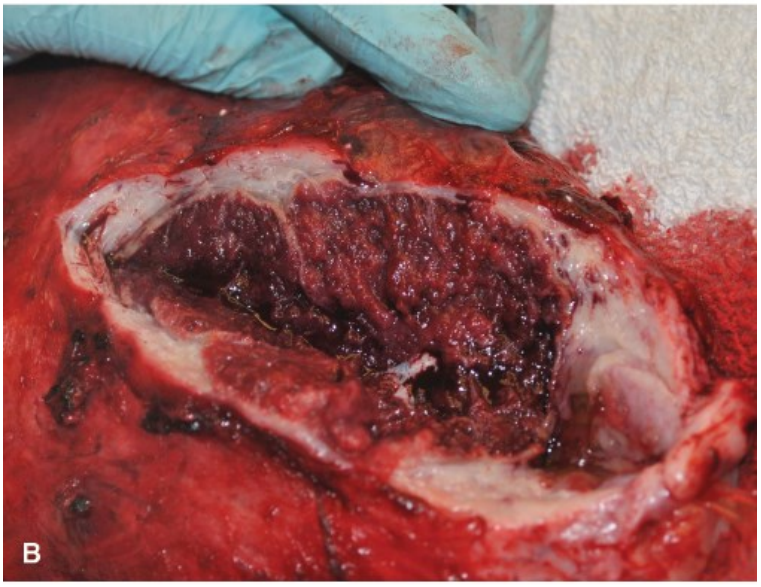
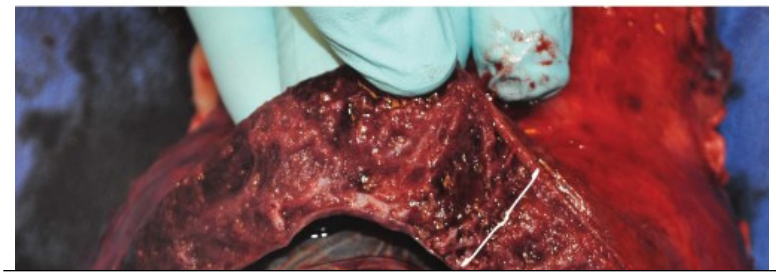


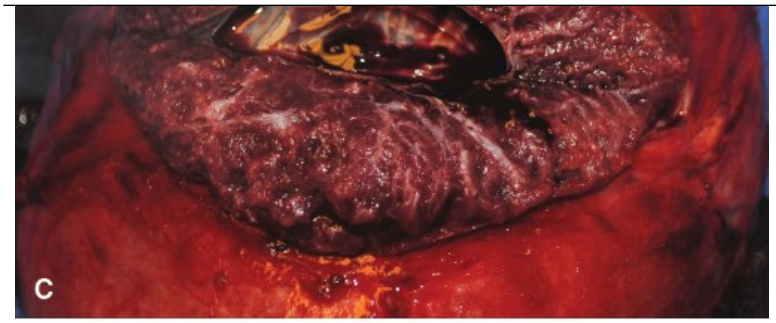
FIGURE 41-25

Varying degrees of myometrial invasion with the accrete syndromes. Incisions begin on the serosal surface and extend through to the placenta. **A.** In this case, the myometrium (*M*) shows minimal invasion by the placenta (*P*). S = uterine serosa. **B.** A greater degree of myometrial invasion is seen here. **C.** In this example, the placenta (*brackets*) extends to the serosal edge, held by the surgeon's hand. No myometrium remains at this site. (Reproduced with permission from Dr. C. Edward Wells in Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)









Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Incidence

The frequency of accrete syndromes was 1 in 20,000 births almost 100 years ago (McKeogh, 1951). As late as 1971, Hellman and Pritchard in the 14th edition of *Williams Obstetrics* described accreta to be the subject of case reports. Since then, the incidence has grown remarkably in direct relationship to the rising cesarean delivery rate. For example, incidence was 1 in 2500 births in the 1980s, but it was 1 per 731 births in the report from the MFMU Network comprising 115,502 women (Bailit, 2015). And a Canadian study of more than 570,000 births found an incidence of 1 in 700 deliveries (Mehrabadi, 2015). In the Nationwide Inpatient Sample, the prevalence of accreta was 3.7 per 1000 births—1 per 270 (Mogos, 2016).

This rising frequency has made accrete syndromes one of the most formidable problems in obstetrics. In one review of 5367 pregnancy-related maternal deaths in the United States from 2006 to 2013, 13 percent were due to hemorrhage caused by accrete syndromes (Creanga, 2015, 2017). In addition, they are a leading cause of hemorrhage and emergency peripartum hysterectomy (Awan, 2011; Eller, 2011; Rossi, 2010). The American College of Obstetricians and Gynecologists (2017c) and the Society for Maternal-Fetal Medicine (2010) have taken the lead to address and optimize management.

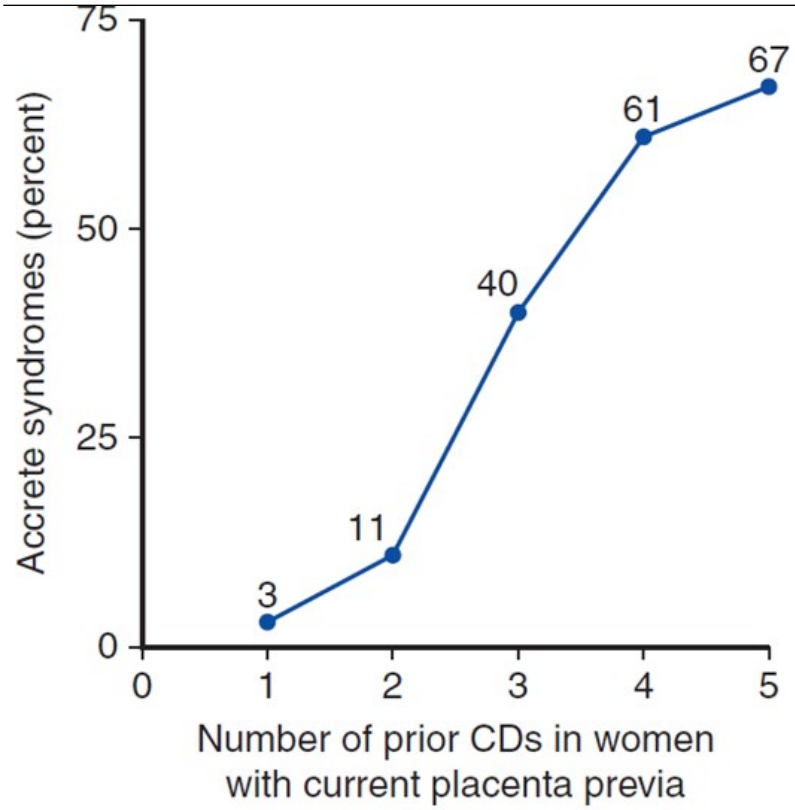
In subsequent pregnancies following placenta accreta, recurrence risks are high. Women in whom hysterectomy is avoided have an estimated 20-percent incidence of recurrence (Cunningham, 2016; Roeca, 2017). In addition, some evidence shows that these women have greater risks for previa, uterine rupture, and hysterectomy (Eshkoli, 2013).

Risk Factors

These are similar in many aspects to those for placenta previa (Classification). That said, the two most important risk factors are an associated previa, a prior cesarean delivery, and more likely a combination of the two (Klar, 2014). A classical hysterotomy incision has a higher risk for a subsequent accrete placenta (Gyamfi-Bannerman, 2012). In fact, almost half of women with a prior cesarean delivery had myometrial fibers seen microscopically adhered to the placenta (Hardardottir, 1996; Miller, 2016). An associated previa confers an even higher risk. This is shown in Figure 41-26, and the astonishing increase in frequency of associated accrete syndromes is apparent with a concomitant previa.

FIGURE 41-26

Frequency of morbidly adherent placenta in women with 1 to 5 prior cesarean deliveries (CDs) now with a previa. (Data from Silver, 2006.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Dysfunctional decidual formation also may follow any other type of myometrial trauma such as curettage or endometrial ablation (Benirschke, 2012; Gill, 2015). Even without a prior hysterotomy, coexisting placenta previa is additive to frequency, and in one study, 10 percent of such women with a previa had an associated accrete syndrome. A shorter cervical length with placenta accrete syndromes did not confer a greater risk for preterm delivery (Rac, 2017).

Another risk marker became apparent with widespread use of MSAFP and human chorionic gonadotropin (hCG) screening for neural-tube defects and aneuploidies. In one study of more than 9300 women screened at 14 to 22 weeks' gestation, the risk for accrete syndromes was eightfold higher with MSAFP levels >2.5 MoM, and it was increased fourfold with maternal serum free β-hCG levels >2.5 MoM (Hung, 1999).

Clinical Presentation and Diagnosis

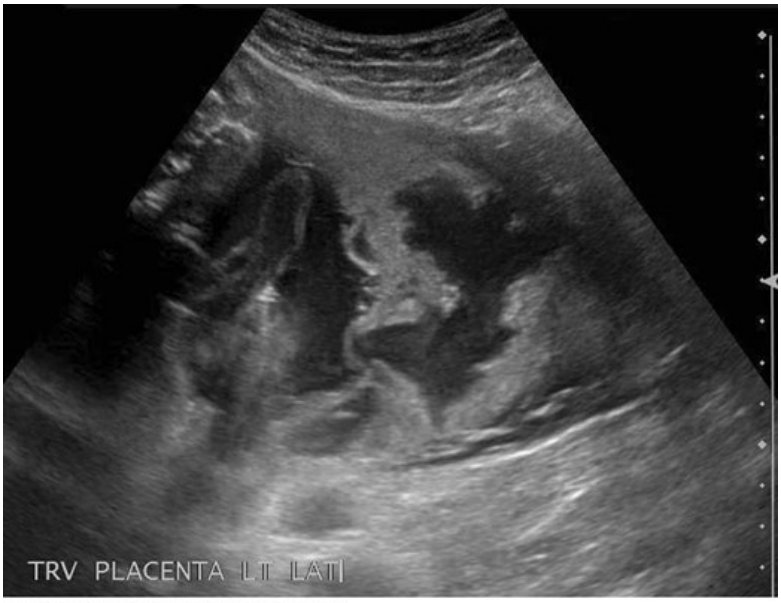
In cases of first- and second-trimester accrete syndromes, there is usually hemorrhage that is the consequence of coexisting placenta previa. Such bleeding will typically prompt evaluation and management. In some women who do not have an associated previa, accreta may not be identified until third-stage labor when an adhered placenta is encountered. Unfortunately, imaging modalities are less than perfect to identify all of these placentas early.

Ideally, sonography is used for antepartum identification of abnormal placental ingrowth (Chantraine, 2013; Jauniaux, 2016; Reddy, 2014; Tam Tam, 2012). Happe and colleagues (2018) found that first-trimester measurement of the smallest myometrial thickness can be used to predict the necessity for peripartum hysterectomy with an accrete syndrome. Other findings include loss of the normal hypoechoic retroplacental zone between the placenta and uterus, placental vascular lacunae, and placental bulging into the posterior bladder wall (Fig. 41-27). Using these criteria, Warshak and associates (2006) calculated the following values: sensitivity of 77 percent; specificity of 96 percent; positive-predictive value of 98 percent. Similar values are cited by the American College of Obstetricians and Gynecologists (2017c) and others (Chalubinski, 2013; Elhawary, 2013; Maher, 2013).

FIGURE 41-27

Transabdominal sonogram of placental percreta shows multiple and massive placental "lakes" or "lacunae". (Reproduced with permission from Dr.

Martha Rac in Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)

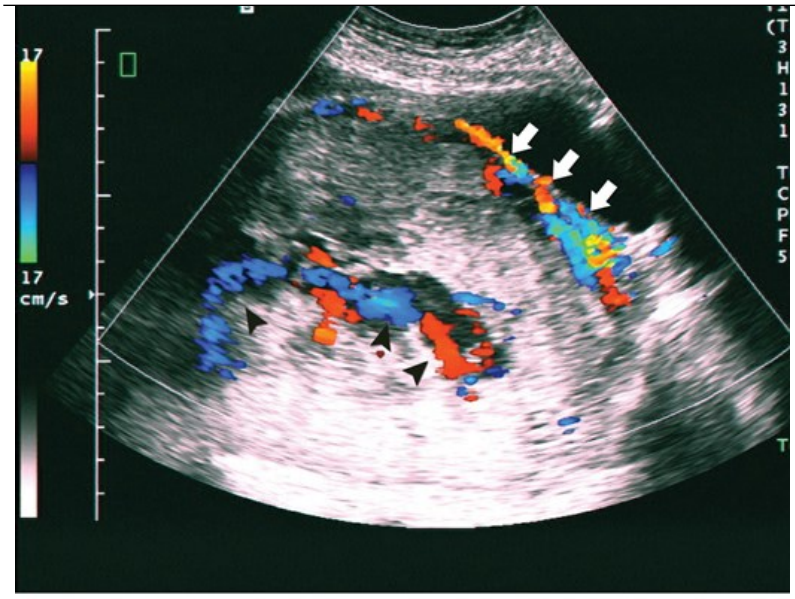


Despite these findings, some investigators report less spectacular results with sonography (Jauniaux, 2016; Primo, 2014). Bowman and colleagues (2014) described the sensitivity of sonography to be 54 percent; specificity, 88 percent; positive-predictive value, 82 percent; negative-predictive value, 65 percent; and accuracy, 65 percent. Location affects sonographic accuracy. In one study, the detection rate was 90 percent for anterior placenta accreta compared with 50 percent for posterior wall ones (Pilloni, 2016). Nageotte (2014) concluded that identification of the morbidly adherent placenta with sonography should be interpreted along with clinical and operative findings.

Better results have been reported by some using three-dimensional (3-D) sonography and power Doppler (Collins, 2015; Doyle, 2015). We too have found that the addition of Doppler color flow mapping is highly predictive of myometrial invasion (Fig. 41-28). This is suspected if the distance between the uterine serosa–bladder wall interface and the retroplacental vessels measures <1 mm and if there are large intraplacental lacunae (Rac, 2015a; Twickler, 2000). Similarly, Cali and associates (2013) reported that hypervascularity of the uterine serosa–bladder wall interface had the highest positive- and negative-predictive values for placenta percreta.

FIGURE 41-28

Transvaginal sonogram of placental invasion with a morbidly adherent placenta. Retroplacental vessels (*white arrows*) invade the myometrium and obscure the bladder–serosal interface. Abnormal intraplacental venous lakes (*black arrowheads*) are commonly seen in this setting.



MR imaging can be added to outline anatomy and to identify invasion of adjacent structures, including possible ureteral involvement (Chalubinski, 2013; Reddy, 2014). Although gadolinium is usually not added during pregnancy, this contrast may enhance images (Millischer, 2017). Lax and coworkers (2007) described three MR imaging findings that suggest accreta: uterine bulging, heterogeneous signal intensity within the placenta indicative of lacunae, and dark intraplacental bands on T2-weighted imaging. Some recommend use of MR imaging if sonography results are inconclusive or there is a posterior previa (American College of Obstetricians and Gynecologists, 2017c; Silver, 2015a).

Management

Preoperative assessment ideally begins once a possible accrete syndrome is recognized antenatally (Fitzpatrick, 2014; Sentilhes, 2013). *A major decision concerns the timing of and the ideal facility for delivery.* Considerations include appropriate surgical, anesthesia, intensive care, and blood banking capabilities. An obstetrical surgeon or gynecological oncologist and surgical, urological, and interventional radiological consultants should be available (Brennan, 2015; Shamshirsaz, 2015). The American College of Obstetricians and Gynecologists (2017c) and the Society for Maternal-Fetal Medicine (2010) recommend planned delivery in a tertiary-care facility. In some of these, specially designed teams have been assembled and are on call (Al-Khan, 2014; Erfani, 2017a; Smulian, 2017; Walker, 2013).

Silver and colleagues (2015b) have provided criteria for accreta centers of excellence. Shown in Table 41-5 are some criteria to consider transfer to a higher level-of-care facility. Women who refuse blood or its derivatives pose especially difficult management dilemmas (Barth, 2011). If possible, delivery is best scheduled for peak availability of all resources and team members. Even so, a third of cases require unscheduled delivery, and contingency plans should be ready (Pettit, 2017).

TABLE 41-5

Criteria for Consideration of Delivery in an Accrete Center of Excellence

Suspicion for morbidly adherent placenta on sonogram
Placenta previa with abnormal ultrasound appearance
Placenta previa with ≥3 prior cesarean deliveries
Prior classical cesarean delivery and anterior placentation
Prior endometrial ablation or pelvic irradiation
Inability to adequately evaluate or exclude placenta accreta
Any other reason to suspect morbidly adherent placenta

Reproduced with permission from Silver, 2015b.

Timing of Delivery

Timing balances fetal immaturity risks against serious adverse maternal consequences of emergency cesarean delivery (Stephenson, 2016). The American College of Obstetricians and Gynecologists (2017c) recommends individualization of delivery timing. It cites a decision-analysis study that justifies elective delivery without fetal lung maturity testing after 34 completed weeks (Robinson, 2010). The Society for Maternal-Fetal Medicine (2017) recommends delivery between 34 and 37 weeks. Two recent surveys found that most practitioners do not deliver these women until 36 weeks or later (Esakoff, 2012; Wright, 2013). At Parkland Hospital, we generally schedule these procedures after 36 completed weeks but are prepared also to manage them in nonelective situations (Rac, 2015b). Perlman and colleagues (2017) recommend individualization based on specific risk criteria.

In some cases, placenta accrete syndrome is not recognized until laparotomy. If there are inadequate resources to surgically manage the percreta, and if the woman is stable and not bleeding, then the fetus is not delivered, the abdominal incision is closed, and she is transferred to a tertiary-care facility.

Preoperative Prophylactic Catheterization

In cases that may involve one or both ureters, catheterization may aid in dissection or identification and repair of injury. Some, but not all, advocate preoperative ureteral catheterization (Eller, 2011; Society for Maternal-Fetal Medicine, 2010; Tam Tam, 2012).

Balloon-tipped intraarterial catheters to mitigate blood loss and thereby enhance surgical visibility have also gained supporters. Catheters are advanced preoperatively into the internal iliac arteries, and then after delivery, they are inflated to occlude pelvic blood flow (Ballas, 2012; Desai, 2012). Alternatively, the catheters can be used to deliver occluding emboli to bleeding arterial sites. Others have concluded that these procedures offer borderline efficacy and have serious risks (Salim, 2015; Sentilhes, 2009). Complications have included thromboses of the common and left iliac arteries (Bishop, 2011). At this time, the American College of Obstetricians and Gynecologists (2017c) concludes that a firm recommendation cannot be made for or against intraarterial catheter use. Similarly, there are no obvious benefits to internal artery ligation (Eller, 2011; Po, 2012).

Cesarean Delivery and Hysterectomy

Before commencing with delivery, the risk of hysterectomy to prevent exsanguination should be estimated. Some of these abnormal placentations, especially if partial, may be amenable to placental delivery with hemostatic suture placement. Confirmation of a percreta or increta almost always mandates hysterectomy. Because the scope of invasion may not be apparent before delivery of the fetus, we complete many dissection steps early. This also minimizes blood loss during potentially tedious dissection after hysterotomy. Thus, we usually attempt to create a wide bladder flap *before*

making the hysterotomy incision (Cunningham, 2017b). The round ligaments are divided, and the lateral edges of the peritoneal reflection are dissected downward. If possible, these incisions are extended to encircle the entire placental implantation site that visibly occupies the prevesical space and posterior bladder wall. Following this, a classical hysterotomy or transverse fundal incision is made to avoid the placenta (Kotsuji, 2013).

After fetal delivery, the extent of placental invasion is assessed without attempts at manual placental removal. In a report from the United Kingdom, attempts for partial or total placental removal prior to hysterectomy were associated with twice as much blood loss (Fitzpatrick, 2014). Generally speaking, with obvious percreta or increta, hysterectomy is usually the best course, and the placenta is left in situ (Eller, 2011). With more extensive placental ingrowth, there may be little or no bleeding until manual placental removal is attempted. Unless there is spontaneous separation with bleeding that mandates emergency hysterectomy, the operation begins after full assessment is made. With bleeding, successful treatment depends on immediate blood replacement therapy and other measures that can include uterine or internal iliac artery ligation, balloon occlusion, or embolization.

The group at Baylor College of Medicine has described a modified radical hysterectomy for surgical management of the morbidly adherent placenta (Shamshirsaz, 2015). For a description of this technique, refer to *Cunningham and Gilstrap's Operative Obstetrics* (Yeomans, 2017). At Parkland Hospital, we have had cases in which a traditional radical hysterectomy was necessary to excise all abnormally implanted placenta.

Conservative Management

Occasionally, it may be possible to trim the umbilical cord, repair the hysterotomy incision, leave the placenta in situ, and not pursue hysterectomy. This option may be used for women in whom abnormal placentation was not suspected before cesarean delivery and in whom uterine closure stops bleeding. After this, she can be transferred to a higher-level facility for definitive management. Another consideration is the woman with a strong desire for fertility and who has received extensive counseling.

Conservative management was reviewed by Perez-Delboy (2014) and Fox (2015) and their colleagues. In some of these cases, the placenta spontaneously resorbed between 1 and 12 months with a mean of 6 months. Numerous complications can occur and include sepsis, disseminated intravascular coagulation, pulmonary embolism, and arteriovenous malformation (Fox, 2015; Judy, 2015; Roach, 2015).

In some of these women, a subsequent hysterectomy—either planned or prompted by bleeding or infection—is performed days to weeks postpartum when blood loss might be lessened (Al-Khan, 2014; Sentilhes, 2009). In one study, only 21 percent of such women ultimately required hysterectomy (Bretelle, 2007). In other reports, however, up to 60 percent eventually required emergency hysterectomy (Clausen, 2013; Pather, 2014). Evidence that treatment with methotrexate aids resorption is lacking. Last, for women in whom the placenta is left in situ, serial serum β-hCG measurements are not informative, and serial sonographic or MR imaging is recommended (Timmermans, 2007; Worley, 2008).

At this time, we agree with the American College of Obstetricians and Gynecologists (2017c) that leaving the placenta in situ is seldom indicated. Exceptions are for temporization to permit transfer to a higher level of care.

Pregnancy Outcomes

In sum, these syndromes can have disastrous outcomes for both mother and fetus. Although the depth of placental invasion does not correspond with perinatal outcome, it is of paramount maternal significance (Seet, 2012). Shown in Table 41-6 are outcomes from reports of women from tertiary-care hospitals and in whom the diagnosis of morbidly adherent placenta was made preoperatively. Despite these advantages, a litany of complications included hemorrhage, urinary tract injury, intensive care unit admission, and secondary surgical procedures. Some of these reports chronicle outcomes in a second cohort of women in whom care was not given at a tertiary-care facility or in whom the diagnosis of percreta was not made until delivery, or both. In these cohorts, morbidity was higher, and there was one maternal death.

