Pregnancy-Associated Bleeding

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Introduction and Background

Bleeding is a leading cause of maternal mortality worldwide, second only to preexisting medical conditions such as cardiovascular disease or chronic hypertension [1]. In the United States, approximately 11% of maternal deaths are due to obstetrical hemorrhage [2], and although the number of deaths in developed countries has declined in the last two decades [3], hemorrhage remains a leading *preventable* cause of maternal mortality worldwide. Lack of adequate postpartum monitoring and lack of early, appropriate response to signs and symptoms of hypovolemia have been cited in 66–73% of deaths due to pregnancy-associated bleeding [3, 4]. For every woman who dies due to bleeding, nearly ten others suffer serious major morbidity [1], underscoring both the risks inherent in pregnancy and the need for improved planning and multidisciplinary response for women when bleeding occurs.

Physiologic Changes in Pregnancy

With the exception of fetal and neonatal growth and development, there is no other time during a woman's life in which such marked physiologic changes occur as during pregnancy and the postpartum period. Virtually every major organ system adapts to allow the female body to host a semi-allogenic fetus (or fetuses in the case of multiple gestations) and to meet the demands of providing nutrients and oxygen necessary for fetal growth, of providing respiration and removal of metabolic waste from the fetus, and of preparing the mother for childbirth. Those changes that directly affect obstetrical hemorrhage are discussed below.

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Cardiovascular System, Red Blood Cells, and Circulating Blood Volume

Significant remodeling of the maternal cardiovascular system begins as early as the first trimester. The left ventricular mass increases slightly, mainly due to increased wall thickness, with only little or no change in the ventricular cavity size [5]. Cardiac output (CO) begins to increase as early as 8–11 weeks of pregnancy, from approximately 6.7 ± 0.9 L/min to 8.7 ± 1.4 L/min at 36–39 weeks of gestation, and returns to pre-pregnancy levels by 12 weeks postpartum [5]. This occurs with only up to 21% decrease in systemic vascular resistance (SVR) [5, 6], primarily through a progressive increase in heart rate (HR) and stroke volume (SV). Recall that:

$$CO = SV \times HR \qquad (12.1)$$

It is common for a woman's heart rate to approach 95–100 beats per minute (bpm) in a normal pregnancy. A heart rate of 120 or above is almost always abnormal and warrants investigation for a pathologic cause of tachycardia [7].

Blood Volume

Circulating white and red blood cell volumes both gradually increase, due to increased hematopoiesis and erythropoietin activity [8]. Although red blood cell volume increases by approximately 32%, total blood volume increases by approximately 48% [9]. This relatively greater increase in plasma leads to a physiologic anemia and mild decrease in platelets at term and also results in decreased blood viscosity, which may permit improved perfusion. The total blood volume increases from 3250 mL to 4820 mL [9], which provides sufficient reserve to allow a woman to lose a physiologic volume of blood at delivery without cardiovascular compromise. Higher volumes of blood loss at delivery are required before signs of advanced hemorrhagic shock are evident, compared to a woman in the non-pregnant state. Should decompensation occur, however, it may occur more precipitously. While

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sudden, rapid bleeding may alert the clinician and care team to the risk of hemorrhagic shock, slow, steady, or intermittent bleeding can be equally hazardous should large cumulative losses occur that go unnoticed until vital signs show clear evidence of hemodynamic compromise.

Uterine Blood Supply

The growing fetus requires an ample, consistent supply of oxygen and nutrients, and the maternal circulation acts as the waste removal system for the fetus. As pregnancy progresses, blood flow to the uterus comprises an increasing percentage of total cardiac output, with up to 500–700 mL/min of blood flowing through the uterine arteries at term [10]. Rich collateral blood supply from cervical branches of the uterine arteries and ovarian vessels ensures adequate perfusion and can also be a source of profound bleeding. This can occur whenever the uterus fails to adequately contract after delivery, leaving venous sinuses open to ooze. Postpartum hemorrhage may result from significant lacerations of the uterus, cervix, or vagina or if uterine vessels become injured at the time of cesarean or vaginal delivery. During a normal vaginal delivery, blood loss is approximately 500–700 mL, and up to 1000 mL with cesarean delivery, but can be significantly higher when complications arise.

