A 27-year-old patient with a history of 3 previous cesarean sections presents for her fetal anatomy scan at 22 weeks. On ultrasound (US) examination, an anterior placenta previa is noted with multiple lacunae and attenuation of the retroplacental space.

Hemorrhagic shock is the most common form of shock encountered in obstetric practice. In 2005, in the United States, hemorrhage was the third leading cause of maternal death because of obstetric factors.1

Historically, the most frequent indication for a peripartum hysterectomy has been uterine atony. Recent literature suggests that this indication may be shifting, with abnormal placentation becoming the most common reason for peripartum hysterectomy.2,3 The incidence of placenta accreta is estimated at 1 in 533 pregnancies.4 With the increasing cesarean section rate as well as a decrease in vaginal birth after cesarean section, this number is likely to increase in the future.

In this article, we will address some of the new concepts in the medical management of obstetric hemorrhage. We will focus on a theoretical case of placenta accreta; however, many of the therapeutic recommendations apply to any cause of massive obstetric bleeding.

Antepartum care

In the vast majority of cases, placenta accreta may be presumptively diagnosed on the basis of US alone. Sonographic findings suggestive of accreta include the presence of placental lacunae giving a “Swiss cheese” appearance, loss of the normal retroplacental hypoechoic space, and increased vascularity within uterine wall vessel invasion as noted by the use of color Doppler.

In recent years, there has been increased interest in the use of magnetic resonance imaging (MRI) for the evaluation of patients with suspected placenta accreta because it can provide information on depth of invasion and may be particularly useful in the diagnosis of posteriorly located placertas.

MRI findings suggestive of placenta accreta include lower uterine bulging, heterogeneous placenta, and dark intraplacental linear bands on T2-weighted images.6

In a multicenter retrospective study, Dwyer et al7 compared the accuracy of both US and MRI in the diagnosis of placental accretism. The sensitivities for the diagnosis of placenta accreta with US and MRI were 93% and 80%, respectively. Specificities (negative study in the absence of the condition) were 71% and 65%, respectively. Neither difference achieved statistical significance. The accuracy for the diagnosis may be increased by complementing the abdominal US with transvaginal sonography.9

The use of paramagnetic contrast media in MRI (gadolinium) likely would improve the diagnostic performance of MRI; however, the agent crosses the placenta, and the effects on the fetus are unknown.

At present, it appears that the diagnostic abilities of both US and MRI are similar. In cases where the diagnosis is unclear, MRI and US may be used as complementary tests.8

In patients with suspected placenta percreta, we recommend a complementary MRI to better define the extent of invasion to adjacent organs (eg, bladder, bowel) so that appropriate preoperative planning may be undertaken (eg, placement of ureteral stents).

Once the diagnosis is suspected, patients should receive iron and/or folic acid as needed to maintain normal hemoglobin values. Occasionally, patients may require recombinant erythropoietin as adjuvant therapy. Patients should ideally be referred to a center with a multidisciplinary team available, including maternal fetal medicine, general surgery, urology, vascular surgery, interventional radiology, blood bank, and neonatology.

Maternal morbidity is reduced in women with placental accretism who deliver in tertiary care centers.9

Recent evidence questions the need for serial fetal growth USs in the setting of placenta previa without accretism, as...
Intrapartum interventions

When massive blood loss is expected, one question that comes to mind frequently is which anesthetic technique should be used. A complete sympathetic block (eg, spinal anesthesia) could impair the patient’s ability to cope with sudden hypovolemia, as the capacity to vasoconstrict and increase systemic vascular resistances will be limited. However, regional anesthesia with a continuous epidural technique is safe and may be appropriate for patients with placental accretion.14,15 Emergent situations, with active bleeding, particularly if surgical access to the upper abdomen is needed, may be better served with general anesthesia.

Acute normovolemic hemodilution (ANH) may be undertaken in the operative room before starting cases presumed to be at high risk of bleeding. A central line is placed, and blood is collected from the patient into citrated blood bags from the blood bank. Patients should have a hemoglobin level above 10 g/dL and no history of cardiovascular disease. On average, 500-1000 mL whole blood may be collected and concurrently replaced with either colloid (1:1 ratio) or crystalloid (3:1 ratio) to maintain hemodynamic stability. During surgery, any blood loss will have a lower red cell content. Once surgical bleeding is controlled, the patient is given back the blood previously collected. The collected blood may be stored at room temperature for up to 6 hours.11 This technique is acceptable to some Jehovah’s Witnesses as long as the collection bag remains connected to the central venous line at all times (avoid “circuit” disconnections). Overall, there is minimal evidence to suggest that ANH alone has a significant effect on the need for allogeneic blood.11

Preoperative bilateral common iliac artery balloon catheter placement with inflation after delivery of the fetus has been reported. Theoretically, balloon inflation leads to bilateral vessel occlusion, limiting blood loss. The efficacy of the latter approach has been questioned.16,17 Another option involves preoperative placement of femoral access by interventional radiology with selective embolization of uterine vessels at the time of delivery using polyvinyl alcohol, gel foam, or coils.18

In our institution, the use of balloon occlusion catheters in the pelvic circulation did not reduce transfusion requirements compared with historic controls.19 We do not use this technique.