TABLE 41-6

Selected Maternal Outcomes in Women with a Morbidly Adherent Placenta Identified Prenatally and Delivered in Tertiary-Care Units

Outcome[a]	San Diego[b] n = 62	Utah[c] n = 60	Toronto[d] n = 33	New Jersey[e] n = 42	Houston[f] n = 107
Gestational age (wk)	33.9 ± 1.1	34 (17–41)	~32 (19–39)	~34.6 (25–40)	~33 (29–35)
Operating time (min)	194 ±1.6	NS	107 (68–334)	NS	287 (74–608)
Transfusions	~75%	70%	NS	NS	~65%
RBC (units)	4.7 ± 2.2	≥4 (30%)	3.5 (0–20)	0–11	3 (0–6)
FFP (units)	4.1 ± 2.3	NS	NS	0–6	1 (0–2.5)
Surgical outcomes					
Bladder injury	23%	37%	30%	17%	35%
Ureteral injury	8%	7%	0	NS	2%
Postoperative					
ICU admission	72%	30%	15%	21%	100%
LOS (days)	7.4 ± 1.8	3–13	2–13	4–13	2–12

[a]Outcomes shown as mean ± 1 SD; median (range).

[b]Data from Warshak, 2010.

[c]Data from Eller, 2011.

[d]Data from Walker, 2013.

[e]Data from Al-Khan, 2014.

[f]Data from Erfani, 2017b; Shamshirsaz, 2015.

FFP = fresh-frozen plasma; ICU = intensive care unit; LOS = length of stay; NS = not stated; RBC = red blood cells.

OBSTETRICAL COAGULOPATHIES

The terms *consumptive coagulopathy, defibrination syndrome,* or *disseminated intravascular coagulation (DIC)* are often used interchangeably, but there is an important distinction in these terms. An event related to actual consumption of procoagulants within the intravascular tree results in a *consumptive* coagulopathy. In contrast, massive loss of procoagulants from hemorrhage results in a *dilutional* coagulopathy. Semantics aside, the clinicopathological coagulation disturbances with consumptive coagulopathy culminate in a systemic intravascular activation that completely disrupts natural hemostasis. As a result, an ineffective balance of natural anticoagulant mechanisms leads to widespread fibrin deposition that can cause multiorgan failure (Levi, 2013).

Disseminated Intravascular Coagulation in Pregnancy

Because of the many definitions and variable severity, citing an accurate incidence for consumptive coagulopathy in pregnant women is problematic, but it ranges from 0.03 to 0.35 percent (Erez, 2014; Rattray, 2012). For example, some degree of significant coagulopathy is found in virtually all cases of placental abruption and amnionic fluid embolism. Other instances in which frequently occurring but less recognized degrees of coagulation activation can be found include sepsis, thrombotic microangiopathies, acute kidney injury, acute fatty liver, severe preeclampsia, and hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome (Cunningham, 2015). The overall contribution of each of these obstetrical disorders also varies depending on the population studied (Erez, 2015).

When consumptive coagulopathy is severe, the likelihood of maternal and perinatal morbidity and mortality is increased. In one study of 49 cases, antecedent causes included those listed above, and 59 percent received blood transfusions, 18 percent underwent hysterectomy, 6 percent were dialyzed, and three mothers died (Rattray, 2012). The perinatal mortality rate was 30 percent. Callaghan and associates (2012) reviewed data from the Nationwide Inpatient Sample and found a rising prevalence of DIC from 1998 to 2009. And, from 2010 to 2011, DIC was the second most common severe maternal morbidity indicator (Creanga, 2014). Notably, DIC was associated with nearly a fourth of maternal deaths during this study period. Despite these statistics, consumptive coagulopathy as the sole cause of maternal death is relatively uncommon and accounts for only 0.2 percent of pregnancy-related deaths in the United States (Creanga, 2015).

Pregnancy-Induced Coagulation Changes

During normal pregnancy, extensive changes in coagulation and fibrinolysis develop to create a procoagulant state. Some of these include appreciable increases in the plasma concentrations of factors I (fibrinogen), VII, VIII, IX, and X. A partial list of these normal values is found in the Appendix (Serum and Blood Constituents). At the same time, plasminogen levels rise considerably, but levels of plasminogen activator inhibitor-1 and 2 (PAI-1 and PAI-2) also grow. Thus, *plasmin activity* usually declines until after delivery (Hale, 2012; Hui, 2012). The mean platelet count drops by 10 percent during pregnancy, and platelet activation is enhanced (Kenny, 2015).

The net results of these changes include greater levels of fibrinopeptide A, β-thromboglobulin, platelet factor 4, and fibrinogen-fibrin degradation products, which includes d-dimers. Along with lower concentrations of anticoagulant protein S, hypercoagulability, and decreased fibrinolysis, there is augmented—yet compensated—intravascular coagulation that may function to maintain the uteroplacental interface.

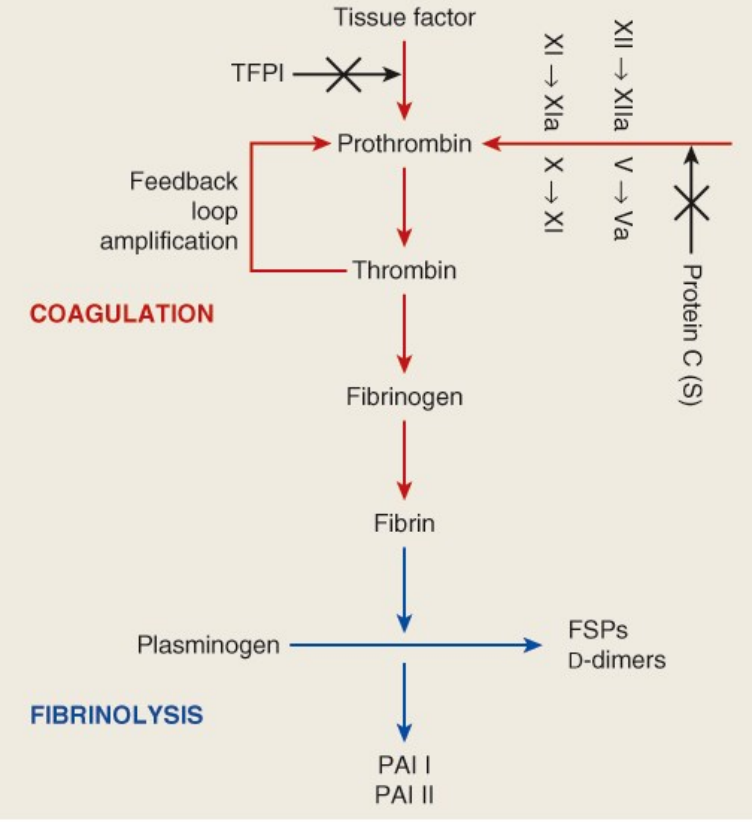
Activation of Normal Coagulation

Instead of the “waterfall” sequential activation of clotting, a current theory proposes that tissue factor—an integral membrane glycoprotein—serves as the principal initiator of coagulation (Levi, 2010b). Coagulation then moves forward but incorporates a feedback loop. To begin, tissue factor forms complexes with factor VII/VIIa to activate factors IX and X. Tissue factor is found in highly vascularized organs such as the brain, lungs, and placenta; in amnionic fluid; and in certain other cell types (Kuczyński, 2002; Østerud, 2006; Uszyński, 2001).

Tissue factor-factor VIIa complexes ultimately generate activated factor X (Xa) to initiate clotting. Subsequently, the previously labeled “intrinsic” pathway amplifies this process. Specifically, the initial thrombin produced directly activates factor XI by providing a feedback amplification loop. This primary role of tissue factor–factor VIIa complex in coagulation and consequent amplification loop of thrombin is depicted in Figure 41-29 (Rapaport, 1995). The end result of this amplified coagulation process is fibrin formation. This is then counterbalanced by the fibrinolytic system, in which plasminogen is activated. As shown in Figure 41-29, even this process is tied initially to tissue factor. The final result is production of fibrinogen/fibrin degradation products, which include d-dimers.

FIGURE 41-29

Schematic of coagulation pathway. FSP = fibrin split products; PAI = plasminogen activator inhibitor; TFPI = tissue factor pathway inhibitor.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Activation of Pathological Coagulation

The initiation of DIC begins with the release of tissue factor by pathological entities. Tissue factor is released by subendothelial tissue and stimulated monocytes, which in turn provoke release of cytokines from the endothelium. With generalized endothelial activation, diffuse activation of coagulation follows. This pathological cycle of coagulation and fibrinolysis becomes clinically important when coagulation factors and platelets are sufficiently depleted to create consumptive coagulopathy.

Several obstetrical syndromes can trigger consumptive coagulopathy. The best known and most common is placental abruption with its significant release of thromboplastin. Another is embolization of amniotic fluid and debris into the maternal circulation. This causes activation of factor X by abundant mucin found in fetal squames. Other causes include endotoxins from gram-negative bacteria and exotoxins from gram-positive bacteria.

Diagnosis

Bioassay is an excellent method to detect or suspect clinically significant coagulopathy. Excessive bleeding at sites of modest trauma characterizes defective hemostasis. Examples include persistent bleeding from venipuncture sites, nicks from shaving the perineum or abdomen, trauma from bladder catheterization, and spontaneous bleeding from the gums, nose, or gastrointestinal tract. Purpura or petechiae at pressure sites such as sphygmomanometer cuffs or tourniquets suggest significant thrombocytopenia. Any surgical procedure provides the ultimate bioassay and elicits generalized oozing from abdominal wall layers, the retroperitoneal space, the episiotomy, or incisions and dissections for cesarean delivery or hysterectomy.

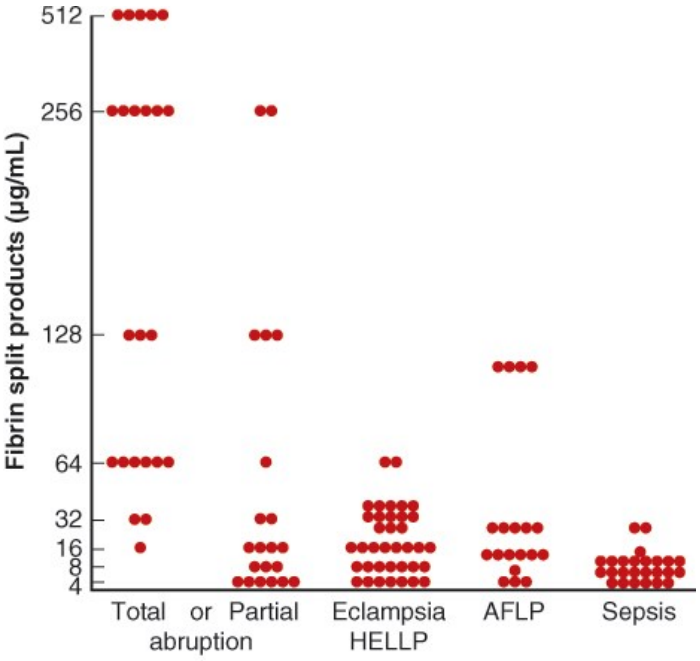
Of laboratory tests, fibrinogen, fibrin, and degradation product levels can be informative. In late pregnancy, plasma fibrinogen levels typically have risen to 300 to 600 mg/dL. Even with severe consumptive coagulopathy, levels may sometimes be sufficiently high to protect against clinically significant hypofibrinogenemia. For example, defibrination caused by a placental abruption might lower an initial fibrinogen level of 600 mg/dL to 250 mg/dL. Although this would indicate massive fibrinogen consumption, levels are still adequate to promote clinical coagulation—usually about 150

mg/dL. If serious *hypofibrinogenemia*—less than 50 mg/dL—is present, the clot formed from whole blood in a glass tube may initially be soft but not necessarily remarkably reduced in volume. Then, over the next half hour or so, as platelet-induced clot retraction develops, the clot becomes quite small. When many of the erythrocytes are extruded, the volume of liquid in the tube clearly exceeds that of clot.

As depicted in Figure 41-29, fibrinolysis cleaves fibrin and fibrinogen into various fibrin degradation products that are detected by several sensitive assays. There are many fragment types, and monoclonal antibodies in assay kits usually measure d-dimers specific for that assay. These values are always abnormally high with clinically significant consumptive coagulopathy. At least in obstetrical disorders, quantification has not been correlated with outcomes. Examples of the magnitude of fibrin split product elevations in various obstetrical coagulopathies is shown in Figure 41-30.

FIGURE 41-30

Quantification of fibrin-split products in various obstetrical syndromes that cause disseminated intravascular coagulation. AFLP = Acute fatty liver of pregnancy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count. (Reproduced with permission from Cunningham FG, Nelson DB: Disseminated intravascular coagulation syndromes in obstetrics. Obstet Gynecol. 2015 Nov;126(5):999–1011.)



Thrombocytopenia is likely if petechiae are abundant or if clotted blood fails to retract within an hour or so. Confirmation is provided by a low platelet count. If severe preeclampsia syndrome is comorbid, there may also be *qualitative platelet dysfunction* (Chap. 40, Maternal Thrombocytopenia).

Prothrombin time (PT) and partial thromboplastin time (PTT) are standard coagulation tests. Prolongation may stem from very low fibrinogen concentrations, from appreciably reduced levels of the procoagulants needed to generate thrombin, or from large amounts of circulating fibrinogen-fibrin degradation products.

Thromboelastometry and thromboelastography are point-of-care tests used as adjuncts to conventional laboratory studies (Abdul-Kadir, 2014). Their current role may serve to guide blood product replacement, discussed later (Viscoelastic Assays).

Using many of these tests, several organizations have attempted to establish a more uniform definition of DIC. One is the International Society on Thrombosis and Haemostasis (ISTH) scoring system. The score is used *only after* a condition known to cause intravascular coagulation is identified and is calculated using a combination of laboratory tests. Composite ISTH-DIC scores <5 suggest nonovert DIC, whereas scores ≥5 are compatible with overt DIC. Other than one report of acute fatty liver of pregnancy, this scoring system has not been applied widely in obstetrics (Nelson, 2014).

General Management

To halt ongoing defibrination, prompt identification and removal of the inciting source of the coagulopathy is a priority. With surgical incisions or extensive lacerations accompanied by severe hemorrhage, rapid replacement of procoagulants is usually indicated. Vigorous restoration and maintenance of the circulation to treat hypovolemia cannot be overemphasized. Adequate perfusion restores hepatic and endothelial synthesis of procoagulants and permits prompt removal of activated coagulation factors, fibrin, and fibrin degradation products by the reticuloendothelial system.

Aside from these fundamental steps, few other agents have proven soundly effective. Although seemingly counterintuitive, unfractionated heparin had been recommended but has now been abandoned. Other examples include use of antifibrinolytic agents—either tranexamic acid or epsilon-aminocaproic acid (Amicar) (American College of Obstetricians and Gynecologists, 2017d; Pacheco, 2017). Currently, use of these two agents is not recommended because the fibrinolytic system is necessary for dissolution of widespread fibrin thromboses caused by generalized intravascular coagulation (Hunt, 2014). Discussed later (Packed Red Blood Cells), recombinant factor VIIa (rFVIIa) has been used to help control severe obstetrical hemorrhage from other causes. However, current clinical evidence is insufficient to make firm recommendations on its administration for obstetrical coagulopathies.

Specific Comorbid Conditions

Placental abruption is the most common cause of severe consumptive coagulopathy in obstetrics and is discussed more fully in Placental Abruption. Typical quantified levels of fibrin-split products with abruption are shown in Figure 41-30. With *preeclampsia, eclampsia,* and *HELLP syndrome,* endothelial activation is a hallmark and is discussed in Chapter 40 (Pathogenesis). In general, the clinical severity of preeclampsia is directly correlated with thrombocytopenia and fibrinogen-fibrin degradation products (Kenny, 2015; Levi, 2010b). As shown in Figure 41-30, intravascular coagulation is seldom severe enough to be clinically worrisome (Pritchard, 1976).

Fetal Death and Delayed Delivery

Consumptive coagulopathy associated with prolonged retention of a dead fetus is unusual today because fetal death can be easily confirmed and there are highly effective methods for labor induction. With singleton pregnancies, if the dead fetus is undelivered, most women enter spontaneous labor within 2 weeks. Gross disruption of maternal coagulation rarely develops before 4 weeks (Pritchard, 1959, 1973). After 1 month, however, almost a fourth will develop consumptive coagulopathy.

Obvious coagulation derangement occasionally develops in a multifetal pregnancy in which one fetus dies while the other survives (Chescheir, 1988; Landy, 1989). This situation is uncommon, and in one study of 22 such pregnancies, none developed a coagulopathy (Petersen, 1999). Most cases are seen in monochorionic twins with shared circulations, which are described in Chapter 45 (Monochorionic Twins and Vascular Anastomoses).

Amnionic Fluid Embolism

The classic triad of abrupt hemodynamic and respiratory compromise along with DIC underpins its diagnosis (Clark, 2016). Most reports describe a frequency of 1 in 40,000 to 1 in 50,000 (Clark, 2014; Knight, 2010; Kramer, 2012). The case-fatality rate in all of these studies ranges from 11 to 43 percent. From another perspective, amnionic fluid embolism was the cause of 5 to 15 percent of all pregnancy-related deaths in the United States and Canada (Berg, 2003, 2010; Creanga, 2015; Kramer, 2012).

Predisposing conditions are rapid labor, meconium-stained fluid, and tears into uterine and other large pelvic veins that permit an exchange of fluids between the maternal and fetal compartment (Society for Maternal-Fetal Medicine, 2016). Other commonly cited risks include older maternal age; postterm pregnancy; labor induction or augmentation; eclampsia; cesarean, forceps, or vacuum delivery; placental abruption or previa; and hydramnios (Knight, 2010, 2012; Kramer, 2012). The association of uterine hypertonus appears to be the *effect* rather than the *cause* because uterine blood flow ceases when intrauterine pressures exceed 35 to 40 mm Hg. Thus, a hypertonic contraction would be the *least* likely circumstance for amnionic fluid and other debris to enter uterine veins (Clark, 1985). For this reason, hypertonus from oxytocin is not implicated.

Diagnosis

Proposed criteria for diagnosis of amnionic fluid embolism are shown in Table 41-7. The classic example is dramatic, and a woman in the late stages of labor or immediately postpartum begins gasping for air. Seizures or cardiorespiratory arrest rapidly follows accompanied by massive hemorrhage from consumptive coagulopathy. Clinical manifestations are variable. For example, we and others have managed several women in whom otherwise

uncomplicated vaginal or cesarean delivery was followed by severe acute consumptive coagulopathy without overt cardiorespiratory difficulties. In those women, consumptive coagulopathy appears to be the *forme fruste* of amnionic fluid embolism (Kramer, 2012; Porter, 1996).

TABLE 41-7

Diagnostic Criteria for Amnionic Fluid Embolism

Abrupt onset of cardiorespiratory arrest, or both hypotension and respiratory compromise.
Documentation of overt disseminated intravascular coagulation. Coagulopathy must be detected prior to loss of sufficient blood to cause dilutional or shock-related consumptive coagulopathy.
Clinical onset during labor or within 30 minutes of placental delivery.
No fever ≥38°C.

Adapted from Clark, 2016.

Because of this clinical variability, other sources of acute cardiac or respiratory failure should be considered. These include myocardial infarction, pulmonary or air embolism, high spinal blockade, eclampsia, and anaphylactic shock. In some cases, the temporal relationship of events aids diagnosis. *Unfortunately, no specific diagnostic laboratory test confirms or refutes the diagnosis of amnionic fluid embolism, and it remains a clinical diagnosis.* Importantly, women suffering from excessive blood loss and resulting coagulopathy may be misdiagnosed with amnionic fluid embolism, when the true culprit is unrecognized or underappreciated hemorrhage (Clark, 2016). In either event, a woman with cardiopulmonary compromise should receive immediate resuscitation (Society for Maternal-Fetal Medicine, 2016).

Pathophysiology

The mechanism of injury from amnionic fluid embolism has evolved. Early theories proposed that amnionic fluid and debris entered maternal circulation and obstructed pulmonary artery flow, which led to hypoxia, right heart failure, and death. However, during normal delivery, amnionic fluid commonly enters the maternal circulation through venous channels at the placental implantation site or from small lacerations. Accordingly, squames, fetal cells, and trophoblasts can often be identified in maternal peripheral blood at delivery (Clark, 1986; Lee, 1986). And, infused amnionic fluid is generally innocuous, even in large amounts (Adamsons, 1971; Stolte, 1967).

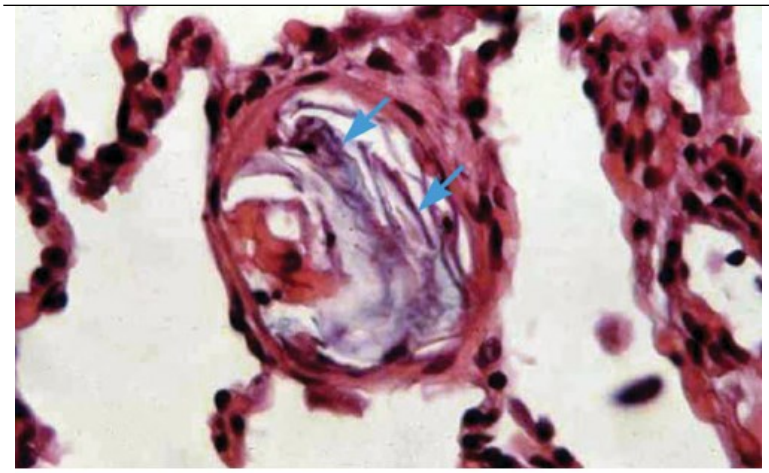
Current explanations describe disruption of the maternal-fetal interface, which allows material from the fetal compartment to enter maternal circulation. This leads to abnormal activation of proinflammatory mediator systems, similar to the systemic inflammatory response syndrome (SIRS), and causes initial, transient pulmonary vasoconstriction and hypertension. Acute right ventricular failure is then followed by hemodynamic collapse from right ventricular infarction coupled with interventricular septum displacement to the left and ultimately decreased left-sided cardiac output. This right and now left ventricular dysfunction is followed by cardiogenic pulmonary edema and systemic hypotension. Concurrently in this process, acute respiratory failure with severe hypoxemia from shunting develops. Notably, the resulting multiorgan dysfunction is an interrelated process, with both the cardiac and pulmonary systems affecting each other.

Women who survive beyond these first phases invariably have the third component of the classic triad—a consumptive coagulopathy. Similar to the coagulation process described earlier, the material from the fetal compartment containing tissue factor activates factor VII. This leads to the development of DIC (see Fig. 41-29).