Respiratory System

During pregnancy, functional residual capacity decreases due to upward displacement of the diaphragm by the growing fetus. The respiratory rate remains constant, but under the influence of circulating progesterone, minute ventilation increases by 30–50% due to an increase in tidal volume [11]. This leads to a mild physiologic respiratory alkalosis [12], with a normal arterial pH of 7.44 in pregnancy, compared to 7.40 in the non-pregnant state. The kidney partially compensates by increasing excretion of bicarbonate ions, which then results in a serum bicarbonate concentration closer to 18–22 mEq/L during pregnancy [13]. These changes facilitate gas exchange between mother and fetus and are important to recognize when treating hemorrhagic shock. Arterial blood gases in a pregnant patient may appear relatively normal in a pregnant patient in the early stages of acidosis, if the physiologic norms in pregnancy are not considered. In other words, if maternal arterial blood gas values are consistent with acidosis using non-pregnant values, the pregnant or newly delivered patient is most certainly acidotic.

Coagulation Factors

Bleeding after delivery of the placenta is universal; the increase in maternal blood volume and red cell expansion buffer losses from normal postpartum bleeding. Additionally, there are significant alterations in circulating coagulation factors during pregnancy that further mitigate the risk of postpartum hemorrhage. Specifically, there are marked increases (20–1000%) in circulating levels of factors VII, VIII, IX, X, and XII and von Willebrand factor [14]. Fibrinogen levels increase throughout pregnancy and particularly just prior to delivery [15]. In addition to increased hypercoagulability, fibrinolytic activity decreases due to increases in plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) [14, 15].

Any underlying inherited or acquired deficiency in coagulation factors and von Willebrand factor predisposes the pregnant patient to an increased risk of peripartum hemorrhage. Conversely, obstetrical hemorrhage alone can quickly lead to disseminated intravascular coagulopathy (DIC), particularly in the setting of massive hemorrhage, when blood loss is sufficient to cause hypofibrinogenemia. This may occur in the setting of moderate bleeding in which intravascular resuscitation is limited to the use of large volumes of crystalloid or red blood cells only, leading to a dilutional effect of factors essential to coagulation. Erez and colleagues [15] illustrated this phenomenon in their efforts to modify the International Society on Thrombosis and Hemostasis DIC score to account for changes in pregnancy. Within their cohort of 19,889 women with 24,693 deliveries, the authors found a rate of DIC of 0.35%. They found that prolongation of the prothrombin time (PT), low platelet count, and low fibrinogen significantly increased a patient's risk of progression to DIC and a fibrinogen level of <3.0 g/L conferred the highest relative risk (59.0) [15]. Low fibrinogen levels are one of the earliest identifiable laboratory changes in the setting of obstetrical hemorrhage, with a drop in fibrinogen often preceding PT prolongation, making this a clinically useful parameter for evaluation of and monitoring for treatment of DIC.

Special Considerations

Preeclampsia is characterized by hypertension (defined as systolic blood pressure of 140 mmHg or greater, diastolic of 110 mmHg or greater) developing after 20 weeks of gestation and is variably associated with multi-organ dysfunction, including renal dysfunction resulting in proteinuria or oliguria; liver dysfunction or injury; and capillary leakage, resulting in peripheral, pulmonary, and/or cerebral edema [16]. In women who develop preeclampsia, the physiologic expansion of blood volume may not occur, and even in the presence of marked edema, the intravascular volume is relatively diminished, making women with preeclampsia particularly susceptible to hemorrhagic shock.

Deterioration may occur at lower volumes of blood loss, relative hypotension resulting from hemorrhage may appear to be in the normotensive range, and it may be difficult to

determine whether oliguria is due to ongoing preeclampsia or blood loss. Women with preeclampsia should be monitored closely for signs and symptoms of occult blood loss whenever hypertension resolves rapidly, especially if an operative delivery is performed. Paradoxically, women with preeclampsia may be more susceptible to volume overload, pulmonary edema, and acute lung injury secondary to resuscitation and transfusion due to capillary endothelial cell injury.

HELLP syndrome is defined as hemolysis, elevated liver enzymes, and low platelets. A hallmark of HELLP is thrombocytopenia (platelet count less than 100,000/mm^3). Accompanying liver dysfunction can result in coagulopathy due to lack of synthesis of coagulation factors. Liver capsule hematoma formation can add to the risk for morbidity and mortality. Frequent laboratory evaluation, including coagulation factors and fibrinogen, is recommended whenever HELLP is suspected.