Intraoperative cell salvage has been successfully used in obstetric hemorrhage. Blood is aspirated from the surgical field and filtered into a collecting reservoir. Filters in the device will remove molecules like tissue factor, alpha fetoprotein, platelets, and circulating procoagulants.20 After filtration, packed red cells concentrated to a hematocrit of 55-80% are obtained and can be readministered to the patient.

Postoperatively, patients who are Rh negative should receive anti-D immunoglobulin as soon as possible with a dose given according to results of a Kleihauer Betke stain to prevent alloimmunization.11 A theoretical concern with the use of the cell saver in obstetrics is the occurrence of iatrogenic amniotic fluid embolism (AFE) because small amounts of amniotic fluid will bypass the filters of the device and be present in the packed red cells. However, more than 400 cases of cell saver use in obstetrics have been published, and no evidence of iatrogenic AFE exists. This technique is safe and effective in obstetric cases where massive blood loss is expected.21

Recombinant factor VIIa (rFVIIa) is licensed for use in patients with hemophilia and inhibitory alloantibodies.22 It has increasingly been used for off-label indications including trauma, heart surgery after cardiopulmonary bypass, vascular surgery, warfarin reversal, and obstetric hemorrhage. More than 75% of level I trauma centers in the United States recommend the use of rFVIIa in their massive transfusion protocols. An example of a massive transfusion protocol is provided in Figure 1.

Once endothelial injury has occurred, subendothelial collagen and tissue factor are exposed to the circulation. Factor VII (endogenously and exogenously administered) will bind to tissue factor and activate the clotting cascade, leading to local fibrin deposition. Systemically, rFVIIa may not be acceptable to Jehovah’s Witnesses as long as the collection bag remains connected to the central venous line at all times (avoid “circuit” disconnections). Overall, there is minimal evidence to suggest that ANH alone has a significant effect on the need for allogeneic blood.11
FIGURE 1
Example of a massive transfusion protocol

Consider activation of a MT protocol when patient actively bleeding and any of the following:

- Systolic blood pressure < 90 mmHg
- Ph < 7.1
- Base deficit > 6 meq/L
- Temperature below 34°C
- INR > 2.0
- Platelet count < 50,000/mm³

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Once activated, the blood bank will send 6 units of PRBC, 6 units of FFP, 6 units of platelets, and 10 units of cryoprecipitate. After this, if the patient remains bleeding (the protocol has not being inactivated), 6 more units of PRBC and FFP will be prepared along with 20 units of cryoprecipitate. The latter product is given in order to elevate the fibrinogen level since the next step of the protocol is to administer recombinant activated factor VII. At any point, if the patient’s hemorrhage stops, the blood bank should be notified so that the protocol can be terminated.

If bleeding persists, the sequence is started again.

PRBC, packed red blood cells; FFP, fresh frozen plasma; INR, international normalized ratio; MT, massive transfusion; Pacheco. Medical management of obstetric hemorrhage. Am J Obstet Gynecol 2011.

VIIa will also bind activated platelets, leading to fibrin formation away from the site of injury. Despite having a very short half-life (2-6 hours), concerns about thromboembolism as a complication are real. A recent systematic review of the literature showed a higher risk of arterial thrombosis (not venous) among patients who received rFVIIa as an adjuvant therapy for life-threatening bleeding.23 rFVIIa is not a first-line treatment for hemorrhage and is effective only once major sources of bleeding have been controlled. The use of this product should be combined with best practice use of blood products.24 Before administration, the patient should ideally have a platelet count >50,000/mm³, fibrinogen >50–100 mg/dL, temperature >32°C, Ph >7.2, and normal ionized calcium.24 These preconditions will facilitate adequate functioning of the clotting cascade.

Seventeen randomized controlled trials in which rFVIIa was used to control hemorrhage in different subgroups of patients have been published. Four studies found a reduction in transfusion requirements or blood loss, but none reported a survival benefit.25 Overall, it appears that rFVIIa is effective in limiting the amount of blood products transfused, but data on survival benefit are lacking.

The obstetric literature has numerous case reports and case series involving the use of rFVIIa. Publication bias is a major concern, and we are not aware of any published randomized trials involving rFVIIa in obstetric practice. The optimal dose is still unknown. Many reports in obstetric hemorrhage have used a dose of 90 mg/kg. If used in obstetric cases, we recommend deep venous thrombosis prophylaxis once the bleeding risk is considered to be low.