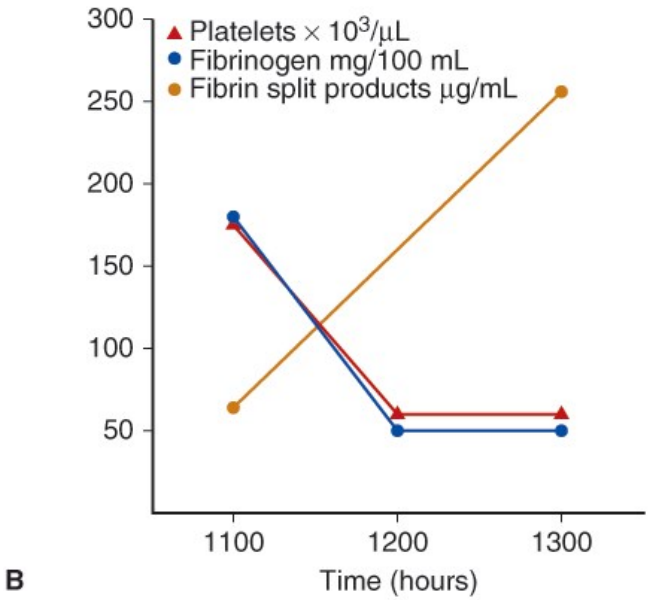
In those who succumb, postmortem histopathological findings may be obvious (Fig. 41-31). However, detection of such material may require special stains, and even then, debris may not be seen. In one study, fetal elements were detected in 75 percent of autopsies and in 50 percent of specimens prepared from concentrated buffy coat aspirates taken antemortem from a pulmonary artery catheter (Clark, 1995).

FIGURE 41-31

Fatal amnionic fluid embolism. **A.** Autopsy findings of fetal squames (*arrows*) packed into a small pulmonary artery. **B.** Results of coagulation studies from the same woman with abruptly decreased fibrinogen levels and platelets and simultaneously increased fibrin split products.



A



B

Management

The initial period of systemic and pulmonary hypertension with amnionic fluid embolism is transient. Thus, immediate high-quality cardiopulmonary resuscitation and advanced cardiac life support must be initiated without delay (Society for Maternal-Fetal Medicine, 2016). These are discussed in detail in Chapter 47 (Cardiopulmonary Resuscitation).

If resuscitation is successful, hemodynamic instability is common in survivors. Both fever and hyperoxia will worsen ischemia–reperfusion injury to the brain, and thus both are avoided. A suitable goal for temperature is 36°C and for mean arterial pressure is 65 mm Hg (Society for Maternal-Fetal Medicine, 2016). Additional supportive care measures such as intubation are usually necessary. During the phase of right ventricular failure, inotropic agents such as dobutamine may improve right heart output, and later systemic hypotension should be treated with vasopressors such as norepinephrine. Excess fluid administration is discouraged due to risks of worsening dilation of an already engorged right ventricle, which may cause right-sided myocardial infarction and displacement of the interventricular septum.

Beginning either immediately after cardiopulmonary collapse or during the ensuing phases of injury, a coagulopathy develops in most cases from activation of factor VII and X. This may be exacerbated by ongoing hemorrhage. A common source of obstetrical bleeding is uterine atony. Therefore, immediate evaluation of coagulation parameters is prudent with concurrent clinical management of bleeding.

Clinical Outcomes

Most reports describe dismal outcomes with amnionic fluid embolism. This is likely influenced by underdiagnosis and reporting biases that favor the most severe cases with the highest mortality rates. Several reports are illustrative. From a California database of 1.1 million deliveries, the mortality rate with amnionic fluid embolism was 60 percent (Gilbert, 1999). In a report of 34 mothers from China, 90 percent died (Weiwen, 2000). Death can be amazingly rapid, and 12 of the 34 died within 30 minutes. The mortality rate was somewhat better in the largest study from Canada. Of 120 women with an amnionic fluid embolism, only a fourth died. Survivors commonly have profound neurological impairment. Clark (1995) observed that only 8 percent of women who lived despite cardiac arrest survived neurologically intact. Overall, prognosis appears to be more associated with disease severity and the attendant cardiac arrest than with any specific treatment modality (Clark, 2014).

As perhaps expected, perinatal outcomes are also poor and are inversely related to the maternal cardiac arrest-to-delivery interval. Even so, neonatal survival rate is 70 percent, but unfortunately, up to half of survivors suffer residual neurological impairment. In the Canadian study, 28 percent of infants were considered to be asphyxiated at birth (Kramer, 2012).

Sepsis Syndrome

Various infections that are accompanied by endo- or exotoxin release can lead to sepsis syndrome. Although a feature of this syndrome includes activation of coagulation, seldom does sepsis alone cause massive procoagulant consumption. *Escherichia coli* bacteremia is frequently seen with antepartum pyelonephritis and puerperal infections, however, accompanying consumptive coagulopathy is usually not severe. Some notable exceptions are septicemia associated with puerperal infection or septic abortion caused by exotoxins released from infecting organisms such as group A *Streptococcus pyogenes, Staphylococcus aureus*, or *Clostridium perfringens, C sordellii*, or *C novyi* (Herrera, 2016). Treatment of sepsis syndrome and septic shock is discussed in Chapter 47 (Sepsis Syndrome).

Purpura Fulminans

This severe—often lethal—form of consumptive coagulopathy is caused by microthrombi in small blood vessels leading to skin necrosis and sometimes vasculitis. Debridement of large areas of skin over the extremities and buttocks frequently requires treatment in a burn unit. Purpura fulminans usually complicates sepsis in women with heterozygous protein C deficiencies and low protein C serum levels (Levi, 2010b). Note that homozygous protein C or S deficiency results in fatal *neonatal purpura fulminans* (Chap. 52, Protein S Deficiency).

Abortion

Septic abortion—especially associated with the organisms just discussed—can incite coagulation and worsen hemorrhage, especially with midtrimester abortions. Indeed, sepsis syndrome accompanied by intravascular coagulation accounts for 25 percent of abortion-related deaths (Saraiya, 1999). In the past, especially with illegal abortions, infections with *C perfringens* were a frequent cause of intense intravascular hemolysis at Parkland Hospital (Pritchard, 1971). More recently, however, septic abortions from infection with *C sordellii* have emerged as important causes (Chap. 18, Inevitable Abortion).

Second-trimester induced abortions can stimulate intravascular coagulation even in the absence of sepsis. Ben-Ami and associates (2012) described a 1.6-percent incidence in 1249 late second-trimester pregnancies terminated by dilation and evacuation. Two thirds were done for fetal demise, which may have been contributory to coagulopathy. Another source of intense coagulation is from instillation of hypertonic solutions to effect midtrimester abortions. These are not commonly used currently for pregnancy terminations. The mechanism is thought to initiate coagulation by thromboplastin release into maternal circulation from the placenta, fetus, and decidua by the necrobiotic effect of hypertonic solutions (Burkman, 1977).

MANAGEMENT OF HEMORRHAGE

Recognition of obstetrical hemorrhage severity is crucial to its management. Visual estimation of blood loss, especially when excessive, is notoriously inaccurate, and true blood loss is often two to three times the clinical estimate. Consider also that in obstetrics, part and sometimes even all of the lost blood may be concealed. Estimation is further complicated in that peripartum hemorrhage also includes the pregnancy-induced augmented blood volume. After pregnancy hypervolemia is lost at delivery, blood loss can be estimated by calculating 500 mL loss for each 3 volume percent drop in

hematocrit. The hematocrit nadir depends on the speed of resuscitation with intravenous crystalloids. *With acute blood loss, the real-time hematocrit is at its maximum whenever measured in the delivery, operating, or recovery room.*

A prudent rule is that any time blood loss is considered more than average, then the hematocrit is determined and plans are made for close observation for potential physiological deterioration. Urine output measured hourly is one of the most important "vital signs." *Unless diuretic agents are given—and these are seldom indicated with active bleeding—accurately measured urine flow reflects renal perfusion, which in turn reflects perfusion of other vital organs.* Urine flow of at least 30 mL, and preferably ≥50 mL per hour, should be maintained.

Hypovolemic Shock

Shock from hemorrhage evolves through several stages. Early in the course of massive bleeding, mean arterial pressure, stroke volume, cardiac output, central venous pressure, and pulmonary capillary wedge pressure decline. Increases in arteriovenous oxygen content difference reflect a relative rise in tissue oxygen extraction, although overall oxygen consumption falls.

Blood flow to capillary beds in various organs is controlled by arterioles. These are resistance vessels that are partially controlled by the central nervous system. However, approximately 70 percent of total blood volume is contained in venules, which are passive resistance vessels controlled by humoral factors. Catecholamine release during hemorrhage prompts greater venular tone, which provides an autotransfusion from this capacitance reservoir (Barber, 1999). This is accompanied by compensatory rises in heart rate, systemic and pulmonary vascular resistance, and myocardial contractility. In addition, cardiac output and blood volume are redistributed from the effect of selective, centrally mediated arteriolar constriction or relaxation—*autoregulation*. Thus, although perfusion to the kidneys, splanchnic beds, muscles, skin, and uterus is diminished, relatively more blood flow is diverted to the heart, brain, and adrenal glands.

When the blood volume deficit exceeds approximately 25 percent, compensatory mechanisms usually are inadequate to maintain cardiac output and blood pressure. Importantly, additional small losses of blood will now cause rapid clinical deterioration. Following an initial augmented *total oxygen extraction* by maternal tissue, maldistribution of blood flow results in *local* tissue hypoxia and metabolic acidosis. This creates a vicious cycle of vasoconstriction, organ ischemia, and cellular death.

Another important clinical effect of hemorrhage is activation of lymphocytes and monocytes, which in turn causes endothelial cell activation and platelet aggregation. These promote release of vasoactive mediators that occlude small vessels and further impair microcirculatory perfusion. Other common obstetrical syndromes—preeclampsia and sepsis—also lead to loss of capillary endothelial integrity, additional loss of intravascular volume into the extracellular space, and platelet aggregation. These then can incite DIC.

The pathophysiological events just described create important but often overlooked extracellular fluid and electrolyte shifts involved in both the genesis and successful treatment of hypovolemic shock. These include changes in the cellular transport of various ions such as sodium and water into skeletal muscle as well as potassium loss. Replacement of extracellular fluid and intravascular volume are both necessary. *Survival is enhanced in acute hemorrhagic shock if blood plus crystalloid solution is given compared with blood transfusions alone.*

Fluid Resuscitation

Whenever excessive blood loss is suspected in a pregnant woman, steps are simultaneously taken to identify the bleeding source and to begin resuscitation. If she is undelivered, restoration of blood volume is beneficial to mother and fetus, and it also prepares for emergent delivery. If she is postpartum, it is essential to immediately identify uterine atony, retained placental fragments, or genital tract lacerations. At least one and preferably more large-bore intravenous infusion systems are established promptly with rapid administration of crystalloid solutions, while blood is made available. An operating room is readied, and a surgical and anesthesia team are assembled immediately. Specific management of hemorrhage is further dependent on its etiology.

It cannot be overemphasized that treatment of serious hemorrhage demands prompt and adequate refilling of the intravascular compartment with crystalloid solutions. These rapidly equilibrate into the extravascular space, and only 20 percent of crystalloid remains intravascularly in critically ill patients after 1 hour (Zuckerbraun, 2010). *Because of this, initial fluid is infused in a volume two to three times the estimated blood loss.*

Resuscitation of hypovolemic shock with colloid versus crystalloid solutions has been debated. In a Cochrane review of resuscitation of nonpregnant critically ill patients, Perel and coworkers (2013) found equivalent benefits but concluded that colloid solutions were more expensive. Similar results

were found in the Saline versus Albumin Fluid Evaluation (SAFE) randomized trial of almost 7000 nonpregnant patients (Finfer, 2004). We concur with Zuckerbraun and colleagues (2010) that acute volume resuscitation is preferably done with crystalloid and blood.

Blood Replacement

The hematocrit level or hemoglobin concentration that mandates blood transfusion is controversial. Cardiac output does not substantively drop until the hemoglobin concentration falls to approximately 7 g/dL or hematocrit of 20 volume percent. At this level, several organizations recommend consideration for red cell transfusions (Carson, 2017). Also, Military Combat Trauma Units in Iraq used a target hematocrit of 21 volume percent (Barbieri, 2007). In general, with *ongoing* obstetrical hemorrhage, we recommend rapid blood infusion when the hematocrit is <25 volume percent. This decision is dependent on whether the fetus has been delivered; surgery is imminent or ongoing operative blood loss is expected; or acute hypoxia, vascular collapse, or other factors are present.

Scant clinical data elucidate these issues. In a study from the Canadian Critical Care Trials Group, nonpregnant patients were randomly assigned to restrictive red cell transfusions to maintain hemoglobin concentration >7 g/dL or to liberal transfusions to maintain the hemoglobin level at 10 to 12 g/dL. The 30-day mortality rate was similar—19 versus 23 percent in the restrictive versus liberal groups, respectively (Hébert, 1999). Transfusion therapy in nonpregnant patients with septic shock had similar mortality rates when 7 g/dL was compared with 9 g/dL as targets for transfusions (Holst, 2014). *The number of units transfused in a given woman to reach a target hematocrit depends on her body mass and on expectations of additional blood loss.*

Blood Component Products

Contents and effects of transfusion of various blood components are shown in Table 41-8. *Compatible whole blood is ideal for treatment of hypovolemia from catastrophic hemorrhage.* It has a shelf life of 40 days, and 70 percent of the transfused red cells function for at least 24 hours following transfusion. One unit raises the hematocrit by 3 to 4 volume percent. Important for obstetrical hemorrhage, whole blood replaces many coagulation factors in obstetrics—especially fibrinogen—and its plasma treats hypovolemia. A collateral derivative is that women with severe hemorrhage are resuscitated with fewer blood donor exposures than with packed red cells and components (Shaz, 2009).

TABLE 41-8

Blood Products Commonly Transfused in Obstetrical Hemorrhage

Product	Volume per Unit	Contents per Unit	Effect on Hemorrhage
Whole blood	About 500 mL; Hct ~40 percent	RBCs, plasma, 600–700 mg fibrinogen, no platelets	Restores blood volume and fibrinogen, increases Hct 3–4 volume percent per unit
Packed RBCs	250–300 mL; Hct ~55–80 percent	RBCs, minimal fibrinogen, no platelets	Increases Hct 3–4 volume percent per unit
Fresh-frozen plasma (FFP)	About 250 mL; 30-minute thaw	Colloid, 600–700 mg fibrinogen, no platelets	Restores circulating volume and fibrinogen
Cryoprecipitate	About 15 mL, frozen	One unit ~200 mg fibrinogen, other clotting factors, no platelets	15–20 units or 3–4 g will increase baseline fibrinogen ~150 mg/dL
Platelets	About 50 mL, stored at room temperature	One unit raises platelet count about 5000/µL; single-donor apheresis bag preferable	6–10 units transfused: single-donor bag preferable to raise platelets ~30,000/µL

Hct = hematocrit; RBCs = red blood cells.

Evidence supports the preferable use of whole blood for massive hemorrhage, including our experiences at Parkland Hospital (Alexander, 2009;

Hernandez, 2012). Of more than 66,000 deliveries, women with obstetrical hemorrhage treated with whole blood had significantly lower incidences of renal failure, acute respiratory distress syndrome, pulmonary edema, hypofibrinogenemia, intensive care unit admissions, and maternal death compared with those given packed red cells and component therapy. Freshly donated whole blood has also been used successfully for life-threatening massive hemorrhage at combat support hospitals (Murdock, 2014; Stubbs, 2016).

In most institutions today, however, whole blood is rarely available. Thus, most women with obstetrical hemorrhage and ongoing massive blood loss are given packed red cells and crystalloid. In these instances, no data support a 1:1 plasma: red cell transfusion ratio. As subsequently discussed, many institutions use *massive transfusion protocols* designed to anticipate all facets of massive obstetrical hemorrhage. These "recipes" commonly contain a combination of red cells, plasma, cryoprecipitate, and platelets (Cunningham, 2015; Pacheco, 2011; Shields, 2011).

Several studies have assessed plasma:red cell ratio with massive transfusion protocols used in civilian trauma units and military combat hospitals (Borgman, 2007; Gonzalez, 2007; Hardin, 2014; Johansson, 2007). Patients undergoing massive transfusion—defined as 10 or more units of blood—had much higher survival rates as the ratio of plasma to red cell units neared 1:1.4, that is, one unit of plasma given for each 1.4 units of packed red cells. By way of contrast, the highest mortality group had a ratio of 1:8. *Most of these studies found that component replacement is rarely necessary with acute replacement of 5 to 10 units of packed red cells.*

From the foregoing, when red cell replacement exceeds five units or so, evaluation of platelet count, clotting studies, and plasma fibrinogen concentration is reasonable. In the woman with obstetrical hemorrhage, the platelet count should be maintained >50,000/μL by the infusion of platelet concentrates. A fibrinogen level <150 mg/dL or a sufficiently prolonged PT or PTT in a woman with surgical bleeding is an indication for replacement. Fresh-frozen plasma is administered in doses of 10 to 15 mL/kg, or alternatively, cryoprecipitate is infused (see Table 41-8).

Dilutional Coagulopathy

A major drawback of treatment for massive hemorrhage with crystalloid solutions and packed red blood cells is depletion of platelets and clotting factors. This can lead to a *dilutional coagulopathy* that is clinically indistinguishable from DIC (Hossain, 2013).

Thrombocytopenia is the most frequent coagulation defect found with blood loss and multiple transfusions (Counts, 1979). In addition, packed red cells have only very small amounts of soluble clotting factors, and stored whole blood is deficient in platelets and in factors V, VIII, and XI. As discussed, massive replacement with red cells only and without factor replacement can also cause *hypofibrinogenemia* and prolongation of the PT and PTT. Because many causes of obstetrical hemorrhage also cause consumptive coagulopathy, the distinction between dilutional and consumptive coagulopathy can be confusing. Fortunately, treatment for both is similar.

Type and Screen versus Crossmatch

A blood type and antibody screen should be performed for any woman at significant risk for hemorrhage. Screening involves mixing maternal serum with standard reagent red cells that carry antigens to which most of the common clinically significant antibodies react. Crossmatching involves the use of actual donor erythrocytes rather than the standardized red cells. This process is efficient, and only 0.03 to 0.07 percent of patients identified as having no antibodies are subsequently found to have antibodies (Boral, 1979). *Importantly, administration of screened blood rarely results in adverse clinical sequelae.*

Packed Red Blood Cells

One unit of packed erythrocytes is derived from one unit of whole blood to have a hematocrit of 55 to 80 volume percent. One unit will increase the hematocrit by 3 to 4 volume percent.

Platelets

With surgical delivery or with lacerations, platelet transfusions are considered with ongoing obstetrical hemorrhage when the platelet count falls below 50,000/μL (Kenny, 2015). In the *nonsurgical patient*, bleeding is rarely encountered if the platelet count is 10,000/μL or higher (Murphy, 2010). The preferable source of platelets is one "bag" obtained by single-donor apheresis. This contains the equivalent of six units from six individual donors. Depending on maternal size, each single-donor apheresis six-unit bag raises the platelet count by approximately 20,000/μL (Schlicter, 2010). If these bags are not available, then individual-donor platelet units are used, and six to eight such units are generally transfused one at a time.

Importantly, the donor plasma in platelet units must be compatible with recipient erythrocytes. Further, because some red blood cells are invariably transfused along with the platelets, only units from D-negative donors should be given to D-negative recipients. If it is necessary to give these, however, adverse sequelae are unlikely (Lin, 2002).

Fresh-Frozen Plasma

This component is prepared by separating plasma from whole blood and then freezing it. Approximately 30 minutes are required for frozen plasma to thaw. It is a source of all stable and labile clotting factors, including fibrinogen. Thus, it is often used for treatment of women with consumptive or dilutional coagulopathy. *Plasma is not appropriate for use as a volume expander in the absence of specific clotting factor deficiencies.* It should be considered in a bleeding woman with a fibrinogen level <150 mg/dL or with an abnormal PT or PTT.

An alternative to frozen plasma is *liquid plasma (LQP).* This never-frozen plasma is stored at 1 to 6°C for up to 26 days, and in vitro, it appears to be superior to thawed plasma (Matijevic, 2013).

Cryoprecipitate and Fibrinogen Concentrate

Each unit of cryoprecipitate is prepared from one unit of fresh-frozen plasma. Each 10- to 15-mL unit contains at least 200 mg of fibrinogen along with factor VIII:C, factor VIII:von Willebrand factor, factor XIII, and fibronectin (American Association of Blood Banks, 2014). It is usually given as a "pool" or "bag" using an aliquot of fibrinogen concentrate taken from 8 to 120 donors. Cryoprecipitate is an ideal source of fibrinogen when levels are dangerously low and there is oozing from surgical incisions. Another alternative is virus-inactivated fibrinogen concentrate. Each gram of this raises the plasma fibrinogen level approximately 40 mg/dL (Ahmed, 2012; Kikuchi, 2013).

Recombinant Activated Factor VII

This synthetic vitamin K-dependent protein is available as *NovoSeven.* It binds to exposed tissue factor at the site of injury to generate thrombin that activates platelets and the coagulation cascade. Since its introduction, rFVIIa has been used to help control hemorrhage from surgery, trauma, and obstetrical causes (Goodnough, 2016; Murakami, 2015). Most Level I trauma centers include it in their massive transfusion protocols, and it is included in the one used at Parkland Hospital. Importantly, rFVIIa will not be effective if the plasma fibrinogen level is <50 mg/dL or the platelet count is <30,000/μL.

One major concern with rFVIIa use is arterial—and to a lesser degree venous—thrombosis. In a review of 35 randomized trials with nearly 4500 subjects, arterial thromboembolism developed in 55 percent (Levi, 2010a). A second concern is that it was found to be only marginally effective (Pacheco, 2011).

Tranexamic Acid

This antifibrinolytic drug has been used for traumatic and obstetrical hemorrhage. Tranexamic acid inhibits clot lysis to help forestall bleeding by preventing plasmin from degrading fibrin. Its use has been associated with a higher incidence of renal cortical necrosis (Frimat, 2016). The evidence supporting its use as an adjunct in obstetrical hemorrhage is limited, and its routine use for prophylaxis is not recommended American College of Obstetricians and Gynecologists, 2017d; Pacheco, 2017).

Massive Transfusion Protocols

These function to speed blood product delivery to the bedside or operating room, which permits product infusion early in the resuscitation process. The rationale is to prevent adverse effects of aggressive resuscitation solely with crystalloid and packed red blood cells. That said, it is not necessary to activate massive transfusions until at least four to five units of red cells have been given within 2 hours or so. Once activated, red cells, plasma, platelets, and fibrinogen are given by protocol in amounts shown in Table 41-9. Some protocols include rFVIIa and others include tranexamic acid.