Bleeding in the Antenatal Period

Conditions in pregnancy associated with bleeding are listed in Table 12.1, but the most common will be discussed below.

First and Early Second Trimester Bleeding

Ectopic Pregnancy

Bleeding from ectopic pregnancy is a leading direct cause of pregnancy-related death during the first trimester [2]. Ectopic pregnancies, defined as embryo implantation outside the intrauterine cavity, occur in 1.2–1.4% of all pregnancies and develop 95.5% of the time within the ampulla of the fallopian tube [17]. Ectopic pregnancy may also present in the cervix, cesarean scar, uterine cornua, or outside the uterine cavity, implanted on intraabdominal structures. The risks of death from ruptured ectopic pregnancy appear to be declining in developed countries due to improvements in early diagnosis and management [18, 19], but still account for up to 80% of deaths in early pregnancy [17].

In ectopic pregnancy, the growing embryo may outgrow the confines of the tissue into which it implants, causing rupture of the structure and bleeding [20]. This may occur after attempts at conservative or medical management. In some cases, bleeding consists of slow, consistent oozing which may present with no or relatively mild symptoms such as non-specific abdominal pain with only a mild drop in hemoglobin and lack of visible intrauterine pregnancy on ultrasound, despite a serum β-hCG level above the discriminatory zone at which an intrauterine pregnancy should be readily seen (usually 1000–2000 IU/L) [20]. Left untreated this can progress to frank rupture with profound blood loss, hypovolemic shock, and DIC. In other cases, rupture is more rapid and may lead to a more pronounced presentation of symptoms when blood loss occurs acutely.

Medical management with methotrexate is a reasonable first-line option in women without evidence of active bleeding and low serum β-hCG level. In cases in which significant bleeding has occurred or is ongoing, surgery – laparoscopic or open – is required [21]. The intraabdominal cavity can hold up to 1–2 liters of blood and clot, and preparation for adequate blood and blood product replacement to prevent the development or worsening of DIC is essential.

Molar Pregnancy

A molar pregnancy arises when a triploid zygote implants and develops. The pregnancy is considered a *complete mole* when there are no embryo and no normal placental tissue and all three sets of chromosomes are parental in origin. A *partial mole* may contain an embryo/fetus and some normal

Table 12.1 Pregnancy-specific conditions associated with postpartum hemorrhage

First trimester	Special considerations
Ectopic pregnancy	May rupture after medical management Surgery definitive treatment
Spontaneous (especially septic) abortion	
Hemorrhagic cyst	
Spontaneous hemoperitoneum	Rare-associated with endometriosis, abdominal vessel aneurysms
Second/third trimesters	
Abruption	More common in 2nd trimester than 3rd, usually associated with pain and/or contractions
Trauma	With or without abruption
Placenta previa	Usually painless
Placenta accreta/increta/percreta	
Intra-/primary postpartum	
Abruption	May present acutely
Placenta previa	
Placenta accreta/increta/percreta	Massive blood loss frequent
Uterine atony	Approx. 80% of postpartum hemorrhage
Genital tract lacerations	
Uterine inversion	Associated with bleeding and vasovagal shock
Uterine rupture	Associated with vaginal birth after cesarean, rarely occurs spontaneously
Amniotic fluid embolism	Catastrophic
Delayed postpartum	
Retained products of conception	Required dilatation and curettage
Subinvolution of the placental bed	May present 3–4 weeks postpartum

placental tissue combined with abnormal placental tissue, and the tissue consists of one set of maternal chromosomes and two paternal sets of chromosomes. Fetal growth restriction and a thick, hydropic placenta are seen later in pregnancy, and women pregnant with a partial mole may develop symptoms that mimic preeclampsia or hyperthyroidism. Bleeding is the most common presentation [22]. Treatment often consists of dilatation and curettage. At the time of uterine evacuation, heavy bleeding may ensue, and preparations should be made for appropriate blood product replacement.

Second and Third Trimesters

Bleeding occurs far less frequently in the second trimester than in the first or third trimesters. Once in the second trimester, the risk of spontaneous abortion or likelihood that an ectopic pregnancy is ongoing is markedly lower than in the first. The overall rate of preterm birth has declined from 12.8% of all births in the United States in 2006 to 11.4% in 2013 with evidence-based interventions [23]; therefore, bleeding associated with preterm labor and delivery may occur in the second trimester which comprises a far smaller proportion of cases compared to those that occur later in the third trimester. The most common etiologies of bleeding in the second and third trimesters are discussed below.

Placental Abruption and Placenta Previa

Placental abruption, when part or all of the placenta separates from the uterine wall prior to delivery of the fetus, occurs in approximately 0.6–1% of all pregnancies [24]. The incidence of abruption is highest at 24–26 weeks of gestation and declines slowly as pregnancy advances [24]. Dozens of risk factors for abruption have been identified. Hypertension – whether due to chronic disease, preeclampsia, or substance abuse, particularly smoking and amphetamine and cocaine use – is associated with a 1.5- to 5-fold increased odds of abruption. Perturbations of amniotic fluid levels, including oligohydramnios, polyhydramnios, and preterm premature rupture of membranes (PPROM), increase the risk of placental separation, as does inflammation caused by chorioamnionitis.

Trauma is among the leading causes of placental abruption. Abruption complicates up to 50% of major trauma and 1–5% of minor injuries such as a fall not involving the abdomen. Both a direct "shearing" stress between utero-placental interface and subsequent tensile or "countercoup" effect may occur. Forward displacement of the uterus creates negative pressure due to differential elasticity of the uterus and placenta, further increasing the risk of placental separation and bleeding [25, 26]. Pregnant women of 20 weeks of gestation or later should be monitored for a minimum of 4 h after trauma or for 24–48 h or more, if contractions, vaginal bleeding, maternal tachycardia, or fetal heart rate decelerations occur [27]. Continuous fetal heart rate monitoring and tocodynamometry of uterine activity are more sensitive than use of ultrasound [28].

Fetomaternal hemorrhage occurs 4–5 times more frequently when a woman suffers a traumatic injury; therefore, any Rh-negative woman should have Kleihauer-Betke testing and Rh immunoglobulin administered as needed to prevent isoimmunization [28].

Abruption may present subtly with chronic, slow amounts of bleeding that do not cause immediate maternal or fetal compromise, but may remain stable and manageable with close monitoring. In other cases, abruption presents acutely, sometimes catastrophically. Significant abruption may be *concealed*, if retro-placental bleeding occurs, but does not cause separation of the placental edges, from which blood can be allowed to escape vaginally, especially if accompanied by pain, contractions, or fetal heart decelerations. Coagulopathy, particularly hypofibrinogenemia, is common in cases in which a mother presents with intrauterine fetal demise due to complete abruption or when slow, steady bleeding accumulates. In these cases, early utilization of fibrinogen-containing products including fresh frozen plasma (FFP) and cryoprecipitate in addition to red blood cells (RBCs) is essential.

Placenta previa complicates approximately 1 in 200 births, and occurs when all or part of the placenta covers the internal cervical os [29], and is associated with an approximate 10-fold risk of antepartum bleeding [30]. Planned cesarean delivery is recommended in cases of placenta previa, but in cases in which the placental edge is low-lying, defined as <20 mm from the internal os, vaginal delivery may be considered, but an increased risk of bleeding remains. In 1 study of 98 pregnancies with low-lying placenta, defined as placental distance within 20 mm of the os, bleeding necessitating cesarean delivery occurred in 25% of patients, and 43% of women developed postpartum hemorrhage [31]. Even among women undergoing elective cesarean delivery, presence of placenta previa significantly increased the risks of postpartum hemorrhage (OR 1.91, 95% CI 1.74 to 2.09), blood transfusion (OR 4.39, 95% CI 3.76 to 5.12), and hysterectomy (OR 39.7, 95% CI 22.42 to 70.3) [32]. Additionally, placenta previa is one of the major risk factors for placenta accreta spectrum disorders, including placenta accreta, increta, and percreta, especially in women with prior cesarean deliveries (see Sect. 11.4.3) [33].