TABLE 41-9

Parkland Hospital Obstetrical Massive Transfusion Protocol

Round No.	PRBC 5 Units	FFP 3 Units	Plts 6-pack	Cryo 1 Unit	rVIIa 2 mg
1	X	X			
2	X	X	X		X
3	X	X		X	
4	X	X	X		X
5	X	X			
6	X	X	X	X	X
7	X	X			
8	X	X	X		X

Cryo = cryoprecipitate; FFP = fresh frozen plasma; Plts = Platelets; PRBC = packet red blood cells; rVIIa = recombinant activated factor VII (NovoSeven).

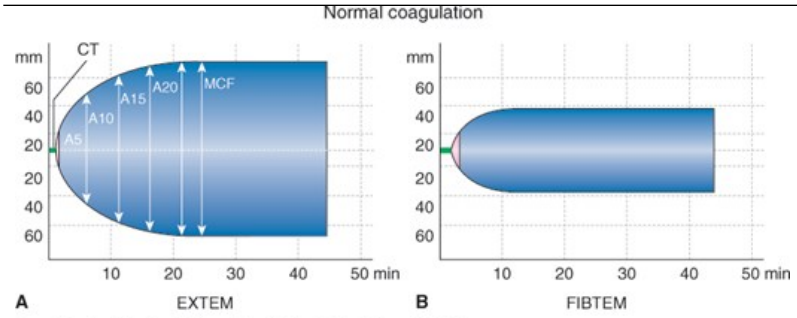
As expected, studies attesting to the superiority for survival with massive transfusion protocols are limited. Most reports describe nonpregnant trauma victims, but some observational studies address obstetrical hemorrhage (Green, 2016; Pacheco, 2016). More data with use of these protocols is needed.

Viscoelastic Assays

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point-of-care tests that assess coagulation in whole blood during massive transfusions. These tests work by analyzing both clot formation and breakdown in a whole blood sample from a given patient. Testing produces a profile of coagulation dynamics, and displayed values indicate the speed and quality of clot formation (Fig. 41-32). These assays provide information regarding time to clot formation, clot strength, and fibrinolysis. Currently, they guide blood product replacement in trauma, liver transplant, and cardiac surgery patients. Studies of TEG and ROTEM techniques in pregnant women have confirmed the hypercoagulable state of pregnancy and provide reference ranges for use in this population (Butwick, 2015; de Lange, 2014; Solomon, 2012).

FIGURE 41-32

TEG/ROTEM based viscoelastic assays of coagulation profiles in a pregnant woman. **A.** EXTEM clot profile: CT = clotting time; A5–20 = clot amplified at 5, 10, 15, 20 min; MCF = maximum clot firmness. **B.** FIBTEM clot profile showing excellent fibrin-based clot quality. (Reproduced with permission from Solomon C, Collis RE, Collins PW: Haemostatic monitoring during postpartum haemorrhage and implications for management, Br J Anaesth. 2012 Dec;109(6):851–863.)



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Although these point-of-care tests appear promising, they also have several limitations. For example, they cannot be used to detect disorders of primary hemostasis (Solomon, 2012). Additionally, these tests cannot diagnose coagulopathies stemming from platelet dysfunction or antiplatelet drugs. A major drawback is the risk of misinterpretation when tests are used by inadequately trained personnel. Further study is necessary before these tests are widely applied for treatment of obstetrical hemorrhage.

Topical Hemostatic Agents

Several agents can be used to control persistent surgical oozing. These were recently reviewed by Miller and colleagues (2015). Other than for cesarean hysterectomy, these are seldom used in obstetrical hemorrhage.

Cell Salvage and Autologous Transfusion

Preoperative patient phlebotomy and autologous blood storage for transfusion has been disappointing. Exceptions are women with a rare blood type or with unusual antibodies. Most have concluded that autologous transfusions are not cost effective (Etchason, 1995; Pacheco, 2011, 2013).

Intraoperative blood salvage with reinfusion is considered to be a safe intervention in obstetrical patients. As discussed in Chapter 30 (Patient Preparation), this practice may be helpful for women declining transfusion. Prior concern centered on amnionic fluid contamination and embolism (Dhariwal, 2014; Goucher, 2015; Pacheco, 2011). A recent randomized trial involving 3028 women compared routine cell salvage use against routine care, in which salvage was employed only for bleeding indications. The rate of nonautologous donor blood transfusion was reduced in the cell salvage group—2.5 versus 3.5 percent, but this was not a significant difference (Khan, 2017). Similar to prior reports, no cases of amnionic fluid embolism were reported.

Transfusion Complications

Of serious known risks, *transfusion of an incompatible blood component* may result in acute hemolysis. If severe, this can cause DIC, acute kidney injury, and death. Preventable errors responsible for most of such reactions frequently include mislabeling of a specimen or incorrectly transfusing a patient not slated for those products. The rate of such errors in the United States is estimated to be 1 in 14,000 units, but these events are likely underreported (Lerner, 2010). A transfusion reaction is characterized by fever, hypotension, tachycardia, dyspnea, chest or back pain, flushing, severe anxiety, and hemoglobinuria. Immediate supportive measures include stopping the transfusion, treating hypotension and hyperkalemia, provoking diuresis, and alkalinizing the urine.

Transfusion-related acute lung injury (TRALI) is the most common cause of transfusion-related mortality. The syndrome is characterized by severe dyspnea, hypoxia, and noncardiogenic pulmonary edema that develop within 6 hours of transfusion (Peters, 2015). TRALI is estimated to complicate at least 1 in 12,000 transfusions (Carson, 2017). Although the pathogenesis is incompletely understood, injury to the pulmonary capillaries may arise from anti-human leukocyte antigen (HLA) and neutrophil (HNA) antibodies in donor plasma (Lerner, 2010). A delayed form of TRALI has been reported to begin 6 to 72 hours following transfusion (Marik, 2008). Management is supportive and may include mechanical ventilation (Chap. 47, Clinical Course).

Bacterial infection from transfusion of a contaminated blood component is unusual because organism growth is discouraged by refrigeration. The most often implicated contaminants of red cells include *Yersinia, Pseudomonas, Serratia, Acinetobacter,* and *Escherichia* species. The more important risk is from bacterial contamination of platelets, which are stored at room temperature. Current estimates are that 1 in 1000 to 2000 platelet units are

contaminated. Death from transfusion-related sepsis is 1 per 17,000 for single-donor platelets and 1 per 61,000 for apheresis-donor packs (Lerner, 2010).

Viral infection risks from transfusion have been curtailed. The risk of HIV or hepatitis C virus infection in screened blood is estimated to be 1 case per 1 to 2 million units transfused (Carson, 2017; Stramer, 2004). The risk for HIV-2 infection is less. Other viral infections include hepatitis B transmission, which is estimated to be <1 per 100,000 transfused units (Jackson, 2003). Because of its high prevalence, cytomegalovirus-infected leukocytes are often transfused. Thus, precautions are taken for immunosuppressed recipients, keeping in mind that this includes the fetus.

Also, risks for transmitting West Nile virus, human T-lymphotropic virus type I, parvovirus B19, and toxoplasmosis are slight (American Association of Blood Banks, 2013; Foroutan-Rad, 2016). Finally, Zika virus has emerged as another relevant transfusion-transmitted infection (Motta, 2016). The Food and Drug Administration (2016) revised recommendations for collection of all whole blood components to include testing for Zika virus. This practice has been affirmed by the Centers for Disease Control and Prevention (2016).

Adjunctive Surgical Procedures

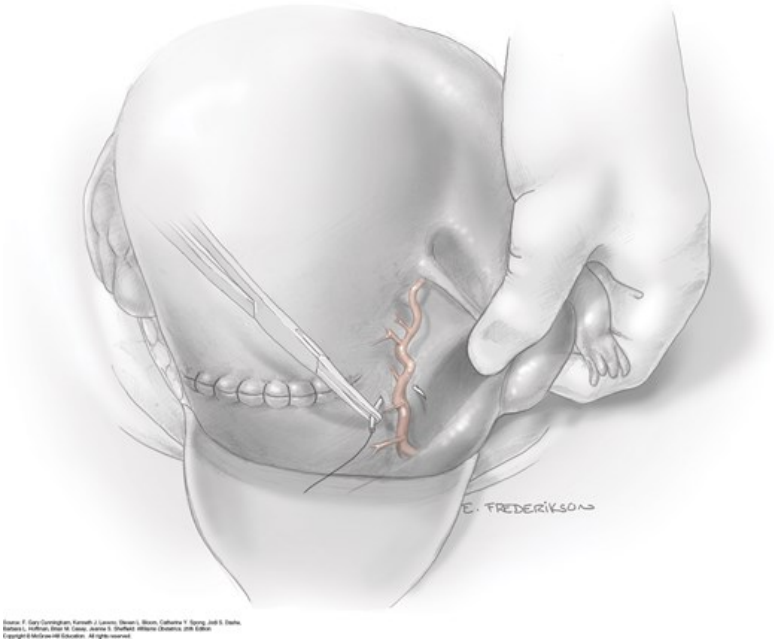
Several invasive procedures can help arrest postpartum hemorrhage. A report from the Agency for Healthcare Research and Quality concluded that most studies addressing these methods are of poor quality (Likis, 2015). In one study of 6660 women with postpartum hemorrhage, 4.4 percent underwent an invasive procedure, and 1.1 percent had a hysterectomy (Kayem, 2016). The failure rate of conservative measures was 15 percent in surgical and embolization procedures.

Uterine Artery Ligation

The technique for unilateral or bilateral uterine artery ligation is used primarily for lacerations at the lateral part of a hysterotomy incision (Fig. 41-33). In our experiences, this procedure is less helpful for hemorrhage from uterine atony.

FIGURE 41-33

Uterine artery ligation. The suture goes through the lateral uterine wall anteriorly, curves around posteriorly, then re-enters anteriorly. When tied, it encompasses the uterine artery.



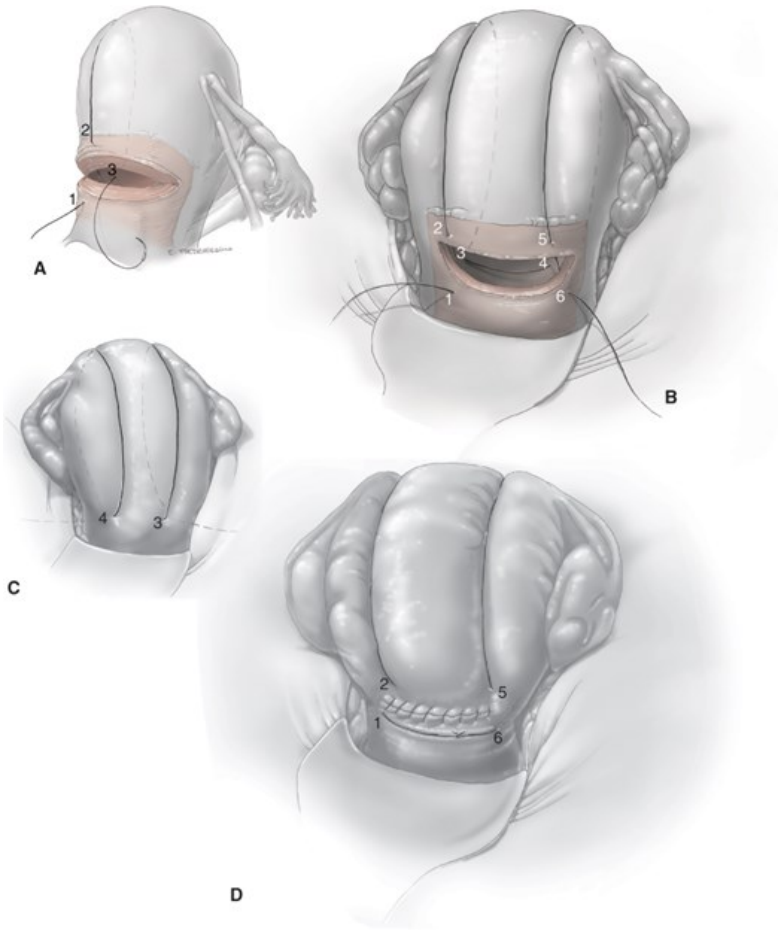
Uterine Compression Sutures

This surgical technique uses a no. 2 chromic suture to compress the anterior and posterior uterine walls together (B-Lynch, 1997). Because they give

the appearance of suspenders, they are also called *braces* (Fig. 41-34). Several modifications of the B-Lynch technique have been described (Cho, 2000; Hayman, 2002; Matsubara, 2013; Nelson, 2007). Indications vary for its application, and this will affect the success rate. For example, B-Lynch (2005) cited 948 cases with only seven failures. Conversely, Kayem and associates (2011) described 211 women who had an overall failure rate of 25 percent, which did not differ between B-Lynch sutures and their modifications. In another series, the failure rate was 20 percent (Kaya, 2016). From their review, Sathe and coworkers (2016) reached similar conclusions.

FIGURE 41-34

Uterine compression suture or "brace." The B-Lynch suture technique is illustrated from an anterior view of the uterus in Figures **A**, **B**, and **D** and a posterior view in Figure **C**. The numbers denote the sequential path of the suture and are shown in more than one figure. **Step 1.** Beginning below the incision, the needle pierces the lower uterine segment to enter the uterine cavity. **Step 2.** The needle exits the cavity above the incision. The suture then loops up and around the fundus to the posterior uterine surface. **Step 3.** The needle pierces the posterior uterine wall to reenter the uterine cavity. The suture then traverses to the opposite side within the cavity. **Step 4.** The needle exits the uterine cavity through the posterior uterine wall. From the back of the uterus, the suture loops up and around the fundus to the front of the uterus. **Step 5.** The needle pierces the myometrium above the incision to reenter the uterine cavity. **Step 6.** The needle exits below the incision and the sutures at points 1 and 6 are tied below the incision. The hysterotomy incision is then closed in the usual fashion.



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Some unique complications can rarely follow compression sutures (Matsubara, 2013). Most involve variations of uterine ischemic necrosis with peritonitis (Gottlieb, 2008; Joshi, 2004; Ochoa, 2002; Treloar, 2006). In one case, total uterine necrosis followed B-Lynch sutures that were placed in combination with bilateral ligation of uterine, uteroovarian, and round ligament arteries (Friederich, 2007). In most cases, subsequent pregnancies are uneventful if compression sutures are used (An, 2013). A few women, however, with B-Lynch or Cho sutures developed uterine wall defects (Akoury, 2008). Another long-term complication is uterine cavity synechiae (Alouini, 2011; Ibrahim, 2013; Poujade, 2011).

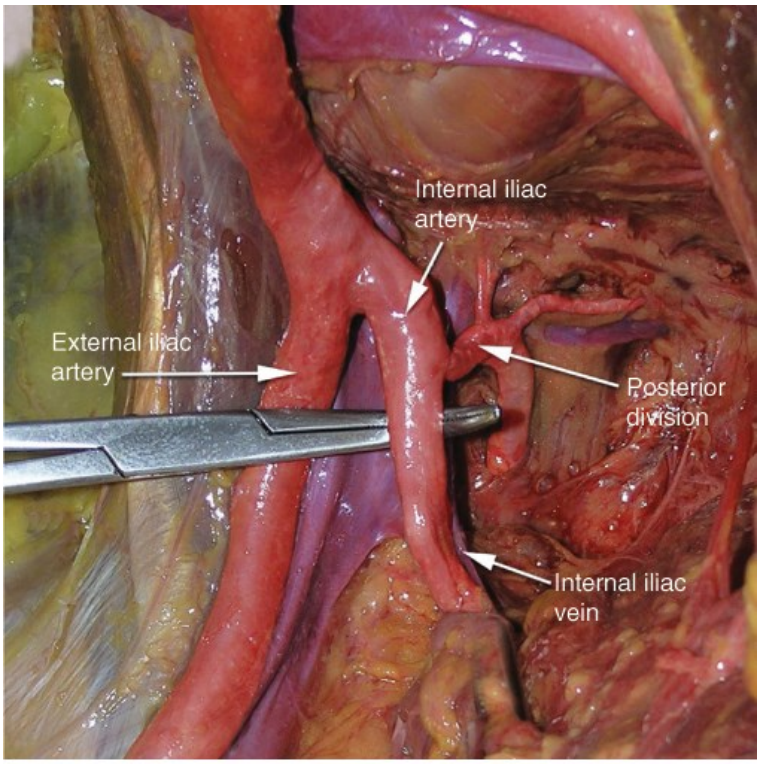
Internal Iliac Artery Ligation

For years, ligation of one or both internal iliac arteries has been used to reduce pelvic hemorrhage. Drawbacks are that the procedure may be technically difficult and is only successful half of the time (American College of Obstetricians and Gynecologists, 2017d). It is not particularly helpful for abating hemorrhage with postpartum atony (Clark, 1985).

For ligation, adequate exposure is obtained by opening the peritoneum over the common iliac artery and dissecting down to the bifurcation of the external and internal iliac arteries (Fig. 41-35). Branches distal to the external iliac arteries are palpated to verify pulsations at or below the inguinal area. Ligation of the internal iliac artery 5 cm distal to the common iliac bifurcation will usually avoid the posterior division branches (Bleich, 2007). The areolar sheath of the artery is incised longitudinally, and a right-angle clamp is carefully passed just beneath the artery from lateral to medial. Care must be taken not to perforate contiguous large veins, especially the internal iliac vein. Suture—usually nonabsorbable—is passed under the artery with a clamp, and the vessel is then securely ligated.

FIGURE 41-35

Ligation of the right internal iliac artery. Unembalmed cadaveric dissection shows the right-angle clamp passing underneath the anterior division of the internal iliac artery just distal to its posterior division. (Used with permission from Dr. Marlene Corton.)



The most important mechanism of action with internal iliac artery ligation is an 85-percent reduction in pulse pressure in those arteries distal to the ligation (Burchell, 1968). This converts an arterial pressure system into one with pressures approaching those in the venous circulation. This creates vessels more amenable to hemostasis via pressure and clot formation.

Even bilateral internal iliac artery ligation does not appear to interfere with subsequent reproduction. Nizard and colleagues (2003) reported follow-up in 17 women who had bilateral artery ligation. From a total of 21 pregnancies, 13 were normal, three ended with miscarriage, three were terminated, and two were ectopic.

Angiographic Embolization

This modality is now used for many causes of intractable hemorrhage when surgical access is difficult. In more than 500 women reported, embolization was 90-percent effective (Grönvall, 2014; Lee, 2012; Poujade, 2012; Zhang, 2015). After his review, Rouse (2013) concluded that embolization can be used to arrest refractory postpartum hemorrhage. Other reports have been less enthusiastic. Fertility is not impaired, and many subsequent successful pregnancies have been reported (Chauleur, 2008; Fiori, 2009; Kolomeyevskaya, 2009). *An important caveat for these procedures is that women with hemodynamic instability related to active bleeding should not be removed from the operating room.*

Complications of embolization are relatively uncommon but can be severe. Case reports detail instances of iatrogenic iliac artery rupture, uterine ischemic necrosis, and uterine infection (Grönvall, 2014; Katakam, 2009; Nakash, 2012). Finally, Al-Thunyan and coworkers (2012) described a woman with massive buttock necrosis and paraplegia following bilateral internal iliac artery embolization.

In a few instances, massive blood loss and difficult surgical dissection is anticipated. The use of balloon-tipped catheters preoperatively inserted into the iliac or uterine arteries was described earlier in management of placenta accrete syndromes (Management).

Pelvic Packing

For significant bleeding refractory to suture or topical hemostats, pelvic packing with gauze and termination of the operation may be considered. Rolls of gauze are packed to provide constant local pressure. This may serve as a temporizing step prior to interventional embolization. In other cases, packing alone may be left for 24 to 48 hours. If the patient is stable and bleeding appears to have stopped, packing is removed.

The *umbrella* or *parachute pack* uses a similar concept (Logothetopulos, 1926). Although seldom used today, it can be lifesaving if all other measures have failed, especially in low-resource areas (Dildy, 2006; Howard, 2002). The pack is constructed of a sturdy sterile plastic bag that is filled with gauze rolls that are unwound and knotted together. Sufficient rolls are used to provide enough volume to fill the pelvis. The pack is introduced transabdominally with the stalk exiting the vagina. Mild traction is applied by tying the stalk to a 1-liter fluid bag, which is hung over the foot of the bed. The umbrella pack is removed vaginally after 24 hours.