Postpartum Hemorrhage

Postpartum hemorrhage is classified as *primary*, when it occurs within the first 24 h after delivery and is most commonly due to uterine atony, reproductive tract injury such as

lacerations, hematoma formation, uterine inversion, or coagulopathy. *Secondary* postpartum hemorrhage occurs between 24 h and 6–12 weeks postpartum and is more commonly associated with retained products of conception, subinvolution of the placental site, infection, or inherited coagulation disorders such as von Willebrand disease [34]. During active bleeding, anticipation of the next steps in management is essential. Transfusion and identification/control of the source(s) of bleeding often must occur concomitantly. Although estimated blood loss of 500 mL for vaginal delivery and 1000 mL for cesarean delivery have been used to define postpartum hemorrhage and are practical guidelines, in actuality, some women may have blood loss up to 700 mL after vaginal delivery and up to 1200 ml after cesarean without significant physiologic detriment. For this reason, the American College of Obstetricians and Gynecologists now defines postpartum hemorrhage as "a cumulative blood loss of greater than or equal to 1000 mL, or blood loss accompanied by signs or symptoms of hypovolemia within 24 h after the birth process" [35].

Blood loss is most readily estimated either visually or by weighing pads and measuring accessible volumes in collection bags/containers, but is underestimated up to 50% of the time, regardless of the level of training and experience of providers deriving the estimates. Careful attention to vital signs, clinical signs, and urine output are essential in recognition and monitoring of hemorrhagic shock. Laboratory values may guide therapy, but may be misleading in the setting of early or active hemorrhage, before a patient equilibrates. Continual or unrecognized losses may contribute to or exacerbate coagulopathy.

Planning and preparation for postpartum hemorrhage ideally begins early in pregnancy. Early identification of preexisting conditions such as von Willebrand disease or immune thrombocytopenia allows ample time for consultation with a hematologist and/or transfusion medicine specialist and for delivery planning. Other conditions that increase risks for postpartum hemorrhage or the need for transfusion include iron deficiency anemia, multiple gestations, and abnormal placentation, such as with placenta previa or the placenta accreta spectrum [35]. While not all underlying conditions can be prevented, risk stratification can identify which patients may benefit from having typed and cross-matched blood ordered and available upon admission for delivery and whether additional resources should be in place for hemorrhage control.

Uterine Atony

Approximately 80% of primary postpartum hemorrhage is due to uterine atony or the failure of the uterus to become firm and contracted after delivery [36]. Risk factors for uterine atony include any condition that increases intrauterine volume, such as large fetal size, multifetal gestation, or polyhydramnios; chorioamnionitis; multiparity; history of atony; and prolonged labor, particularly after induction, and operative delivery [34]. Active management of the third stage of labor includes prophylactic use of uterotonics and delivery of the placenta by use of gentle, controlled traction on the umbilical cord while manually supporting the uterus from the abdomen. Active management of the third stage has been shown in two large trials to reduce the incidence postpartum hemorrhage by approximately 10% compared to expectant management [37, 38].

First-line management of uterine atony includes bimanual uterine massage (elevation of the uterus and cervix with a vaginal hand, combined with transabdominal pressure on the fundus and use of uterotonics (Table 12.2)). Oxytocin is the preferred agent in developed countries; however, it must be stored at 4 °C to maintain its efficacy and is given intravenously or intramuscularly. Misoprostol tablets are shelf stable for several years if kept dry, even in warm climates, and can be administered sublingually, buccally, or per rectum and therefore may be an alternative agent for use in low-resource settings [39–41]. Second-line agents such as methylergonovine (Methergine) or 15-methyl PGF2α may be needed. Should medical management fail to stop bleeding, the cervix and vagina should be inspected for lacerations needing repair.

Secondary therapy includes mechanical uterine tamponade with an inflatable balloon, such as the SOS Bakri™

Table 12.2 Commonly used uterotonic medications

Medication	Dose	Route	Precautions
Oxytocin	10 milliunits	IM	
	0.5–40 milliunits/min	IV	Avoid rapid IV infusion – may cause hypotension, hyponatremia
Methylergonovine (Methergine)	200 μg	IM, IV May repeat every 2–4 h	Avoid in patients with hypertension
	200 μg	Oral, 3–4 × daily up to 7 days	
Carboprost (Hemabate)	250 μg, may repeat at 1.5–3.5 h intervals, do not exceed 12 mg total dose or continuous administration >2 days	IM	Causes bowel motility Avoid in patients with asthma

(Cook, Spencer, IN, USA) or Ebb™ (Glenveigh, Chattanooga, TN, USA) balloons, which are specifically designed for intrauterine tamponade, or with a Sengstaken-Blakemore tube, Foley catheter, or condom secured to a straight catheter, placed within the intrauterine cavity, and filled with sterile saline. Packing with gauze can also effectively temporize bleeding long enough to correct coagulopathy and sometimes enough to avoid further intervention [42–44]. Reported success rates with balloon tamponade range between 65 and 100% [45, 46].