REFERENCES

Abbassi-Ghanavati M, Casey BM, Spong CY, et al: Pregnancy outcomes in women with thyroid peroxidase antibodies. Obstet Gynecol 116:381, 2010 [PubMed: 20664399]

Abdel-Aleem H, El-Nashar I, Abdel-Aleem A: Management of severe postpartum hemorrhage with misoprostol. Int J Gynaecol Obstet 72:75, 2001 [PubMed: 11146081]

Abdella TN, Sibai BM, Hays JM Jr, et al: Perinatal outcome in abruptio placentae. Obstet Gynecol 63:365, 1984 [PubMed: 6700860]

Abdul-Kadir R, McLintock C, Ducloy AS, et al: Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion 54(7):1756, 2014 [PubMed: 24617726]

Abramovici A, Gandley RE, Clifton RG, et al: Prenatal Vitamin C and E supplementation in smokers is associated with reduced placental abruption and preterm birth: a secondary analysis. BJOG 122(13):1740, 2015 [PubMed: 25516497]

Adamsons K, Mueller-Heubach E, Myers RE: The innocuousness of amniotic fluid infusion in the pregnant rhesus monkey. Am J Obstet Gynecol 109:977, 1971 [PubMed: 4994277]

Addis A, Moretti ME, Ahmed Syed F, et al: Fetal effects of cocaine: an updated meta-analysis. Reprod Toxicol 15:341, 2001 [PubMed: 11489591]

Ahmed S, Harrity C, Johnson S, et al: The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage—an observational study. Transfus Med 22(5):344, 2012 [PubMed: 22994449]

Akoury H, Sherman C: Uterine wall partial thickness necrosis following combined B-Lynch and Cho square sutures for the treatment of primary post-partum hemorrhage. J Obstet Gynaecol Can 30:421, 2008 [PubMed: 18505666]

Al-Khan A, Gupta V, Illsley NP, et al: Maternal and fetal outcomes in placenta accreta after institution of team-managed care. Reprod Sci 21(6):761, 2014 [PubMed: 24336676]

Al-Thunyan A, Al-Meshal O, Al-Hussainan H, et al: Buttock necrosis and paraplegia after bilateral internal iliac artery embolization for postpartum hemorrhage. Obstet Gynecol 120(2 Pt 2):468, 2012 [PubMed: 22825268]

Altman D, Carroli G, Duley L, et al: Do women with preeclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 359:1877, 2002 [PubMed: 12057549]

Al-Zirqi I, Daltveit AK, Forsén L, et al: Risk factors for complete uterine rupture. Am J Obstet Gynecol 216(2):165.e1, 2017

Al-Zirqi I, Vangen S, Forsen L, et al: Prevalence and risk factors of severe obstetric haemorrhage. BJOG 115:1265, 2008 [PubMed: 18715412]

Al-Zirqi L, Stray-Pedersen B, Forsen L, et al: Uterine rupture: trends over 40 years. BJOG 123(5):780, 2016 [PubMed: 25846698]

Albayrak M, Ozdemir I, Koc O, et al: Post-partum haemorrhage from the lower uterine segment secondary to placenta previa/accreta: successful conservative management with Foley balloon tamponade. Aust N Z J Obstet Gynaecol 51(4):377, 2011 [PubMed: 21806571]

Alexander JM, Cunningham FG: Management. In Taylor RN, Roberts JM, Cunningham FG (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Alexander JM, Sarode R, McIntire DD, et al: Use of whole blood in the management of hypovolemia due to obstetric hemorrhage. Obstet Gynecol 113:1320, 2009 [PubMed: 19461429]

Alouini S, Coly S, Megier P, Lemaire B, et al: Multiple square sutures for postpartum hemorrhage: results and hysteroscopic assessment. Am J Obstet Gynecol 205(4):335, 2011 [PubMed: 21722873]

American Association of Blood Banks: Circular of information for the use of human blood and blood components. 2014. Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm364593.pdf. Accessed July 31, 2017

American Association of Blood Banks: Human parvovirus B19. 2013. Available at: https://www.aabb.org/tm/eid/Documents/Human-Parvovirus-B19.pdf. Accessed July 31, 2017

American College of Obstetricians and Gynecologists: Premature rupture of membranes. Practice Bulletin No. 172, January 2016a

American College of Obstetricians and Gynecologists: Prevention and management of obstetric lacerations at vaginal delivery. Practice Bulletin No. 165, July 2016b

American College of Obstetricians and Gynecologists: Antiphospholipid syndrome. Practice Bulletin No. 132, December 2012, Reaffirmed 2017a

American College of Obstetricians and Gynecologists: Inherited thrombophilias in pregnancy. Practice Bulletin No. 138, September 2013, Reaffirmed 2017b

American College of Obstetricians and Gynecologists: Placenta accreta. Committee Opinion No. 529, July 2012, Reaffirmed 2017c

American College of Obstetricians and Gynecologists: Postpartum hemorrhage. Practice Bulletin No. 183, October 2006, Reaffirmed 2017d

American Institute of Ultrasound in Medicine: AIUM practice guideline for the performance of obstetric ultrasound examinations. J Ultrasound Med 32(6):1063, 2013 [PubMed: 23716530]

An GH, Ryu HM, Kim My, et al: Outcomes of subsequent pregnancies after uterine compression sutures for postpartum hemorrhage. Obstet Gynecol 122(3):565, 2013 [PubMed: 23921861]

Ananth CV, Berkowitz GS, Savitz DA, et al: Placental abruption and adverse perinatal outcomes. JAMA 282:1646, 1999a

Ananth CV, Demissie K, Smulian JC, et al: Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. Obstet Gynecol 98:299, 2001 [PubMed: 11506849]

Ananth CV, Friedman AM, Lavery JA, et al: Neurodevelopmental outcomes in children in relation to placental abruption. BJOG 124(3):463, 2017 [PubMed: 27102365]

Ananth CV, Getahun D, Peltier MR, et al: Placental abruption in term and preterm gestations. Obstet Gynecol 107:785, 2006 [PubMed: 16582113]

Ananth CV, Lavery JA, Vintzileos AM, et al: Severe placental abruption: clinical definition and associations with maternal complications. Am J Obstet Gynecol 214(2):272.e1, 2016

Ananth CV, Oyelese Y, Srinivas N, et al: Preterm premature rupture of membranes, intrauterine infection, and oligohydramnios: risk factors for placental abruption. Obstet Gynecol 104:71, 2004 [PubMed: 15229003]

Ananth CV, Oyelese Y, Yeo L, et al: Placental abruption in the United States, 1979 through 2001: temporal trends and potential determinants. Am J Obstet Gynecol 192(1):191, 2005 [PubMed: 15672024]

Ananth CV, Peltier MR, Kinzler WL, et al: Chronic hypertension and risk of placental abruption: is the association modified by ischemic placental disease? Am J Obstet Gynecol 197:273.e1, 2007

Ananth CV, Smulian JC, Vintzileos AM: Incidence of placental abruption in relation to cigarette smoking and hypertensive disorders during pregnancy: a meta-analysis of observational studies. Obstet Gynecol 93:622, 1999b

Ananth CV, Smulian JC, Vintzileos AM: The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. Am J Obstet Gynecol 188:1299, 2003 [PubMed: 12748502]

Antony KM, Racusin DA, Belfort MA, et al: Under pressure: intraluminal filling pressures of postpartum hemorrhage tamponade balloons. AJP Rep 7(2):e86, 2017 [PubMed: 28497006]

Arazi ES, Kessous R, Shoham-Vardi I, et al: Is there an association between a history of placental abruption and long-term maternal renal complications? J Matern Fetal Neonatal Med 28(14):1641, 2015 [PubMed: 25234099]

Arici V, Corbetta R, Fossati G, et al: Acute first onset of Ehlers-Danlos syndrome type 4 with spontaneous rupture of posterior tibial artery pseudoaneurysm. Vascular 21(1):43, 2013 [PubMed: 22871544]

Atkinson AL, Santolaya-Forgas J, Matta P, et al: The sensitivity of the Kleihauer-Betke test for placental abruption. J Obstet Gynaecol 35(2):139, 2015 [PubMed: 25093255]

Aviram A, Salzer L, Hiersch L, et al: Association of isolated polyhydramnios at or beyond 34 weeks of gestation and pregnancy outcome. Obstet Gynecol 125(4):825, 2015 [PubMed: 25751210]

Awan N, Bennett MJ, Walters WA: Emergency peripartum hysterectomy: a 10-year review at the Royal Hospital for Women, Sydney. Aust N Z J Obstet Gynaecol 51(3):210, 2011 [PubMed: 21631438]

B-Lynch C: Partial ischemic necrosis of the uterus following a uterine brace compression suture. BJOG 112:126, 2005 [PubMed: 15663415]

B-Lynch CB, Coker A, Laval AH, et al: The B-Lynch surgical technique for control of massive postpartum hemorrhage: an alternative to hysterectomy? Five cases reported. BJOG 104:372, 1997

Babinszki A, Kerenyi T, Torok O, et al: Perinatal outcome in grand and great-grand multiparity: effects of parity on obstetric risk factors. Am J Obstet Gynecol 181:669, 1999 [PubMed: 10486482]

Bailit JL, Grobman WA, Rice MM, et al: Morbidly adherent placenta treatments and outcomes. Obstet Gynecol 125(3):683, 2015 [PubMed: 25730233]

Ballas J, Hull AD, Saenz, et al: Preoperative intravascular balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta: a management paradox. Am J Obstet Gynecol 207(3):216.e1, 2012

Bankada V, Purra P, Ningappa AM, et al: A rare case of bilateral broad ligament haematoma in twin pregnancy. J Clin Diagn Res 9(10):QD03, 2015 [PubMed: 26557572]

Barber A, Shires GT III, Shires GT: Shock. In Schwartz SI, Shires GT, Spencer FC, et al (eds): Principles of Surgery, 7th ed. New York, McGraw-Hill, 1999

Barbieri RL: Control of massive hemorrhage: lessons from Iraq reach the U.S. labor and delivery suite. OBG Management 19:8, 2007

Barth WH Jr, Kwolek CJ, Abrams JL, et al: Case records of the Massachusetts General Hospital. Case 23–2011. A 40-year-old pregnant woman with placenta accreta who declined blood products. N Engl J Med 365(4):359, 2011 [PubMed: 21793748]

Ben-Ami I, Fuchs N, Schneider D, et al: Coagulopathy associated with dilation and evacuation for second-trimester abortion. Acta Obstet Gynecol Scand 91(1):10, 2012 [PubMed: 22004118]

Benirschke K, Burton, Baergen RN: Pathology of the Human Placenta, 6th ed. New York, Springer, 2012, p 204

Berg CJ, Callaghan WM, Syverson C, et al: Pregnancy-related mortality in the United States, 1998–2005. Obstet Gynecol 116(6):1302, 2010 [PubMed: 21099595]

Berg CJ, Chang J, Callaghan WM, et al: Pregnancy-related mortality in the United States, 1991–1997. Obstet Gynecol 101:289, 2003 [PubMed: 12576252]

Berg CJ, MacKay AP, Qin C, et al: Overview of maternal morbidity during hospitalizations for labor and delivery in the United States. 1993–1997 and 2001–2005. Obstet Gynecol 113(5):1075, 2009 [PubMed: 19384123]

Berhie SH, Molina RL, Davis MR, et al: Laparoscopic hysterectomy for 7-week cesarean delivery scar implantation pregnancy. Am J Obstet Gynecol 212:247.e1, 2015

Bhandari S, Raja EA, Shetty A, et al: Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. BJOG 121(1):44, 2014 [PubMed: 24125550]

Bingol N, Fuchs M, Diaz V, et al: Teratogenicity of cocaine in humans. J Pediatr 110:93, 1987 [PubMed: 3794893]

Biro MA, Davey MA, Carolan M, et al: Advanced maternal age and obstetric morbidity for women giving birth in Victoria, Australia: a population-based study. Aust N Z J Obstet Gynaecol 52(3):229, 2012 [PubMed: 22497578]

Bishop S, Butler K, Monaghan S, et al: Multiple complications following the use of prophylactic internal iliac artery balloon catheterization in a patient with placenta percreta. Int J Obstet Anesth 20(1):70, 2011 [PubMed: 21168325]

Biswas R, Sawhney H, Dass R, et al: Histopathological study of placental bed biopsy in placenta previa. Acta Obstet Gynecol Scand 78:173, 1999

[PubMed: 10078576]

Bleich AT, Rahn DD, Wieslander CK, et al: Posterior division of the internal iliac artery: anatomic variations and clinical applications. Am J Obstet Gynecol 197:658.e1, 2007

Bohrer J, Goh W, Hirai C, et al: Obstetrical outcomes in patients with low-lying placenta in the second trimester. Abstract No. 129, Am J Obstet Gynecol 206(1):S69, 2012

Bond AL, Edersheim TG, Curry L, et al: Expectant management of abruptio placentae before 35 weeks' gestation. Am J Perinatol 6:121, 1989 [PubMed: 2712908]

Boral LI, Hill SS, Apollon CJ, et al: The type and antibody screen, revisited. Am J Clin Pathol 71:578, 1979 [PubMed: 110134]

Borgman MA, Spinella PC, Perkins JC, et al: The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 63:805, 2007 [PubMed: 18090009]

Bose DA, Assel BG, Hill JB, et al: Maintenance tocolytics for preterm symptomatic placenta previa: a review. Am J Perinatol 28(1):45, 2011 [PubMed: 20607648]

Bowman ZS, Eller AG, Kennedy AM, et al: Accuracy of ultrasound for the prediction of placenta accreta. Am J Obstet Gynecol 211(2):177.e1, 2014

Boyle RK, Waters BA, O'Rourke PK: Blood transfusion for caesarean delivery complicated by placenta praevia. Aust N Z J Obstet Gynaecol 49(6):627, 2009 [PubMed: 20070711]

Brame RG, Harbert GM Jr, McGaughey HS Jr, et al: Maternal risk in abruption. Obstet Gynecol 31:224, 1968 [PubMed: 5638748]

Brennan DJ, Schulze B, Chetty N, et al: Surgical management of abnormally invasive placenta: a retrospective cohort study demonstrating the benefits of a standardized operative approach. Acta Obstet Gynecol Scand 94(12):1380, 2015 [PubMed: 26344420]

Bretelle f, Courbière B, Mazouni C, et al: Management of placenta accreta: morbidity and outcome. Eur J Obstet Gynecol Reprod Biol 133(1):34, 2007 [PubMed: 16965851]

Brosens I, Pijnenborg R, Vercruysse L, et al: The "great obstetrical syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 204(3):193, 2011 [PubMed: 21094932]

Budden A, Chen LJ, Henry A: High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database Syst Rev 10:CD009701, 2014

Burchell RC: Physiology of internal iliac artery ligation. J Obstet Gynaecol Br Commonw 75:642, 1968 [PubMed: 5659060]

Burkman RT, Bell WR, Atienza MF, et al: Coagulopathy with midtrimester induced abortion: association with hyperosmolar urea administration. Am J Obstet Gynecol 127:533, 1977 [PubMed: 836654]

Butwick AJ, Goodnough LT: Transfusion and coagulation management in major obstetric hemorrhage. Curr Opin Anesthesiol 28:275, 2015

Cali G, Biambanco L, Puccio G, et al: Morbidly adherent placenta: evaluation of ultrasound diagnostic criteria and differentiation of placenta accreta from percreta. Ultrasound Obstet Gynecol 41(4):406, 2013 [PubMed: 23288834]

Callaghan WM, Creanga AA, Kuklina EV: Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol 120(5):1029, 2012 [PubMed: 23090519]

Carson JL, Triulzi DJ, Ness PM: Indications for and adverse effects of red-cell transfusion. N Engl J Med 377:13, 2017 [PubMed: 28604169]

Casey B, de Veciana M: Thyroid screening in pregnancy. Am J Obstet Gynecol 211:351, 2014 [PubMed: 25139139]

Catanzarite V, Cousins L, Daneshmand S, et al: Prenatally diagnosed vasa previa. A single-institution series of 96 cases. Obstet Gynecol 128(5):1153, 2016 [PubMed: 27741189]

Centers for Disease Control and Prevention: Zika and blood transfusions. 2016. Available at: https://www.cdc.gov/zika/transmission/blood-transfusion.html. Accessed March 3, 2017

Chalubinski KM, Pils S, Klein K, et al: Prenatal sonography can predict the degree of placental invasion. Ultrasound Obstet Gynecol 42(5):518, 2013 [PubMed: 23471888]

Chantraine F, Braun T, Gonser M, et al: Prenatal diagnosis of abnormally invasive placenta reduces maternal peripartum hemorrhage and morbidity. Acta Obstet Gynecol Scand 92(4):439, 2013 [PubMed: 23331024]

Chantry AA, Deneux-Tharaux C, Bonnet MP, et al: Pregnancy-related ICU admissions in France: trends in rate and severity, 2006–2009. Crit Care Med 43:78, 2015 [PubMed: 25377016]

Chauleur C, Fanget C, Tourne G, et al: Serious primary post-partum hemorrhage, arterial embolization and future fertility: a retrospective study of 46 cases. Hum Reprod 23:1553, 2008 [PubMed: 18460450]

Chen AL, Goldfarb IT, Scourtas AO et al.: The histologic evolution of revealed, acute abruptions. Hum Pathol 67:187, 2017 [PubMed: 28823573]

Chescheir NC, Seeds JW: Spontaneous resolution of hypofibrinogenemia associated with death of a twin in utero: a case report. Am J Obstet Gynecol 159:1183, 1988 [PubMed: 3056004]

Cho JH, Jun HS, Lee CN: Haemostatic suturing technique or uterine bleeding during cesarean delivery. Obstet Gynaecol 96:129, 2000

Cho JY, Kim SJ, Cha KY, et al: Interrupted circular suture: bleeding control during cesarean delivery in placenta previa accreta. Obstet Gynecol 78:876, 1991 [PubMed: 1923215]

Cichowski S, Rogers RG: Managing complications of perineal lacerations. Contemp Ob/Gyn 62:22, 2017

Clark SL: Amniotic fluid embolism. Obstet Gynecol 123:337, 2014 [PubMed: 24402585]

Clark SL, Hankins GDV, Dudley DA, et al: Amniotic fluid embolism: analysis of the National Registry. Am J Obstet Gynecol 172:1158, 1995 [PubMed: 7726251]

Clark SL, Pavlova Z, Greenspoon J, et al: Squamous cells in the maternal pulmonary circulation. Am J Obstet Gynecol 154:104, 1986 [PubMed: 2418682]

Clark SL, Phelan JP, Yeh SY: Hypogastric artery ligation for obstetric hemorrhage. Obstet Gynecol 66:353, 1985 [PubMed: 3875064]

Clark SL, Romero R, Dildy GA, et al: Proposed diagnostic criteria for the case definition of amniotic fluid embolism in research studies. Am J Obstet Gynecol October, 2016

Clausen C, Stensballe J, Albrechtsen CK, et al: Balloon occlusion of the internal iliac arteries in the multidisciplinary management of placenta percreta. Acta Obstet Gynecol Scand 92(4):386, 2013 [PubMed: 22574880]

Cleary-Goldman J, Malone FD, Vidaver J, et al: Impact of maternal age on obstetric outcome. Obstet Gynecol 105:983, 2005 [PubMed: 15863534]

Coad S, Dahlgren L, Hutcheson JA: Risk and consequences of puerperal uterine inversion in the United States, 2004–2013. Am J Obstet Gynecol 217:377, 2017 [PubMed: 28522320]

Collins SL, Stevenson GN, Al-Khan A, et al: Three-dimensional power Doppler ultrasonography for diagnosing abnormally invasive placenta and quantifying the risk. Obstet Gynecol 126(3):645, 2015 [PubMed: 26214694]

Colón I, Berletti M, Garabedian MJ, et al: Randomized, double-blinded trial of magnesium sulfate tocolysis versus intravenous normal saline for preterm nonsevere placental abruption. Am J Perinatol 33(7):696, 2016 [PubMed: 26871905]

Combs CA, Nyberg DA, Mack LA, et al: Expectant management after sonographic diagnosis of placental abruption. Am J Perinatol 9:170, 1992 [PubMed: 1575837]

Conrad LB, Groome KJ, Black DR: Management of persistent postpartum hemorrhage caused by inner myometrial lacerations. Obstet Gynecol 126(2):266, 2015 [PubMed: 25923024]

Counts RB, Haisch C, Simon TL, et al: Hemostasis in massively transfused trauma patients. Ann Surg 190:91, 1979 [PubMed: 464685]

Crane JM, Van Den Hof MC, Dodds L, et al: Neonatal outcomes with placenta previa. Obstet Gynecol 93:541, 1999 [PubMed: 10214830]

Creanga AA, Bateman BT, Kuklina EV, et al: Racial and ethnic disparities in severe maternal morbidity: a multistate analysis, 2008–2010. Am J Obstet Gynecol 210(5):435.e.1, 2014

Creanga AA, Berg CJ, Syverson C, et al: Pregnancy-related mortality in the United States, 2006–2010. Obstet Gynecol 125(1):5, 2015 [PubMed: 25560097]

Creanga AA, Syverson C, Seed K, et al: Pregnancy-related mortality in the United States, 2011–2013. Obstet Gynecol 130:366, 2017 [PubMed: 28697109]

Cressman AM, Natekar A, Kim E, et al: Cocaine abuse during pregnancy. J Obstet Gynaecol Can 36(7):628, 2014 [PubMed: 25184982]

Crozier TM, Wallace EM: Obstetric admissions to an integrated general intensive care unit in a quaternary maternal facility. Aust N Z J Obstet Gynaecol 51(3):233, 2011 [PubMed: 21631442]

Cummings K, Doherty DA, Magann EF, et al: Timing of manual placenta removal to prevent postpartum hemorrhage: is it time to act? J Matern Fetal Neonatal Med 29(24):3930, 2016 [PubMed: 26953615]

Cunningham FG: Genital tract lacerations and hematomas. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017a

Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017b

Cunningham FG, Nelson DB: Disseminated intravascular coagulation syndromes in obstetrics. Obstet Gynecol 126(5):999, 2015 [PubMed: 26444122]

Cunningham KM, Anwar A, Lindow SW: The recurrence risk of placenta accreta following uterine conserving management. J Neonatal Perinatal Med 8(4):293, 2016

Dagdeviren H, Cengiz H, Heydarova U, et al: Intramuscular versus intravenous prophylactic oxytocin for postpartum hemorrhage after vaginal delivery: a randomized controlled study. Arch Gynecol Obstet 294(5):911, 2016 [PubMed: 26980230]

Dashe JS: Toward consistent terminology of placental location. Semin Perinatol 37(5):375, 2013 [PubMed: 24176163]

De Greve M, Van Mieghem T, Van Den Berghe G, et al: Obstetric admissions to the intensive care unit in a tertiary hospital. Gynecol Obstet Invest 81(4):315, 2016 [PubMed: 26963752]

de Lange NM, van Rheenen-Flach LE, Lance MD, et al: Peri-partum reference ranges for ROTEM thromboelastography. Br J Anesth 112:852, 2014

Deneux-Tharaux C, Sentilhes L, Maillard F, et al: Effect of routine controlled cord traction as part of the active management of the third stage of labour on postpartum hemorrhage: multicentre randomized controlled trial (TRACOR). BMJ 346:f1541, 2013 [PubMed: 23538918]

Derman RJ, Kodkany BS, Gaudar SS, et al: Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. Lancet 368:1248, 2006 [PubMed: 17027730]

DeRoo L, Skjaervan R, Wilcox A, et al: Placental abruption and long-term maternal cardiovascular disease mortality: a population-based registry study in Norway and Sweden. Eur J Epidemiol 31(5):501, 2016 [PubMed: 26177801]

Desai N, Tam HT, Fleischer A: Prophylactic arterial catheterization may improve operative morbidity in suspected placenta accreta and reduce the need for hysterectomy. Am J Obstet Gynecol 206(1):S44, 2012

Dhariwal SK, Khan KS, Allard S, et al: Does current evidence support the use of intraoperative cell salvage in reducing the need for blood transfusion in caesarean section? Curr Opin Obstet Gynecol 26(6):425, 2014 [PubMed: 25259949]

Diemert A, Ortmeyer G, Hollwitz B, et al: The combination of intrauterine balloon tamponade and the B-Lynch procedure for the treatment of severe postpartum hemorrhage. Am J Obstet Gynecol 206(1):65.e1, 2012

Dildy GA, Scott AR, Saffer CS: An effective pressure pack for severe pelvic hemorrhage. Obstet Gynecol 108(5):1222, 2006 [PubMed: 17077246]

Distefano M, Casarella L, Amoroso S, et al: Selective arterial embolization as a first-line treatment for postpartum hematomas. Obstet Gynecol 121(2 Pt 2 Suppl):443, 2013 [PubMed: 23344403]

Downes KL, Grantz KL, Shenassa ED: Maternal, labor, delivery, and perinatal outcomes associated with placental abruption: a systematic review. Am J Perinatol 34:935, 2017 [PubMed: 28329897]

Downes KL, Hinkle SN, Sjaarda LA, et al: Previous prelabor or intrapartum cesarean delivery and risk of placenta previa. Am J Obstet Gynecol 212(5):669.e1, 2015