Should the above methods fail, the next step is surgical intervention. The definitive management of postpartum hemorrhage is hysterectomy; however, many affected women desire future fertility. Sequential vascular ligation of the uterine blood supply, including the bilateral uterine arteries and infundibulopelvic ligaments, reduces perfusion pressure to the uterus and placental bed. Compression sutures, such as B-Lynch [47] and Hayman [48] Cho (square) [49] sutures, physically brace a uterus that is manually compressed, by compressing the anterior and posterior uterine surfaces and by reducing the open spaces within the cavity. Success rates with use of compression sutures range between 76 and 100%, with a decreased rate of success when placement of the sutures was delayed by 2–6 h after delivery [50]. Ultimately, hysterectomy may be necessary as a definitive measure to stop bleeding.

Novel hemostatic agents have come to market serve as adjunctive measures to facilitate hemostatic control on the battlefield and trauma surgery and have increasingly been used for obstetrical hemostasis [51, 52]. These include items such as "trauma gauze" or laparotomy sponges infiltrated with chitosan (Celox Gauze™, MedTrade Products Ltd., Crewe, UK) or kaolin (QuikClot®, Z-Medica, Wallingford, CT, USA). These impregnated gauze products not only provide a source for hemostatic compression with the sponge, but the additional agents also activate the clotting cascade and activate clot formation without causing thermal reactions. Improvements in rotational thromboelastometry measures of clot formation and integrity have been demonstrated *in vitro* with the use of chitosan- or kaolin-impregnated gauze [53]. Cellulose mesh, collagen or gelatin foam, and microfibrillar collagen powders have long been available as hemostatic agents and provide a lattice upon which a clot may form (including, but not limited to, Surgicel®, Surgifoam®, and Surgiflo®, Ethicon US, LLC; AviteneTM, BD Bard, Warwick, RI, USA; Gelfoam®, Pfizer, NY, USA). A novel cellulose mesh product containing powdered thrombin and fibrinogen has been developed (Evarrest®, Fibrin Sealant Patch, Ethicon US, LLC) and used to control bleeding by forming an patch-like "clot" in areas difficult to suture. The fibrin sealant patch been shown to be cost-effective and easy to use for hemostatic control in areas not amenable to suture control; the design of the patch to be left internally gives it a potential advantage over trauma gauze, which must be removed prior to intracavitary closure [54–56].

The Placenta Accreta Spectrum (PAS): Placenta Accreta/Increta/Percreta

The placenta accreta spectrum (PAS) includes the various forms of placental invasion into or through the myometrium including placenta accreta, increta, and percreta. PAS affects between 1 in 533 [33] and 1 in 731 [57] pregnancies based on data from large, multi-center studies in the United States but may be lower, based on population-based national surveillance data. The United Kingdom Obstetric Surveillance System identified a rate of 1.7/10,000 maternities between 1 May 2010 and 30 April 2011 [58]. The Nordic Obstetrical Surveillance System identified 4.6/10,000 deliveries [59], and in Canada the most recent incidence is 14.4/10,000 deliveries [60].

The risk for a woman to have a placenta accreta spectrum disorder correlates with the number of prior cesarean deliveries (OR = 7 [95% CI 4.4–9.8] after 1 cesarean, OR = 55.9 [95% CI 25–110] after 3 or more cesareans), especially in the presence of placenta previa (OR = 292 [95% CI 196–40) [59]. Other risk factors include advanced maternal age, smoking, and other uterine surgery, such as myomectomy or septum revision, and in vitro fertilization, with a particularly high risk of invasion with cryopreserved embryos [58].

Cesarean hysterectomy is the definitive surgical treatment of PAS; however, increasingly conservative interventions have been employed, with an attempt to leave all or a majority of the uterus intact. Such measures include use of intrauterine balloon tamponade, partial myometrial resection along areas of invasion, intra-arterial balloon occlusion, and sequential devascularization [61]. Conservative management offers an alternative for women who are strongly motivated to preserve the uterus; however, in one of the most comprehensive reviews of case series in which patients with placenta accreta were managed conservatively, 58% of parturients required a delayed hysterectomy due to infection, hemorrhage, or DIC, in some cases as long as 9 months after delivery [62].

Massive hemorrhage at the time of delivery for PAS is common, with a mean estimated blood loss ranging between 4 and 7.5 liters, but may far exceed this in extreme cases [33, 63–65]. In 1 study of 66 patients with PAS, transfusion was required in 95% of patients, with mean RBC use of 10 +/− 9 units, with 11% of patients requiring 20 or more RBC units [66]. The invasive placenta often bulges out into the confined spaces of the pelvis, obstructing visualization and easy access to the uterine arteries. Additionally, placental invasion promotes abundant, irregular neovascularization – immature vessels that are a potential source of bleeding (Fig. 12.1).

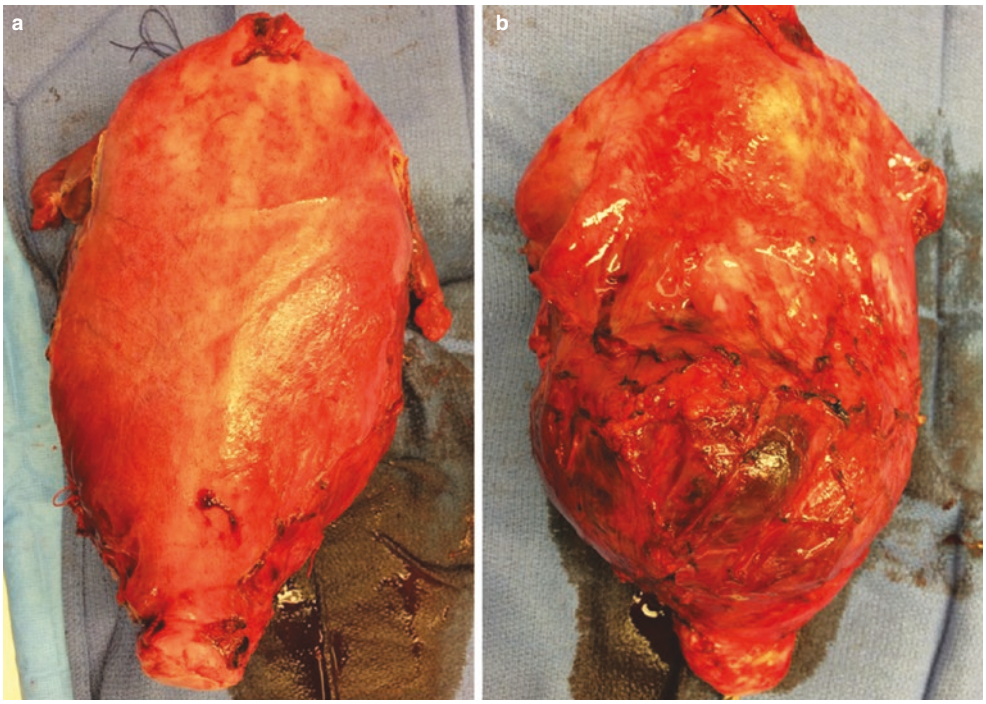

Fig. 12.1 Panel a: Normal, posterior uterine surface. Panel b: Anterior uterine with placenta accreta. Note the bulging placental tissue, covered by tortuous, irregular neovascularization

Any disruption of the placental surface can lead to torrential hemorrhage. Antenatal diagnosis and proper preparation; experienced, multidisciplinary team support; and avoidance of removal of the placenta have been shown to reduce mean estimated blood loss [65, 67]. Still, the rate of massive transfusion in PAS cases remains significant, and the early availability of blood and blood products in 1:1:1 or 2:1:1 ratio of RBC:FFP:PLT is essential to optimal outcomes [33].

Amniotic Fluid Embolism

Perhaps one of the most dreaded complications of pregnancy is amniotic fluid embolism (AFE), which occurs in approximately 1 in 40,000 deliveries [68]. AFE results from a maternal systemic, anaphylactoid reaction to exposure to multiple fetal antigens during delivery that trigger a cascade of responses, including initial pulmonary and systemic hypertension, followed by left ventricular depression, acute systemic hypotension, hypoxia, cardiac arrest, and fulminant, consumptive DIC. The maternal death rate is approximately 40–60% [68], and of survivors, only approximately 15% remain neurologically intact [69]. Amniotic fluid embolism occurs classically during delivery or within 30 min postpartum. The onset of symptoms is usually brisk and unpredictable. Emergent release and administration of group O Rh-negative or type-specific RBCs, plasma, and cryoprecipitate is essential to resuscitation efforts and should occur concomitantly with airway management, circulatory support, and hemorrhage control.