Downes LK, Shenassa ED, Grantz KL: Duration of labor associated with placental abruption. Abstract No. 692, Am J Obstet Gynecol 214(1):S365, 2016

Doyle N, Pullen J, Holliday N, et al: 3D ultrasound: the best view of placenta accreta. Abstract No. 108, Am J Obstet Gynecol 212(1):S72, 2015

Drakeley AJ, Le Roux PA, Anthony J, et al: Acute renal failure complicating severe preeclampsia requiring admission to an obstetric intensive care unit. Am J Obstet Gynecol 186:253, 2002 [PubMed: 11854645]

Driessen M, Bouvier-Colle MH, Dupont C, et al: Postpartum hemorrhage resulting from uterine atony after vaginal delivery. Factors associated with severity. Obstet Gynecol 117(1):21, 2011 [PubMed: 21173641]

Dugoff L, Hobbins JC, Malone FD, et al: First trimester maternal serum PAPPA and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (The FASTER Trial). Am J Obstet Gynecol 191:1446, 2004 [PubMed: 15507981]

Duzyj CM, Barishansky S, Khan S, et al: Evidence of active wound remodeling at the site of trophoblast invasion in placenta accreta. Abstract No. 147, Am J Obstet Gynecol 216:S99, 2017

Duzyj CM, Buhimschi IA, Motawea H, et al: The invasive phenotype of placenta accreta extravillous trophoblasts associates with loss of E-cadherin. Placenta 36(6):645, 2015 [PubMed: 25904157]

Einerson BD, Son M, Schneider P, et al: The association between intrauterine balloon tamponade duration and postpartum hemorrhage outcomes. Am J Obstet Gynecol 216:300.e1, 2017

Elhawary TM, Dabees NL, Youssef MA: Diagnostic value of ultrasonography and magnetic resonance imaging in pregnant women at risk for placenta accreta. J Matern Fetal Neonatal Med 26(14):1443, 2013 [PubMed: 23489020]

Eller AG, Bennett MA, Sharshiner M, et al: Maternal morbidity in cases of placenta accreta managed by a multidisciplinary care team compared with standard obstetric care. Obstet Gynecol 117(2 Pt 1):331, 2011 [PubMed: 21309195]

Elliott JP, Gilpin B, Strong TH Jr, et al: Chronic abruption–oligohydramnios sequence. J Reprod Med 43:418, 1998 [PubMed: 9610464]

Erez O, Mastrolia SA, Thachil J: Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management. Am J Obstet Gynecol 213(4):452, 2015 [PubMed: 25840271]

Erez O, Novack L, Beer-Weisel R, et al: DIC score in pregnant women—a population based modification of the International Society on Thrombosis and Hemostasis score. PLoS One 9:e93240, 2014 [PubMed: 24728139]

Erfani H, Fox KA, Bateni ZH, et al: Morbidly adherent placenta—comparison of characteristics and outcomes between scheduled and unscheduled deliveries managed within a single, multidisciplinary team-based referral center. Abstract No. 724, Am J Obstet Gynecol 216:S422, 2017a

Erfani H, Fox KA, Bateni ZH, et al: Multidisciplinary team learning in management of morbidly adherent placenta—outcome improvements over time. Abstract No. 865, Am J Obstet Gynecol 216:S494, 2017b

Esakoff TF, Handler SJ, Granados JM, et al: PAMUS: placenta accreta management across the United States. J Matern Fetal Neonatal Med 25:761, 2012 [PubMed: 21843108]

Eshkoli T, Weintraub AY, Sergienko R, et al: Placenta accreta: risk factors, perinatal outcomes, and consequences for subsequent births. Am J Obstet Gynecol 208(3):219.e1, 2013

Etchason J, Petz L, Keeler E, et al: The cost effectiveness of preoperative autologous blood donations. N Engl J Med 332:719, 1995 [PubMed: 7854380]

Ezzedine D, Norwitz ER: Are women with uterine fibroids at increased risk for adverse pregnancy outcome? Clin Obstet Gynecol 59(1):119, 2016 [PubMed: 26670833]

Farine D, Fox HE, Jakobson S, et al: Vaginal ultrasound for diagnosis of placenta previa. Am J Obstet Gynecol 159:566, 1988 [PubMed: 3048096]

Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247, 2004 [PubMed: 15163774]

Fiori O, Deux JF, Kambale JC, et al: Impact of pelvic arterial embolization for intractable postpartum hemorrhage on fertility. Am J Obstet Gynecol 200:384.e1, 2009

Fitzpatrick K, Sellers S, Spark P, et al: The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. BJOG 121(1):62, 2014 [PubMed: 23924326]

Food and Drug Administration: Revised recommendation for reducing the risk of Zika virus transmission by blood and blood components. 2016. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf. Accessed

March 3, 2017

Fong A, Wu E, Pan D, et al: Temporal trends and morbidities of vacuum, forceps, and combined use of both. J Matern Fetal Neonatal Med 27(8):1886, 2014 [PubMed: 24635372]

Foroutan-Rad M, Majidan H, Dalvand S, et al: Toxoplasmosis in blood donors: a systematic review and meta-analysis. Transfus Med Rev 30(3):116, 2016 [PubMed: 27145927]

Fox K, Shamshirsaz A, Salmanian B, et al: Is interpregnancy interval a predictor of severity of invasion in morbidly adherent placenta? Abstract No. 821, Am J Obstet Gynecol 212(1):S395, 2015

Frederiksen MC, Glassenberg R, Stika CS: Placenta previa: a 22-year analysis. Am J Obstet Gynecol 180:1432, 1999 [PubMed: 10368483]

Friederich L, Roman H, Marpeau L: A dangerous development. Am J Obstet Gynecol 196:92, 2007 [PubMed: 17240250]

Frimat M, Decambron M, Lebas C, et al: Renal cortical necrosis in postpartum hemorrhage: a case series. Am J Kidney Dis 68(1):50, 2016 [PubMed: 26786299]

Friszer S, Le Ray C, Tort J, et al: Symptomatic placenta praevia: short cervix at admission is a predictive factor for delivery within 7 days. Abstract No. 158, Am J Obstet Gynecol 208(1):S78, 2013

Frolova AI, Stout MJ, Tuuli MG, et al: Duration of the third stage of labor and risk of postpartum hemorrhage. Obstet Gynecol 127(5):951, 2016 [PubMed: 27054942]

Furuhashi M, Kurauchi O, Suganuma N: Pregnancy following placental abruption. Arch Gynecol Obstet 267:11, 2002 [PubMed: 12410366]

Furukawa S, Doi K, Furuta K, et al: The effect of placental abruption on the outcome of extremely premature infants. J Matern Fetal Neonatal Med 28(6):705, 2015a

Furukawa S, Sameshima H: The importance of the monitoring of resuscitation with blood transfusion for uterine inversion in obstetrical hemorrhage. Obstet Gynecol Int 2015:269156, 2015b

Garmi G, Samlim R: Epidemiology, etiology, diagnosis, and management of placenta accreta. Obstet Gynecol Int 2012:873929, 2012 [PubMed: 22645616]

Georgiou C: Balloon tamponade in the management of postpartum haemorrhage: a review. BJOG 116(6):748, 2009 [PubMed: 19432563]

Gerstenfeld TS, Wing DA: Rectal misoprostol versus intravenous oxytocin for the prevention of postpartum hemorrhage after vaginal delivery. Am J Obstet Gynecol 185:878, 2001 [PubMed: 11641670]

Gesteland K, Oshiro B, Henry E, et al: Rates of placenta previa and placental abruption in women delivered only vaginally or only by cesarean section. Abstract No. 403, J Soc Gynecol Invest 11:208A, 2004

Getahun BS, Yeshi MM, Roberts DJ: Case records of the Massachusetts General Hospital: case 34–2012: a 27-year old woman in Ethiopia with severe pain, bleeding, and shock during labor. N Engl J Med 367(19):1839, 2012 [PubMed: 23134385]

Gibbins KJ, Einerson BD, Varner MW, et al: Placenta previa and maternal hemorrhagic morbidity. J Matern Fetal Neonatal Med 31(4):494, 2018 [PubMed: 28140723]

Gibbins KJ, Weber T, Holmgren CM, et al: Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. Am J Obstet Gynecol 213(3):382.e1, 2015

Gilbert WM, Danielsen B: Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 93:973, 1999 [PubMed: 10362165]

Gill LA, Baldwin E, Lessard-Anderson C, et al: Septic abortion with placenta accreta in pregnancy after endometrial ablation. Obstet Gynecol 125(4):822, 2015 [PubMed: 25751195]

Gilliam M, Rosenberg D, Davis F: The likelihood of placenta previa with greater number of cesarean deliveries and higher parity. Obstet Gynecol 99:976, 2002 [PubMed: 12052584]

Gilstrap LC III: Management of postpartum hemorrhage. In Yeomans ER, Hoffman BL, Gilstrap LC, et al (eds): Cunningham and Gilstrap's Operative Obstetrics. New York, McGraw-Hill Education, 2017

Gizzo S, Saccardi C, Paztrelli TS, et al: Bakri balloon in vaginal-perineal hematomas complicating vaginal delivery: a new therapeutic approach. J Low Genit Tract Dis 17:125, 2013 [PubMed: 23343706]

Glantz C, Purnell L: Clinical utility of sonography in the diagnosis and treatment of placental abruption. J Ultrasound Med 21:837, 2002 [PubMed: 12164566]

Goffman D, Nathan L, Chazotte C: Obstetric hemorrhage: a global review. Semin Perinatol 40(2):96, 2016 [PubMed: 26742599]

Goh WA, Zalud I: Placenta accreta: diagnosis, management and the molecular biology of the morbidly adherent placenta. J Matern Fetal Neonatal Med 29(11):1795, 2016 [PubMed: 26135782]

Gonzalez EA, Moore FA, Holcomb JB, et al: Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma 62:112, 2007 [PubMed: 17215741]

Goodnough LT, Levy JH: The judicious use of recombinant factor VIIa. Semin Thromb Hemost 42(2):125, 2016 [PubMed: 26838698]

Gopalakrishnan N, Dhanapriya J, Muthkumar P, et al: Acute kidney injury in pregnancy—a single center experience. Ren Fail 37(9):1476, 2015 [PubMed: 26338215]

Gottlieb AG, Pandipati S, Davis KM, et al: Uterine necrosis. A complication of uterine compression sutures. Obstet Gynecol 112:429, 2008 [PubMed: 18669752]

Goucher H, Wong CA, Patel SK, et al: Cell salvage in obstetrics. Anesth Analg 121(2):465, 2015 [PubMed: 26197375]

Green L, Knight M, Seeney FM, et al: The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. BJOG 123(13):2164, 2016 [PubMed: 26694742]

Grönvall M, Tikkanen M, Metsätähti M, et al: Pelvic arterial embolization in severe obstetric hemorrhage. Acta Obstet Gynecol Scand 93(7):716, 2014 [PubMed: 24617830]

Grönvall M, Tikkanen M, Tallberg E: Use of Bakri balloon tamponade in the treatment of postpartum hemorrhage: a series of 50 cases from a tertiary teaching hospital. Acta Obstet Gynecol Scand 92(4):433, 2013 [PubMed: 22913383]

Gülmezoglu AM, Lumbiganon P, Landoulsi S, et al: Active management of the third stage of labor with and without controlled cord traction: a randomized, controlled, non-inferiority trial. Lancet 379(9827):1721, 2012 [PubMed: 22398174]

Guntupalli KK, Hall N, Karnad DR, et al: Critical illness in pregnancy: part I: an approach to a pregnant patient in the ICU and common obstetric disorders. Chest 148(4):1093, 2015 [PubMed: 26020613]

Gurol-Urganci I, Cromwell DA, Edozien LC, et al: Risk of placenta previa in second birth after first birth cesarean section. BMC Pregnancy Childbirth 11:95, 2011 [PubMed: 22103697]

Gutvirtz G, Walfisch A, Beharier O, et al: Isolated single umbilical artery is an independent risk factor for perinatal mortality and adverse outcomes in term neonates. Arch Gynecol Obstet, 294(5):931, 2016 [PubMed: 27048509]

Gyamfi-Bannerman C, Gilbert S, Landon MB, et al: Risk of uterine rupture and placenta accreta with prior uterine surgery outside of the lower segment. Obstet Gynecol 120(6):1332, 2012 [PubMed: 23168757]

Hackney DN, Kuo K, Petersen RJ, et al: Determinants of the competing outcomes of intrauterine infection, abruption, or spontaneous preterm birth after preterm premature rupture of membranes. J Matern Fetal Neonatal Med 29(2):258, 2016 [PubMed: 25564724]

Haeri S, Rais S, Monks B: Intrauterine tamponade balloon use in the treatment of uterine inversion. BMJ Case Rep January 6, 2015

Hale SA, Sobel B, Benvenuto A, et al: Coagulation and fibrinolytic system protein profiles in women with normal pregnancies and pregnancies complicated by hypertension. Pregnancy Hypertens 2(2):152, 2012 [PubMed: 22712057]

Hamm RF, Wang EY, O'Rourke K, et al: Implementation of quantitative blood loss does not improve prediction of hemoglobin drop in deliveries with average blood loss. Abstract No. 454, Am J Obstet Gynecol 216:S267, 2017

Hankins GD, Berryman GK, Scott RT Jr, et al: Maternal arterial desaturation with 15-methyl prostaglandin F2 alpha for uterine atony. Obstet Gynecol 72:367, 1988 [PubMed: 3261408]

Happe SK, Rac MW, Moschos E, et al: Prospective assessment of morbidly adherent placenta with first trimester ultrasound. Presented at the 38th Annual Meeting of the Society for Maternal-Fetal Medicine, January 29–February 3, 2018

Happe SK, Yule CS, Wells EC: Outcomes in pregnancies complicated by uterine rupture. Unpublished data, 2017

Hardardottir H, Borgida AF, Sanders MM, et al: Histologic myometrial fibers adherent to the placenta: impact of method of placental removal. Am J Obstet Gynecol 174:358, 1996

Hardin MO, Ritchie JD, Aden JK, et al: Plasma-to-red cell ratio and mechanism of injury in massively transfused combat casualties. Mil Med 179(1):92, 2014 [PubMed: 24402992]

Harper LM, Odibo AO, Macones GA, et al: Effect of placenta previa on fetal growth. Am J Obstet Gynecol 203(4):330.e1, 2010

Hayman RG, Arulkumaran S, Steer PJ: Uterine compression sutures: surgical management of postpartum hemorrhage. Obstet Gynecol 99:502, 2002 [PubMed: 11864681]

Hébert PC: Anemia and red cell transfusion in critical care. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Minerva Anestesiol 65(5)293, 1999 [PubMed: 10389407]

Heller HT, Mullen KM, Gordon RW, et al: Outcomes of pregnancies with a low-lying placenta diagnosed on second-trimester sonography. J Ultrasound Med 33(4):691, 2014 [PubMed: 24658950]

Hellman LM, Pritchard JA (eds): Placenta previa. In Williams Obstetrics, 14th ed. New York, Appleton Century Crofts, 1971

Hernandez JS, Alexander JM, Sarode R, et al: Calculated blood loss in severe obstetric hemorrhage and its relation to body mass index. Am J Perinatol 29(7):557, 2012 [PubMed: 22495893]

Herrera C, Meehan R, Poddutori V, et al: Maternal deaths due to *Clostridium novyi* in an injection drug user. Obstet Gynecol 128:876, 2016 [PubMed:

27607862]

Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA: Uterine massage for preventing postpartum haemorrhage. Cochrane Database Syst Rev 7:CD006431, 2013

Hogberg V, Rasmussen S, Irgens L: The effect of smoking and hypertensive disorders on abruptio placentae in Norway 1999–2002. Acta Obstet Gynecol Scand 86:304, 2007 [PubMed: 17364304]

Holst LB, Haase N, Wetterslev J, et al: Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 371(15):1381, 2014 [PubMed: 25270275]

Hossain N, Paidas MJ: Disseminated intravascular coagulation. Semin Perinatol 37(4):257, 2013 [PubMed: 23916024]

Howard RJ, Straughn JM Jr, Huh WK, et al: Pelvic umbrella pack for refractory obstetric hemorrhage secondary to posterior uterine rupture. Obstet Gynecol 100(5 Pt 2):1061, 2002 [PubMed: 12423804]

Hui C, Lili M, Libin C, et al: Changes in coagulation and hemodynamics during pregnancy: a prospective longitudinal study of 58 cases. Arch Gynecol Obstet 285(5):1231, 2012 [PubMed: 22083312]

Hung TH, Shau WY, Hsieh CC, et al: Risk factors for placenta accreta. Obstet Gynecol 93:545, 1999 [PubMed: 10214831]

Hunt BJ: Bleeding and coagulopathies in critical care. N Engl J Med 370:847, 2014 [PubMed: 24571757]

Hurd WW, Miodovnik M, Hertzberg V, et al: Selective management of abruptio placentae: a prospective study. Obstet Gynecol 61:467, 1983 [PubMed: 6828278]

Ibrahim MI, Raafat TA, Ellaithy MI, et al: Risk of postpartum uterine synechiae following uterine compression suturing during postpartum haemorrhage. Aust N Z J Obstet Gynecol 53(1):37, 2013

Ida A, Ito K, Kubota Y, et al: Successful reduction of acute puerperal uterine inversion with the use of a Bakri postpartum balloon. Case Rep Obstet Gynecol 2015:424891, 2015 [PubMed: 25954560]

Iskender C, Topcu HO, Timur H, et al: Evaluation of risk factors in women with puerperal genital hematomas. J Matern Fetal Neonatal Med 29(9):1435, 2016 [PubMed: 26043648]

Jackson BR, Busch MP, Stramer SL, et al: The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. Transfusion 43:721, 2003 [PubMed: 12757522]

Jakobsson M, Tapper AM, Colmorn LB, et al: Emergency peripartum hysterectomy: results from the prospective Nordic Obstetric Surveillance Study (NOSS). Acta Obstet Gynecol Scand 94(7):745, 2015 [PubMed: 25845622]

Jauniaux E, Collins S, Burton GJ: Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol June 24, 2017 [Epub ahead of print]

Jauniaux E, Collins SL, Jurkovic D, et al: Accreta placentation: a systematic review of prenatal ultrasound imaging and grading of villous invasiveness. Am J Obstet Gynecol 215(6):712, 2016 [PubMed: 27473003]

Jenabi E, Fereidooni B: The uterine leiomyoma and placenta previa: a meta-analysis. J Matern Fetal Neonatal Med November 21, 2017 [Epub ahead of print]

Johansson PI, Stensballe J, Rosenberg I, et al: Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic

aneurysm: evaluating a change in transfusion practice. Transfusion 47:593, 2007 [PubMed: 17381616]

Joshi VM, Shrivastava M: Partial ischemic necrosis of the uterus following a uterine brace compression suture. BJOG 111:279, 2004 [PubMed: 14961893]

Judy AE, Lyell DJ, Druzin ML, et al: Disseminated intravascular coagulation complicating the conservative management of placenta percreta. Obstet Gynecol 126(5):1016, 2015 [PubMed: 26132459]

Kaminsky LM, Ananth CV, Prasad V, et al: The influence of maternal cigarette smoking on placental pathology in pregnancies complicated by abruption. Am J Obstet Gynecol 197:275.e1, 2007

Kaplanoglu M, Kaplanoglu D, Bulbul M, et al: Inner myometrial laceration—an unusual presentation of antepartum and postpartum hemorrhage: case reports and review of the literature. J Matern Fetal Neonatal Med 29(16):2621, 2016 [PubMed: 26456511]

Kassir E, Fox KA, Efani H, et al: Placenta previa without morbidly adherent placentation: comparison of characteristics between scheduled and unscheduled (emergency) deliveries in a tertiary center. Abstract No. 726, Am J Obstet Gynecol 216:S423, 2017

Katakam N, Vitthala S, Sasson S, et al: Complications and failure of uterine artery embolization for intractable postpartum haemorrhage. BJOG 116(6):863, 2009 [PubMed: 19432577]

Kawamura Y, Kondoh E, Hamanishi J, et al: Treatment decision-making for postpartum hemorrhage using dynamic contrast-enhanced computed tomography. J Obstet Gynaecol Res 40(1):67, 2014 [PubMed: 23937115]

Kaya B, Guralp O, Tuten A, et al: Which uterine sparing technique should be used for uterine atony during cesarean section? The Bakri balloon or the B-Lynch suture? Arch Gynecol Obstet 294(3):511, 2016 [PubMed: 26781261]

Kayani SI, Walkinshaw SA, Preston C: Pregnancy outcome in severe placental abruption. BJOG 110:679, 2003 [PubMed: 12842059]

Kayem G, Dupont C, Bouvier-Colle MH, et al: Invasive therapies for primary postpartum haemorrhage: a population-based study in France. BJOG 123(4):598, 2016 [PubMed: 26113356]

Kayem G, Kurinczuk JJ, Alfirevic A, et al: Uterine compression sutures for the management of severe postpartum hemorrhage. Obstet Gynecol 117(1):14, 2011 [PubMed: 21213474]

Kenny L, McCrae K, Cunningham FG: Platelets, coagulation, and the liver. In Taylor R, Roberts JM, Cunningham FG (eds): Chesley's Hypertension in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Kettel LM, Branch DW, Scott JR: Occult placental abruption after maternal trauma. Obstet Gynecol 71:449, 1988 [PubMed: 3347433]

Khan K, Moor P, Wilson MJ, et al: Cell salvage during caesarean section: a randomised controlled trial (The SALVO Trial). Abstract No. LB01, Am J Obstet Gynecol 216:S559, 2017

Kibel M, Asztalos E, Barrett J, et al: Outcomes of pregnancies complicated by preterm premature rupture of membranes between 20 and 24 weeks of gestation. Obstet Gynecol 128:313, 2016 [PubMed: 27400016]

Kieser KE, Baskett TF: A 10-year population-based study of uterine rupture. Obstet Gynecol 100:749, 2002 [PubMed: 12383544]

Kikuchi M, Itakura A, Miki A, et al: Fibrinogen concentrate substitution therapy for obstetric hemorrhage complicated by coagulopathy. J Obstet Gynaecol Res 39(4):770, 2013 [PubMed: 23278972]

King DL: Placental migration demonstrated by ultrasonography. Radiology 109:167, 1973 [PubMed: 4798771]

Klar M, Michels KB: Cesarean section and placental disorders in subsequent pregnancies—a meta-analysis. J Perinat Med 42(5):571, 2014 [PubMed: 24566357]

Knight M, Berg C, Brocklehurst P, et al: Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations. BMC Pregnancy Childbirth 12:7, 2012 [PubMed: 22325370]

Knight M, Tuffnell D, Brocklehurst P, et al: Incidence and risk factors for amniotic-fluid embolism. Obstet Gynecol 115(5):910, 2010 [PubMed: 20410762]

Knight M, UKOSS: Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG 114:1380, 2007 [PubMed: 17877772]

Koen S, Synman LC, Pattinson RC, et al: A randomised controlled trial comparing oxytocin and oxytocin +ergotamine for prevention of postpartum hemorrhage at caesarean section. S Afr Med J 106:55, 2016 [PubMed: 27032858]

Kohari KS, Roman AS, Fox NS, et al: Persistence of placenta previa in twin gestations based on gestational age at sonographic detection. J Ultrasound Med 31(7):985, 2012 [PubMed: 22733846]

Kollmann M, Gaulhofer J, Lang U, et al: Placenta previa: incidence, risk factors and outcome. J Matern Fetal Neonatal Med 29(9):1395, 2016 [PubMed: 26043298]

Kolomeyevskaya NV, Tanyi JL, Coleman NM, et al: Balloon tamponade of hemorrhage after uterine curettage for gestational trophoblastic disease. Obstet Gynecol 113:557, 2009 [PubMed: 19155956]

Kotsuji F, Nishihima K, Kurokawa T, et al: Transverse uterine fundal incision for placenta praevia with accreta, involving the entire anterior uterine wall: a case series. BJOG 120(9):1144, 2013 [PubMed: 23639121]

Kramer MS, Berg C, Abenhaim H, et al: Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol 209(5):449.e1, 2013

Kramer MS, Rouleau J, Liu S, et al: Amniotic fluid embolism: incidence, risk factors, and impact on perinatal outcomes. BJOG 119(7):874, 2012 [PubMed: 22530987]

Kuczyński J, Uszyński W, Zekanowska E, et al: Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in the placenta and myometrium. Eur J Obstet Gynecol Reprod Biol 105:15, 2002 [PubMed: 12270558]

Kumru P, Demirci O, Erdogdu E, et al: The Bakri balloon for the management of postpartum hemorrhage in cases with placenta previa. Eur J Obstet Gynecol Reprod Biol 167(2):167, 2013 [PubMed: 23298893]

Kuriya A, Piedimonte S, Spence AR, et al: Incidence and causes of maternal mortality in the USA. J Obstet Gynaecol Res 42(6):661, 2016 [PubMed: 26890471]

Lai J, Caughey AB, Qidwai GI, et al: Neonatal outcomes in women with sonographically identified uterine leiomyomata. J Matern Fetal Neonatal Med 25(6):710, 2012 [PubMed: 22409539]

Landy HJ, Laughon K, Bailit JL, et al: Characteristics associated with severe perineal and cervical lacerations during vaginal delivery. Obstet Gynecol 117(3):627, 2011 [PubMed: 21343766]

Landy HJ, Weingold AB: Management of a multiple gestation complicated by an antepartum fetal demise. Obstet Gynecol Surv 44:171, 1989 [PubMed: 2652011]

Law LW, Chor CM, Leung TY: Use of hemostatic gel in postpartum hemorrhage due to placenta previa. Obstet Gynecol 116(Suppl 2):528, 2010 [PubMed: 20664443]

Lax A, Prince MR, Mennitt KW, et al: The value of specific MRI features in the evaluation of suspected placental invasion. Magn Reson Imaging 25:87, 2007 [PubMed: 17222719]

Lee HY, Shin JH, Kim J, et al: Primary postpartum hemorrhage: outcome of pelvic arterial embolization in 251 patients at a single institution. Radiology 264(3):903, 2012 [PubMed: 22829685]

Lee W, Ginsburg KA, Cotton DB, et al: Squamous and trophoblastic cells in the maternal pulmonary circulation identified by invasive hemodynamic monitoring during the peripartum period. Am J Obstet Gynecol 155:999, 1986 [PubMed: 3777075]

Lerner NB, Refaai MA, Blumberg N: Red cell transfusion. In Kaushansky K, Lichtman M, Beutler K, et al (eds): Williams Hematology, 8th ed. New York, McGraw-Hill, 2010, p 2287

Levi M: Pathogenesis and management of peripartum coagulopathic calamities (disseminated intravascular coagulation and amniotic fluid embolism). Thromb Res 131(Suppl 1):S32, 2013 [PubMed: 23452737]

Levi M, Levy JH, Andersen HF, et al: Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 363(19):1791, 2010a

Levi M, Seligsohn U: Disseminated intravascular coagulation. In Kaushansky K, Lichtman M, Beutler K, et al (eds): Williams Hematology, 8th ed. New York, McGraw-Hill, 2010b

Likis FE, Sathe NA, Morgans AK, et al: Management of postpartum hemorrhage. Agency for Healthcare Research and Quality (US) Report No. 15-EHC013-EF, April 2015

Lin Y, Callum JL, Coovadia AS, et al: Transfusion of ABO-nonidentical platelets is not associated with adverse clinical outcomes in cardiovascular surgery patients. Transfusion 42:166, 2002 [PubMed: 11896330]

Linn RL, Miller ES, Lim G, et al: Adherent basal plate myometrial fibers in the delivered placenta as a risk factor for development of subsequent placenta accreta. Placenta 36(12):1419, 2015 [PubMed: 26494605]

Logothetopulos K: Eine absolut sichere Blutstillungsmethode bei vaginalen und abdominalen gynakologischen Operationen. Zentralbl Gynakol 50:3202, 1926

Luke B, Gopal D, Cabral H, et al: Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology. Am J Obstet Gynecol 217(3):327.e1–327, 2017

Maggio L, Forbes J, Carey LL, et al: Association of Montevideo units with uterine rupture in women undergoing a trial of labor. J Reprod Med 59(9–10):464, 2014 [PubMed: 25330688]

Maher MA, Abdelaziz A, Bazeed MF: Diagnostic accuracy of ultrasound and MRI in the prenatal diagnosis of placenta accreta. Acta Obstet Gynecol Scand 92(9):1017, 2013 [PubMed: 23711014]

Major CA, deVeciana M, Lewis DF, et al: Preterm premature rupture of membranes and abruptio placentae: is there an association between these pregnancy complications? Am J Obstet Gynecol 172:672, 1995 [PubMed: 7856704]

Maraka S, Ospina NM, O'Keeffe DT, et al: Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid 26(4):580, 2016 [PubMed: 26837268]

Marik PE, Corwin HL: Acute lung injury following blood transfusion: expanding the definition. Crit Care Med 36(11):3080, 2008 [PubMed: 18824899]

Masselli G, Brunelli R, Di Tola M, et al: MR imaging in the evaluation of placental abruption: correlation with sonographic findings. Radiology 259(1):222, 2011 [PubMed: 21330568]

Matijevic N, Wang YW, Cotton BA, et al: Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg 74(1):84, 2013 [PubMed: 23271081]

Matsubara S, Yano H, Ohkuchi A, et al: Uterine compression suture for postpartum hemorrhage: an overview. Acta Obstet Gynecol Scand 92(4):378, 2013 [PubMed: 23330882]

Matsubara S, Yano H, Taneichi A, et al: Uterine compression suture against impending recurrence of uterine inversion immediately after laparotomy positioning. J Obstet Gynaecol Res 35(4):819, 2009 [PubMed: 19751352]

Matsuda Y, Maeda T, Kouno S: Comparison of neonatal outcome including cerebral palsy between abruptio placentae and placenta previa. Eur J Obstet Gynecol Reprod Biol 106:125, 2003 [PubMed: 12551776]

Matsuda Y, Ogawa M, Konno J, et al: Prediction of fetal acidemia in placental abruption. BMC Pregnancy Childbirth 13:156, 2013 [PubMed: 23915223]

Matsuwaki T, Khan KN, Inoue T, et al: Evaluation of obstetrical factors related to Sheehan syndrome. J Obstet Gynaecol Res 40(1):46, 2014 [PubMed: 23945005]

McKeogh RP, D'Errico E: Placental accreta: clinical manifestations and conservative management. N Engl J Med 245:159, 1951 [PubMed: 14853058]

Mehrabadi A, Hutcheon J, Lee L, et al: Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-base retrospective cohort study. BJOG 120(7):853, 2013 [PubMed: 23464351]

Mehrabadi A, Hutcheon JA, Liu S, et al: Contribution of placenta accreta to the incidence of postpartum hemorrhage and severe postpartum hemorrhage. Obstet Gynecol 125(4):814, 2015 [PubMed: 25751202]

Melamed N, Ben-Haroush A, Chen R, Kaplan B, et al: Intrapartum cervical lacerations: characteristics, risk factors, and effects on subsequent pregnancies. Am J Obstet Gynecol 200(4):388.e1, 2009

Mhatre MV, Potter JA, Lockwood CJ, et al: Thrombin augments LPS-induced human endometrial endothelial cell inflammation via PARK1 activation. Am J Reprod Immunol 76(1):29, 2016 [PubMed: 27108773]

Michaels AY, Washburn EE, Pocius KD, et al: Outcome of cesarean scar pregnancies diagnosed sonographically in the first trimester. J Ultrasound Med 34(4):595, 2015 [PubMed: 25792574]

Miller DA, Paul RH: Rupture of the unscarred uterus. Am J Obstet Gynecol 174:345, 1996

Miller DT, Roque DM, Santin AD: Use of Monsel solution to treat obstetrical hemorrhage: a review and comparison to other topical hemostatic agents. Am J Obstet Gynecol 212(6):725, 2015 [PubMed: 25577672]

Miller ES, Linn RL, Ernst LM: Does the presence of placental basal plate myometrial fibers in a prior pregnancy improve prediction of placenta accreta? BJOG 123(13):2140, 2016 [PubMed: 26265563]

Millischer AE, Solomon LJ, Porcher R, et al: Magnetic resonance imaging for abnormally invasive placenta: the added value of intravenous gadolinium injection. BJOG 124(1):88, 2017 [PubMed: 27346286]

Misra DP, Ananth CV: Risk factor profiles of placental abruption in first and second pregnancies: heterogeneous etiologies. J Clin Epidemiol 52:453, 1999 [PubMed: 10360341]

Miura K, Higashijima A, Murakami Y, et al: Circulating levels of pregnancy-associated, placenta-specific microRNAs in pregnant women with placental abruption. Reprod Sci June 13, 2016 [Epub ahead of print]

Mogos MF, Salemi JL, Ashley M, et al: Recent trends in placenta accreta in the United States and its impact on maternal-fetal morbidity and healthcare-associated costs, 1998–2011. Ultrasound Obstet Gynecol 29(7): 1077, 2016

Mondal PC, Ghosh D, Santra D, et al: Role of Hayman technique and its modification in recurrent puerperal uterine inversion. J Obstet Gynaecol Res 38(2):438, 2012 [PubMed: 22379624]

Mone F, Elsayed S, McAuliffe FM, et al: Uterine rupture—when, why and emerging trends in an Irish population. Abstract No. 433, Am J Obstet Gynecol 214(1):S238, 2016

Morgan JL, Nelson DB, Roberts SW, et al: The impact of baseline proteinuria in pregnant women with treated chronic hypertension. Obstet Gynecol 128:270, 2016 [PubMed: 27400013]

Motta IJ, Spencer BR, Cordeiro da Silva SG, et al: Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med 375(11):1101, 2016 [PubMed: 27532622]

Mousa HA, Blum J, Abou El Senoun G, et al: Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2:CD003249, 2014

Mukhopadhyay D, Jennings PE, Banerjee M, et al: Ultrasound-guided drainage of supralevator hematoma in a hemodynamically stable patient. Obstet Gynecol 126(6):1188, 2015 [PubMed: 26132458]

Murakami M, Kobayashi T, Kubo T, et al: Experience with recombinant activated factor VII for severe postpartum hemorrhage in Japan, investigated by Perinatology Committee, Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res 41(8):1161, 2015 [PubMed: 26013425]

Murdock AD, Berseus O, Hervig T, et al: Whole blood: the future of traumatic hemorrhagic shock resuscitation. Shock 41(Supp 1):62, 2014 [PubMed: 24662782]

Murphy M, Vassallo R: Preservation and clinical use of platelets. In Kaushansky K, Lichtman M, Beutler K, et al (eds): Williams Hematology, 8th ed. New York, McGraw-Hill, 2010

Naeye RL: Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. Obstet Gynecol 55:701, 1980 [PubMed: 7383456]

Nageotte MP: Always be vigilant for placenta accreta. Am J Obstet Gynecol 211(2):87, 2014 [PubMed: 25077458]

Nakash A, Tuck S, Davies N: Uterine sepsis with uterine artery embolisation in the management of obstetric bleeding. J Obstet Gynecol 32(1):26, 2012

Nath CA, Ananth CV, DeMarco C, et al: Low birthweight in relation to placental abruption and maternal thrombophilia status. Am J Obstet Gynecol 198:293.e1, 2008

Nath CA, Ananth CV, Smulian JC, et al: Histologic evidence of inflammation and risk of placental abruption. Am J Obstet Gynecol 197:319.e1, 2007

Neilson JP: Interventions for suspected placenta praevia. Cochrane Database Syst Rev 2:CD001998, 2003

Nelson DB, Yost NP, Cunningham FG: Acute fatty liver of pregnancy: clinical outcomes and expected durations of recovery. Am J Obstet Gynecol 209(5):456.e1, 2013

Nelson DB, Yost NP, Cunningham FG: Hemostatic dysfunction with acute fatty liver of pregnancy. Obstet Gynecol 124:40, 2014 [PubMed: 24901264]

Nelson EL, Parker AN, Dudley DJ: Spontaneous vulvar hematoma during pregnancy: a case report. J Reprod Med 57(1–2):74, 2012 [PubMed: 22324274]

Nelson WL, O'Brien JM: The uterine sandwich for persistent uterine atony: combining the B-Lynch compression suture and an intrauterine Bakri balloon. Am J Obstet Gynecol 196(5):e9, 2007 [PubMed: 17466689]

Ngai I, Bernstein P, Chazotte C, et al: Maternal serum alpha fetoprotein (MSAFP) and placental abruption. Abstract No. 122, Am J Obstet Gynecol 206(1):S66, 2012

Nikolaou M, Kourea HP, Antonopoulos K, et al: Spontaneous uterine rupture in a primigravid woman in the early third trimester attributed to adenomyosis: a case report and review of literature. J Obstet Gynaecol Res 39(3):727, 2013 [PubMed: 23151226]

Nizard J, Barrinque L, Frydman R, et al: Fertility and pregnancy outcomes following hypogastric artery ligation for severe post-partum haemorrhage. Hum Reprod 18:844, 2003 [PubMed: 12660282]

Noh JJ, Park CH, Jo MH, et al: Rupture of an unscarred uterus in a woman with long-term steroid treatment for systemic lupus erythematosus. Obstet Gynecol 122(2 Pt 2):472, 2013 [PubMed: 23884264]

Nørgaard LN, Pinborg A, Lidegaard Ø, et al: A Danish national cohort study on neonatal outcome in singleton pregnancies with placenta previa. Acta Obstet Gynecol Scand 91(5):546, 2012 [PubMed: 22348742]

O'Brien B, Smoleneic J: Cervical varicosities and placenta praevia. Aust N Z J Obstet Gynaecol 53(5):451, 2013 [PubMed: 23919618]

Ochoa M, Allaire AD, Stitely ML: Pyometria after hemostatic square suture technique. Obstet Gynecol 99:506, 2002 [PubMed: 11864682]

Ogah K, Munjuluri N: Complete uterine inversion after vaginal delivery. J Obstet Gynaecol 31(3):265, 2011 [PubMed: 21417658]

Okby R, Atawaz AA, Wainstock T, et al: Placental abruption in twin pregnancies, risk factors and perinatal outcomes. Abstract No. 978, Am J Obstet Gynecol 216:S551, 2017

Oladapo OT, Adetoro OO, Ekele BA, et al: When getting there is not enough: a nationwide cross-sectional study of 998 maternal deaths and 1451 near-misses in public tertiary hospitals in a low-income country. BJOG 123(6):928, 2016 [PubMed: 25974281]

Oleen MA, Mariano JP: Controlling refractory atonic postpartum hemorrhage with Hemabate sterile solution. Am J Obstet Gynecol 162:205, 1990 [PubMed: 2405676]

Olive EC, Roberts CL, Nassar N, et al: Test characteristics of placental location screening by transabdominal ultrasound at 18–20 weeks. Ultrasound Obstet Gynecol 28(7):944, 2006 [PubMed: 17121427]

Østerud B, Bjorklid E: Sources of tissue factor. Semin Thromb Hemost 32(1):11, 2006 [PubMed: 16479458]

Oyelese Y, Smulian JC: Placenta previa, placenta accreta, and vasa previa. Obstet Gynecol 107:927, 2006 [PubMed: 16582134]

Pacheco LD, Hankins GV, Saad AF, et al: Tranexamic acid for the management of obstetric hemorrhage. Obstet Gynecol 130:765, 2017 [PubMed: 28885402]

Pacheco LD, Saade GR, Costantine MM, et al: An update on the use of massive transfusion protocols in obstetrics. Am J Obstet Gynecol 214(3):340, 2016 [PubMed: 26348379]

Pacheco LD, Saade GR, Constantine MM, et al: The role of massive transfusion protocols in obstetrics. Am J Perinatol 30(1):1, 2013 [PubMed: 22836824]

Pacheco LD, Saade GR, Gei AF, et al: Cutting-edge advances in the medical management of obstetrical hemorrhage. Am J Obstet Gynecol 205(6):526, 2011 [PubMed: 21816382]

Pan J, Zhou L, Huang A, et al: Sonographic diagnosis of complete uterine inversion: an unusual case. Clin Exp Obstet Gynecol 42(2):240, 2015 [PubMed: 26054129]

Pariente G, Shoham-Vardi I, Kessous R, et al: Placental abruption as a marker for long term cardiovascular mortality: a follow-up period of more than a decade. Am J Obstet Gynecol 208(1):S62, 2013

Parrott J, Holland M: Second trimester marginal previa: is follow-up necessary? Abstract No. 653, Am J Obstet Gynecol 212(1):S322, 2015

Pates JA, Hatab MR, McIntire DD, et al: Determining uterine blood flow in pregnancy with magnetic resonance imaging. Magn Reson Imaging 28(4): 507, 2010 [PubMed: 20061112]

Pather S, Strockyj S, Richards A, et al: Maternal outcome after conservative management of placenta percreta at caesarean section: a report of three cases and a review of the literature. Aust N Z J Obstet Gynaecol 54(1):84, 2014 [PubMed: 24471850]

Patterson JA, Roberts CL, Bowen JR, et al: Blood transfusions during pregnancy, birth, and the postnatal period. Obstet Gynecol 123(1):126, 2014 [PubMed: 24463672]

Pearlman MD, Tintinalli JE, Lorenz RP: A prospective controlled study of outcome after trauma during pregnancy. Am J Obstet Gynecol 162:1502, 1990 [PubMed: 2360584]

Pelosi MA III, Pelosi MA: Spontaneous uterine rupture at thirty-three weeks subsequent to previous superficial laparoscopic myomectomy. Am J Obstet Gynecol 177:1547, 1997 [PubMed: 9423770]

Penotti M, Vercellini P, Bolis G: Compressive suture of the lower uterine segment for the treatment of postpartum hemorrhage due to complete placenta previa: a preliminary study. Gynecol Obstet Invest 73(4):314, 2012 [PubMed: 22440887]

Perel P, Roberts I, Ker K: Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2:CD000567, 2013

Perez-Delboy A, Wright JD: Surgical management of placenta accreta: to leave or remove the placenta? BJOG 121:163, 2014 [PubMed: 24373590]

Perlman NC, Little SE, Thomas A, et al: Patient selection for later delivery timing with suspected previa-accreta. Acta Obstet Gynecol Scand 96(8): 1021, 2017 [PubMed: 28374887]

Peters Al, Van Stein D, Vlaar AP: Antibody-mediated transfusion-related acute lung injury: from discovery to prevention. Br J Haematol 170(5):597, 2015 [PubMed: 25921271]

Petersen IR, Nyholm HC: Multiple pregnancies with single intrauterine demise. Description of twenty-eight pregnancies. Acta Obstet Gynecol Scand 78:202, 1999 [PubMed: 10078581]

Pettit KE, Stephenson ML, Truong YN et al.: Maternal and neonatal outcomes among scheduled versus unscheduled deliveries in women with prenatally diagnosed, pathologically proven placenta accreta. J Matern Fetal Neonatal Med November 5, 2017 [Epub ahead of print]

Pilloni E, Alemanno MG, Gaglioti P, et al: Accuracy of ultrasound in antenatal diagnosis of placental attachment disorders. Ultrasound Obstet Gynecol 47(3):302, 2016 [PubMed: 25964123]

Po LK, Simons ME, Levinsky ES: Concealed postpartum hemorrhage treated with transcatheter arterial embolization. Obstet Gynecol 120(2 Pt 2):461, 2012 [PubMed: 22825266]

Porreco RP, Clark SL, Belfort MA, et al: The changing specter of uterine rupture. Am J Obstet Gynecol 200(3):269.e1, 2009

Porter TF, Clark SL, Dildy GA, et al: Isolated disseminated intravascular coagulation and amniotic fluid embolism. Am J Obstet Gynecol 174:486, 1996

Poujade O, Grossetti A, Mougel L, et al: Risk of synechiae following uterine compression sutures in the management of major postpartum haemorrhage. BJOG 118(4):433, 2011 [PubMed: 21199289]

Poujade O, Zappa M, Letendre I, et al: Predictive factors for failure of pelvic arterial embolization for postpartum hemorrhage. Int J Gynaecol Obstet 117(2):119, 2012 [PubMed: 22361480]

Pri-Paz S, Devine PC, Miller RS, et al: Cesarean hysterectomy requiring emergent thoracotomy: a case report of a complication of placenta percreta requiring a multidisciplinary effort. J Reprod Med 57(1–2):58, 2012 [PubMed: 22324270]

Prick BW, Vos AA, Hop WC, et al: The current state of active third stage management to prevent postpartum hemorrhage: a cross-sectional study. Acta Obstet Gynecol Scand 92(11):1277, 2013 [PubMed: 23962221]

Primo LF, Arbogast K, Digiacomo T, et al: Placenta accreta: can we forecast its arrival? Obstet Gynecol 123(Suppl 1):166S, 2014

Pritchard JA: Changes in the blood volume during pregnancy and delivery. Anesthesiology 26:393, 1965 [PubMed: 14313451]

Pritchard JA: Fetal death in utero. Obstet Gynecol 14:573, 1959 [PubMed: 14434964]

Pritchard JA: Haematological problems associated with delivery, placental abruption, retained dead fetus, and amniotic fluid embolism. Clin Haematol 2:563, 1973

Pritchard JA, Baldwin RM, Dickey JC, et al: Blood volume changes in pregnancy and the puerperium, 2. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, cesarean section, and cesarean section plus total hysterectomy. Am J Obstet Gynecol 84:1271, 1962