Massive Transfusion Protocols

Development and utilization of clear, easy-to-use massive transfusion protocols are a systems-level means to facilitate early blood product replacement when needed in obstetrical units, by providing a pathway for emergency release of blood and blood products, and sustained availability of blood until hemostasis is achieved. Use of 1:1:1 or 1.5:1:1 RBC:FFP:PLT ratios has been most widely studied in trauma settings and shown to reduce mortality due to hemorrhage [70–72]; however, obstetrical hemorrhage and trauma are similar in volume and likely in pathophysiologic mechanisms [73].

The American College of Obstetricians and Gynecologists has developed an Obstetrical Hemorrhage Safety Bundle that states “in order to provide safe obstetric care institutions must: have a functioning Massive Transfusion Protocol (MTP), have a functioning Emergency Release Protocol (a minimum of 4 units of O-negative/uncrossmatched RBCs), have the ability to obtain 6 units RBCs and 4 units FFP (compatible or type specific) for a bleeding patient, and have a mechanism in place to obtain platelets and additional products in a timely fashion” [74].

The availability of FFP is especially important, as low fibrinogen levels are a hallmark of acute obstetrical hemorrhage and the best early marker for severity of hemorrhage. In 1 prospective, population-based study of 106 maternity units in France, 738 women developed postpartum hemorrhage (PPH), defined as blood loss exceeding 500 mL in the first 24 h after delivery. Fibrinogen levels were checked at the time of diagnosis of PPH, with an initial mean value of

420 mg/dL in women without severe hemorrhage, but of 340 mg/dL for the 323 women who developed severe hemorrhage, defined as requiring embolization, uterine artery ligation, hysterectomy, transfusion, or transfer to intensive care. Women whose fibrinogen levels were between 200 and 300 mg/dL, which is considered normal outside of pregnancy, had a significantly increased risk for severe hemorrhage. This risk increased 12-fold when the fibrinogen levels dropped below 200 mg/dL [75]. Similarly, in a separate study, the positive predictive value for severe postpartum hemorrhage approached 100% when the fibrinogen level is less than 200 mg/dL [76].

Prospective Therapies/Management

Currently, the standard of care is to replace blood components early and aggressively for resuscitation. Some experts propose that goal-directed transfusion, using guidance by newer technologies such as thromboelastography (TEG™) and rotational thromboelastometry (ROTEM™), may allow rapid results [77, 78] and targeted resuscitation while minimizing use of blood products.

The use of adjunctive or alternative therapies such as recombinant activated factor VII (rFVIIa), factor concentrates, or fibrinogen concentrates for obstetrical hemorrhage is not standard, but has been reported. In one multi-center randomized controlled trial, rVIIa was shown to reduce the number of patients who needed secondary therapies including surgical intervention or transfusion, in about 1 in 3 patients, but with 1 in 20 patients developing non-fatal thrombotic events [79]. This product remains very expensive and only works in the presence of adequate fibrinogen, necessitating adequate transfusion of FFP or cryoprecipitate.

Use of fibrinogen concentrates in the setting of postpartum hemorrhage appears promising in the setting of hypofibrinogenemia [80]. Fibrinogen concentrate use has not proven to reduce the total estimated blood loss or total volume of transfusion if given in patients with normal or slightly altered fibrinogen levels(at or above 200–300 mg/dL) or with the FIBTEM A5 (amplitude of the alpha angle at 5 min) >12 mm (considering a normal A5 >15 mm) [81]. More data is needed before strong recommendations can be made for the routine use of fibrinogen concentrates in the setting of obstetrical hemorrhage.

Conclusion

Early recognition of obstetrical hemorrhage, starting with risk assessment of every patient, prior planning, and prompt attention to and treatment of the patient, including the utilization of massive transfusion protocols, are key to optimal patient outcomes in pregnancy-related hemorrhage. Ongoing efforts to curtail pregnancy-associated hemorrhage are crucial to reduce preventable obstetrical morbidity and mortality.

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