Pritchard JA, Brekken AL: Clinical and laboratory studies on severe abruptio placentae. Am J Obstet Gynecol 97:681, 1967 [PubMed: 6018985]

Pritchard JA, Cunningham FG, Mason RA: Coagulation changes in eclampsia: their frequency and pathogenesis. Am J Obstet Gynecol 124:855, 1976 [PubMed: 1258945]

Pritchard JA, Cunningham FG, Pritchard SA, et al: On reducing the frequency of severe abruptio placentae. Am J Obstet Gynecol 165:1345, 1991 [PubMed: 1957859]

Pritchard JA, Mason R, Corley M, et al: Genesis of severe placental abruption. Am J Obstet Gynecol 108:22, 1970 [PubMed: 5454580]

Pritchard JA, Whalley PJ: Abortion complicated by *Clostridium perfringens* infection. Am J Obstet Gynecol 111:484, 1971 [PubMed: 4328673]

Quant HS, Friedman AM, Wang E, et al: Transabdominal sonography as a screening test for second-trimester placenta previa. Obstet Gynecol 13(3):628, 2014

Rac MW, Dashe JS, Wells CE, et al: Ultrasound predictors of placental invasion: the Placenta Accreta Index. Am J Obstet Gynecol 212:343, 2015a

Rac MW, McIntire DD, Wells CE, et al: Cervical length in patients at risk for placental accreta. J Ultrasound Med 36(7):1431, 2017 [PubMed: 28339114]

Rac MW, Wells CE, Twicker DM, et al: Placenta accreta and vaginal bleeding according to gestational age at delivery. Obstet Gynecol 125(4):808, 2015b

Rafi J, Muppala H: Retroperitoneal haematomas in obstetrics: literature review. Arch Gynecol Obstet 281(3):435, 2010 [PubMed: 19940999]

Räisänen S, Kancherla V, Kramer MR, et al: Placenta previa and the risk of delivering a small-for-gestational-age newborn. Obstet Gynecol 124(2 Pt 1):285, 2014 [PubMed: 25004348]

Ramskill N, Hameed A, Beebeejaun Y: Spontaneous rupture of uterine leiomyoma during labor. BMJ Case Rep 2014:pii: bcr2014204364, 2014

Rana KA, Patel PS: Complete uterine inversion: an unusual yet crucial sonographic diagnosis. J Ultrasound Med 28(12):1719, 2009 [PubMed: 19933488]

Rapaport SI, Rao LV: The tissue factor pathway: how it has become a "prima ballerina." Thromb Haemost 74:7, 1995 [PubMed: 8578528]

Rasmussen S, Irgens LM: Occurrence of placental abruption in relatives. BJOG 116:693, 2009 [PubMed: 19191777]

Rattray DD, O'Connell CM, Baskett TF: Acute disseminated intravascular coagulation in obstetrics: a tertiary centre population review (1980 to 2009). J Obstet Gynaecol Can 34(4):341, 2012 [PubMed: 22472333]

Reddy UM, Abuhamad AZ, Levine D, et al: Fetal imaging: executive summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop. Obstet Gynecol 123(5):1070, 2014 [PubMed: 24785860]

Riihimäki O, Metsäranta M, Ritvanen A, et al: Increased prevalence of major congenital anomalies in births with placental abruption. Obstet Gynecol 122(2 Pt 1):268, 2013 [PubMed: 23969794]

Roach MK, Thomassee MS: Acquired uterine arteriovenous malformation and retained placenta increta. Obstet Gynecol 126(3):642, 2015 [PubMed: 25923029]

Robalo R, Pedroso C, Agapito A, et al: Acute Sheehan's syndrome presenting as central diabetes insipidus. BMJ Case Rep Online Nov 6, 2012

Roberts CL, Algert CS, Warrendorf J, et al: Trends and recurrence of placenta previa: a population-based study. Aust N Z J Obstet Gynaecol 52(5):483, 2012 [PubMed: 22862285]

Robinson CJ, Villers MS, Johnson DD, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes: a cost analysis. Am J Obstet Gynecol 202(6):632, 2010 [PubMed: 20435284]

Roeca C, Little SE, Carusi D: Pathologically-diagnosed accreta and hemorrhagic morbidity in a subsequent pregnancy. Obstet Gynecol 129(2):321, 2017 [PubMed: 28079779]

Romundstad LB, Romundstad PR, Sunde A, et al: Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother. Hum Reprod 21(9):2353, 2006 [PubMed: 16728419]

Rosenberg T, Pariente G, Sergienko R, et al: Critical analysis of risk factors and outcome of placenta previa. Arch Gynecol Obstet 284(1):47, 2011 [PubMed: 20652281]

Rossi AC, Lee RH, Chmait RH: Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systematic review. Obstet Gynecol 115(3):637, 2010 [PubMed: 20177297]

Rotas MA, Haberman S, Luvgur M: Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol 107:1373, 2006 [PubMed: 16738166]

Rouse DJ: Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. Obstet Gynecol 122(3):693, 2013 [PubMed: 23921880]

Rouse DJ, MacPherson C, Landon M, et al: Blood transfusion and cesarean delivery. Obstet Gynecol 108:891, 2006 [PubMed: 17012451]

Ruiter L, Ravelli AC, de Graaf IM, et al: Incidence and recurrence rate of placental abruption: a longitudinal linked national cohort study in the Netherlands. Am J Obstet Gynecol 213(4):573.e1, 2015

Sabourin JN, Lee T, Magee LA, et al: Indications for, timing of, and modes of delivery in a national cohort of women admitted with antepartum hemorrhage at 22+0 to 28+6 weeks' gestation. J Obstet Gynaecol Can 34(11):1043, 2012 [PubMed: 23231842]

Salihu HM, Bekan B, Aliyu MH, et al: Perinatal mortality associated with abruptio placenta in singletons and multiples. Am J Obstet Gynecol 193:198, 2005 [PubMed: 16021079]

Salihu HM, Li Q, Rouse DJ, et al: Placenta previa: neonatal death after live births in the United States. Am J Obstet Gynecol 188:1305, 2003 [PubMed: 12748503]

Salim R, Chulski A, Romano S, et al: Precesarean prophylactic balloon catheters for suspected placenta accreta: a randomized controlled trial. Obstet Gynecol 126(5):1022, 2015 [PubMed: 26444128]

Sanderson DA, Milton PJD: The effectiveness of ultrasound screening at 18–20 weeks gestational age for predication of placenta previa. J Obstet Gynaecol 11:320, 1991

Sangwan N, Nanda S, Singhal S, et al: Puerperal uterine inversion associated with unicornuate uterus. Arch Gynecol Obstet 280(4):625, 2009 [PubMed: 19198865]

Saraiya M, Green CA, Berg CJ, et al: Spontaneous abortion-related deaths among women in the United States—1981–1991. Obstet Gynecol 94:172, 1999 [PubMed: 10432122]

Sathe NA, Likis FE, Young JL, et al: Procedures and uterine-sparing surgeries for managing postpartum hemorrhage: a systematic review. Obstet Gynecol Surv 71(2):99, 2016 [PubMed: 26894802]

Schimmer BP, Parker KL: Contraception and pharmacotherapy of obstetrical and gynecological disorders. In Brunton LL, Chabner BA, Knollmann BC (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th ed. New York, McGraw-Hill, 2011

Schlicter SJ, Kaufman RM, Assmann SF, et al: Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 362(7):600, 2010 [PubMed: 20164484]

Schmitz T, Tararbit K, Dupont C, et al: Prostaglandin E2 analogue sulprostone for treatment of atonic postpartum hemorrhage. Obstet Gynecol 118(Pt 2):257, 2011 [PubMed: 21775840]

Seet EL, Kay HH, Wu S, et al: Placenta accreta: depth of invasion and neonatal outcomes. J Matern Fetal Neonatal Med 25(10):2042, 2012 [PubMed: 22463851]

Sentilhes L, Goffinet F, Kayem G: Management of placenta accreta. Acta Obstet Gynecol Scand 92(10):1125, 2013 [PubMed: 23869630]

Sentilhes L, Gromez A, Clavier E, et al: Predictors of failed pelvic arterial embolization for severe postpartum hemorrhage. Obstet Gynecol 113:992, 2009 [PubMed: 19384113]

Sentilhes L, Merlot B, Madar H, et al: Postpartum hemorrhage: prevention and treatment. Expert Rev Hematol 9(11):1043, 2016 [PubMed: 27701915]

Şentürk S, Kagtitci M, Balik G, et al: The effect of the combined use of methylergonovine and oxytocin during caesarean section in the prevention of postpartum haemorrhage. Basic Clin Pharmacol Toxicol 118:338, 2016 [PubMed: 26449959]

Shamshirsaz AA, Fox KA, Salmanian B, et al: Maternal morbidity in patients with morbidly adherent placenta treated with and without a standardized multidisciplinary approach. Am J Obstet Gynecol 212:218.e1, 2015

Shaz BH, Dente CJ, Harris RS, et al: Transfusion management of trauma patients. Anesth Analg 108:1760, 2009 [PubMed: 19448199]

Shields LE, Smalarz K, Reffigee L, et al: Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. Am J Obstet Gynecol 205:368.e1, 2011

Sholl JS: Abruptio placentae: clinical management in nonacute cases. Am J Obstet Gynecol 156:40, 1987 [PubMed: 3541621]

Sibai BM, Lindheimer M, Hauth J, et al: Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. N Engl J Med 339:667, 1998 [PubMed: 9725924]

Silver RM: Abnormal placentation: placenta previa, vasa previa, and placenta accreta. Obstet Gynecol 126(3):654, 2015a

Silver RM, Fox KA, Barton JR, et al: Center of excellence for placenta accreta. Am J Obstet Gynecol, May 2015b

Silver RM, Landon MB, Rouse DJ, et al: Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol 107:1226, 2006 [PubMed: 16738145]

Smulian JC, DeFulvio JD, Diven L, et al: Sonographic findings in acute uterine inversion. J Clin Ultrasound 41(7):453, 2013 [PubMed: 23339051]

Smulian JC, Pascual AL, Hesham H, et al: Invasive placental disease: the impact of a multidisciplinary team approach to management. J Matern Fetal Neonatal Med 30(12):1423, 2017 [PubMed: 27534584]

Society for Maternal-Fetal Medicine, Belfort MA: Placenta accreta. Am J Obstet Gynecol 203(5):430, 2010 [PubMed: 21055510]

Society for Maternal-Fetal Medicine, Gyamfi-Bannerman C: Management of bleeding in the late preterm period. Consult Series No. 44. Am J Obstet Gynecol October 25, 2017 [Epub ahead of print]

Society for Maternal-Fetal Medicine, Pacheco LK, Saade G, et al: Amniotic fluid embolism; diagnosis and management. Am J Obstet Gynecol 215(2):B16, 2016 [PubMed: 26987420]

Society for Maternal-Fetal Medicine, Sinkey RG, Odibo AO, et al: Diagnosis and management of vasa previa. Am J Obstet Gynecol 213(5):615, 2015 [PubMed: 26292048]

Society of Thoracic Surgeons: 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 91(3):944, 2011 [PubMed: 21353044]

Solomon C, Collis RE, Collins PW: Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anesth 109(6): 851, 2012

Sosa CG, Althabe F, Belizán JM, et al: Risk factors for postpartum hemorrhage in vaginal deliveries in a Latin-American population. Obstet Gynecol 113(6):1313, 2009 [PubMed: 19461428]

Spong CY, Mercer BM, D'Alton M, et al: Timing of indicated late-preterm and early-term birth. Obstet Gynecol 118(2 Pt 1):323, 2011 [PubMed: 21775849]

Stafford IA, Dashe JS, Shivvers SA, et al: Ultrasonographic cervical length and risk of hemorrhage in pregnancies with placenta previa. Obstet Gynecol 116(3):595, 2010 [PubMed: 20733440]

Stafford PA, Biddinger PW, Zumwalt RE: Lethal intrauterine fetal trauma. Am J Obstet Gynecol 159:485, 1988 [PubMed: 3407709]

Stephenson ML, Pettit KE, Henry DE, et al: Complicated accreta: comparison of maternal and neonatal outcomes. Abstract No. 623, Am J Obstet Gynecol 214:S332, 2016

Stettler RW, Lutich A, Pritchard JA, et al: Traumatic placental abruption: a separation from traditional thought. Presented at the American College of Obstetricians and Gynecologists Annual Clinical Meeting, April 27, 1992

Stolte L, van Kessel H, Seelen J, et al: Failure to produce the syndrome of amniotic fluid embolism by infusion of amniotic fluid and meconium into monkeys. Am J Obstet Gynecol 98:694, 1967 [PubMed: 4961377]

Stramer SL, Glynn SA, Kleinman SH, et al: Detection of HIV-I and HCV infections among antibody-negative blood donors by nucleic acid–amplification testing. N Engl J Med 351:760, 2004 [PubMed: 15317889]

Stubbs JR, Zielinski MD, Jenkins D: The state of the science of whole blood: lessons learned at Mayo Clinic. Transfusion 56(Suppl 2):S173, 2016 [PubMed: 27100754]

Sun JN, Zhang BL, Yu HY, et al: Spontaneous uterine rupture due to placenta percreta during pregnancy. Am J Emerg Med 34(9):1918.e1, 2016

Swank ML, Garite TJ, Maurel K, et al: Vasa previa: diagnosis and management. Am J Obstet Gynecol 215(2):223.e1, 2016

Takeda A, Koike W, Imoto S, et al: Three-dimensional computerized tomographic angiography for diagnosis and management of intractable postpartum hemorrhage. Eur J Obstet Gynecol Reprod Biol 176:104, 2014 [PubMed: 24630300]

Tam Tam KB, Dozier J, Martin JN Jr: Approaches to reduce urinary tract injury during management of placenta accreta, increta, and percreta: a systematic review. J Maternal Fetal Neonatal Med 25(4):329, 2012

Tantbirojn P, Crum CP, Parast MM: Pathophysiology of placenta accreta: the role of decidua and extravillous trophoblast. Placenta 29(7):639, 2008 [PubMed: 18514815]

Tarney CM, Whitecar P, Sewell M, et al: Rupture of an unscarred uterus in a quadruplet pregnancy. Obstet Gynecol 121(2 Pt 2 Suppl 1):483, 2013 [PubMed: 23344417]

Thomas S, Meadows J, McQueen KA: Access to cesarean section will reduce maternal mortality in low-income countries: a mathematic model. World J Surg 40(7):1537, 2016 [PubMed: 26932877]

Tikkanen M, Nuutila M, Hiilesmaa V, et al: Prepregnancy risk factors for placental abruption. Acta Obstet Gynecol Scand 85:40, 2006 [PubMed: 16521678]

Timmermans S, van Hof AC, Duvekot JJ: Conservative management of abnormally invasive placentation. Obstet Gynecol Surv 62:529, 2007 [PubMed: 17634154]

Timor-Tritsch IE, Khatib N, Monteagudo A, et al: Cesarean scar pregnancies: experience of 60 cases. J Ultrasound Med 34(4):601, 2015 [PubMed: 25792575]

Timor-Tritsch IE, Monteagudo A, Cali G, et al: Cesarean scar pregnancy is a precursor of morbidly adherent placenta. Ultrasound Obstet Gynecol 44(3):346, 2014 [PubMed: 24890256]

Tita AT, Szychowski JM, Rouse DJ, et al: Higher-dose oxytocin and hemorrhage after vaginal delivery. Obstet Gynecol 119(2 Pt 1):293, 2012 [PubMed: 22227638]

Tola EN: First trimester spontaneous uterine rupture in a young woman with uterine anomaly. Case Rep Obstet Gynecol 2014:967386, 2014 [PubMed: 24551467]

Toledo P, McCarthy RJ, Hewlett BJ, et al: The accuracy of blood loss estimation after simulated vaginal delivery. Anesth Analg 105:1736, 2007 [PubMed: 18042876]

Towers CV, Pircon RA, Heppard M: Is tocolysis safe in the management of third-trimester bleeding? Am J Obstet Gynecol 180:1572, 1999 [PubMed: 10368505]

Treloar EJ, Anderson RS, Andrews HG, et al: Uterine necrosis following B-Lynch suture for primary postpartum haemorrhage. BJOG 113:486, 2006 [PubMed: 16553658]

Trudell A, Stout M, Cahill A, et al: Second trimester cervical length and persistence of placental previa in the third trimester. Abstract No. 91, Presented at the 33rd Annual Meeting of the Society for Maternal-Fetal Medicine, February 11–16, 2013

Twickler DM, Lucas MJ, Balis AB, et al: Color flow mapping for myometrial invasion in women with a prior cesarean delivery. J Matern Fetal Med 9:330, 2000 [PubMed: 11243289]

Ugwu IA, Oluwasola TA, Enabor OO, et al: Randomized controlled trial comparing 200µg and 400µg sublingual misoprostol for prevention of primary postpartum hemorrhage. Int J Gynaecol Obstet 133(2):173, 2016 [PubMed: 26892695]

Usta IM, Hobeika EM, Abu Musa AA, et al: Placenta previa-accreta: risk factors and complications. Am J Obstet Gynecol 193:1045, 2005 [PubMed: 16157109]

Uszyński M, Zekanowska E, Uszyński W, et al: Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in amniotic fluid and blood plasma: implications for the mechanism of amniotic fluid embolism. Eur J Obstet Gynecol Reprod Biol 95:163, 2001 [PubMed: 11301162]

Villar J, Gülmezoglu AM, Hofmeyr GJ, et al: Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol 100:1301, 2002 [PubMed: 12468178]

Vintejoux E, Ulrich D, Mousty E, et al: Success factors for Bakri balloon usage secondary to uterine atony: a retrospective, multicenter study. Aust N Z J Obstet Gynaecol 55(6):572, 2015 [PubMed: 26223852]

Walker MG, Allent L, Windrim RC, et al: Multidisciplinary management of invasive placenta previa. J Obstet Gynaecol Can 35(5):417, 2013 [PubMed: 23756272]

Wang L, Matsunaga S, Mikami Y, et al: Pre-delivery fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption. J Obstet Gynaecol Res 42(7):796, 2016 [PubMed: 27075198]

Warshak CR, Eskander R, Hull AD, et al: Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. Obstet Gynecol 108(3 Pt 1):573, 2006 [PubMed: 16946217]

Warshak CR, Ramos GA, Eskander R, et al: Effect of predelivery diagnosis in 99 consecutive cases of placenta accreta. Obstet Gynecol 115(1):65, 2010 [PubMed: 20027036]

Wehrum MJ, Buhimschi IA, Salafia C, et al: Accreta complicating complete placenta previa is characterized by reduced systemic levels of vascular endothelial growth factor and by epithelial-to-mesenchymal transition of the invasive trophoblast. Am J Obstet Gynecol 204(5):411.e1, 2011

Wei Q, Zhang W, Chen M, et al: Peripartum hysterectomy in 38 hospitals in China: a population-based study. Arch Gynecol Obstet 289(3):549, 2014 [PubMed: 23989933]

Weiner E, Miremberg H, Grinstein E, et al: The effect of placenta previa on fetal growth and pregnancy outcome in correlation with placental pathology. J Perinatol 36(12):1073, 2016 [PubMed: 27583391]

Weiss JL, Malone FD, Vidaver J, et al: Threatened abortion: a risk factor for poor pregnancy outcome, a population-based screening study. Am J Obstet Gynecol 190:745, 2004 [PubMed: 15042008]

Weiwen Y: Study of the diagnosis and management of amniotic fluid embolism: 38 cases of analysis. Obstet Gynecol 95:385, 2000

Wing DA, Paul RH, Millar LK: Management of the symptomatic placenta previa: a randomized, controlled trial of inpatient versus outpatient expectant management. Am J Obstet Gynecol 174:305, 1996

Witteveen T, van Stralen G, Zwart J, et al: Puerperal uterine inversion in the Netherlands: a nationwide cohort study. Acta Obstet Gynecol Scand 92(3):334, 2013 [PubMed: 22881867]

Wong HS, Cheung YK, Zuccollo J, et al: Evaluation of sonographic diagnostic criteria for placenta accreta. J Clin Ultrasound 36(9):551, 2008 [PubMed: 18720525]

Wong TY: Emergency peripartum hysterectomy: a 10-year review in a tertiary obstetric hospital. N Z Med J 124(1345):34, 2011 [PubMed: 22072164]

World Health Organization: WHO recommendations for prevention and treatment of maternal peripartum infections. Geneva, WHO, 2015

Worley KC, Hnat MD, Cunningham FG: Advanced extrauterine pregnancy: diagnostic and therapeutic challenges. Am J Obstet Gynecol 198:297.e1, 2008

Wortman A, Schaefer S, Wilson K, et al: Maternal morbidity associated with placenta previa with and without placental invasion. Abstract No. 601, Am J Obstet Gynecol 212(1):S299, 2015

Wright JD, Silver RM, Bonanno C, et al: Practice patterns and knowledge of obstetricians and gynecologists regarding placenta accreta. J Matern Fetal Neonatal Med 26(16):1602, 2013 [PubMed: 23565991]

Yao R, Goetziner KR, Crimmins SD, et al: Association of maternal obesity with maternal and neonatal outcomes in cases of uterine rupture. Obstet Gynecol 129:683, 2017 [PubMed: 28277366]

Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017

Yoong W, Ridout A, Memtsa M, et al: Application of uterine compression suture in association with intrauterine balloon tamponade ("uterine sandwich") for postpartum hemorrhage. Acta Obstet Gynecol Scand 91(1):147, 2012 [PubMed: 21501126]

You WB, Zahn CM: Postpartum hemorrhage: abnormally adherent placenta, uterine inversion, and puerperal hematomas. Clin Obstet Gynecol 49:184, 2006 [PubMed: 16456355]

Zahn C, Timofeev J: Uterine inversion. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017

Zeeman GG, Cunningham FG, Pritchard JA: The magnitude of hemoconcentration with eclampsia. Hypertens Pregnancy 28(2):127, 2009 [PubMed: 19437224]

Zelop CM: Postpartum hemorrhage. Becoming more evidence-based. Obstet Gynecol 117(1):3, 2011 [PubMed: 21173639]

Zetterstrom K, Lindeberg SN, Haglund B, et al: Maternal complications in women with chronic hypertension: a population-based cohort study. Acta Obstet Gynecol Scand 84:419, 2005 [PubMed: 15842204]

Zhang E, Liu L, Owen R: Pelvic artery embolization in the management of obstetrical hemorrhage: predictive factors for clinical outcomes. Cardiovasc Intervent Radiol 38(6):1477, 2015 [PubMed: 25876518]

Zuckerbraun BS, Peitzman AB, Billiar TR: Shock. In Brunicardi FC, Andersen DK, Billiar TR, et al (eds): Schwartz's Principles of Surgery, 9th ed. New York, McGraw-Hill, 2010

Zwart JJ, Richters JM, Öry F, et al: Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. BJOG 115:842, 2008 [PubMed: 18485162]