Transfusion therapy

Classically, hemorrhage resuscitation has been centered around administration of crystalloids and packed red blood cells (PRBC). Use of other blood products like fresh frozen plasma (FFP), cryoprecipitates, and platelets is indicated if hematologic parameters are abnormal (eg, platelet count <50,000/mm³, fibrinogen <100 mg/dL, prothrombin time [PT], or activated partial thromboplastin time [aPTT] >1.5 × normal). These current transfusion guidelines fail to prevent coagulopathies in massive bleedings.26 Patients with crystalloid/PRBC-based resuscitation will frequently develop dilution of clotting factors and platelets, leading to the so called “dilutional coagulopathy.” The latter may be complicated by hypothermia and acidosis, both of which lead to coagulation dysfunction.

Massive crystalloid resuscitation may actually worsen bleeding before achieving surgical control of hemorrhage because of increases in intravascular hydrostatic pressures and dislodgement of fresh clots at sites of endothelial injury.27 Recent evidence has shown that early coagulopathy may occur before hemodilution and before consumption of clotting factors takes place. This mechanism of early coagulopathy has been studied mainly in trauma; however, obstetric hemorrhage may share some of the mechanisms involved.27 Early tissue hypoperfusion leads to endothelial up-regulation of the receptor thrombomodulin. This receptor interacts with thrombin, leading to activation of the protein C pathway. Protein C is a natural anticoagulant that irreversibly inhibits factors Va and VIIIa and also enhances fibrinolysis through inhibition of plasminogen activator inhibitor 1.28 Increased fibrinolytic activity has been described in obstetric hemorrhage secondary to uterine atony, placental abruption, and accretism.27 These new mechanisms of coagulopathy have challenged the current resuscitation guidelines, suggesting that early clotting factor replacement and early identification of excessive fibrinolysis may be associated with improved outcomes.

Hemostatic resuscitation is a new concept that involves 3 main aspects:

1. Limiting early aggressive crystalloid use and considering permissive hypotension.
2. Early administration of FFP and platelets (with concomitant packed...
red blood cells), achieving a ratio of 1:1:1 without waiting for coagulation laboratory tests.

3. Early use of rFVIIa.

Aggressive crystalloid resuscitation is avoided to prevent hemodilution and early clot dislodgement secondary to increases in blood pressure as a result of volume expansion. Before surgical control of hemorrhage, permissive hypotension with systolic blood pressures between 80–100 mm Hg may be optimal to limit ongoing blood loss.27 Permissive hypotension may be considered in patients with postpartum hemorrhage; however, no data is available during the antenatal period, as uterine perfusion pressure may be compromised.

Early administration of FFP and platelets with PRBC in a ratio of 1:1:1 prevents early development of coagulopathy. Retrospective military and civilian data have demonstrated absolute mortality reductions between 15–62% with the use of higher ratios of FFP:PRBC.29,30 A significant limitation of the available, mostly nonrandomized, studies on this topic is the presence of survival bias. On average, the median time to obtaining the first unit of PRBC is 18 minutes, as opposed to more than 1 hour for FFP (needs to be thawed).31 Sicker patients will likely die before availability of FFP, whereas less sick patients will survive to the moment when FFP is available. The latter may explain why patients with high FFP:PRBC ratios had better survival. A limited number of studies have specifically addressed the survivor bias in high FFP:PRBC studies. When early deaths were excluded, no survival benefit for higher ratios was noted.32 Prospective trials are required to validate the benefit of early FFP administration. Despite the lack of randomized trials, many centers in the United States have adopted massive transfusion protocols involving the use of high FFP:PRBC ratios and early use of rFVIIa.33 These massive transfusion protocols are frequently used in massive obstetric hemorrhage.

Administration of large amounts of blood products could lead to a higher incidence of transfusion-related acute lung injury (TRALI) and transfusion-related immunomodulation (TRIM).34 Others suggest the opposite, with the rationale that early administration of FFP and platelets achieves hemostasis earlier, thus decreasing the total number of blood products given.26

Hemostasis monitoring

Conventional plasma-based coagulation analyses like the PT, aPTT, and international normalized ratio (INR) are poor predictors for transfusion requirements and do not identify specific coagulation anomalies.35 The thromboelastograph (TEG) is an easy test that provides information regarding the specific component of the coagulation process that may be affected. A small amount of blood is placed into a cuvette, and the blood is stirred with an agitator connected to a strain gauge. As the movement of the agitator is impeded by the forming clot, the strain gauge depicts a graphic representation of the strength of the clot. Figure 2 depicts the main components of the TEG. Both the reaction time/clotting time and the alpha angle reflect the activity of clotting factors. Once the clot is formed, the maximum amplitude correlates with platelet function. Lastly, the velocity at which the amplitude decreases correlates with fibrinolytic activity. Obstetric hemorrhage often has a significant component of enhanced fibrinolysis.36 Conventional clotting tests fail to identify such anomaly, whereas the TEG may easily detect it, leading to a change in management where antifibrinolytic agents like tranexamic acid or epsilon aminocaproic acid should be administered. Where available, we recommend the use of the TEG to guide transfusion therapy.

Postpartum considerations

Patients who have had massive obstetric hemorrhage are frequently at high risk of developing thromboembolic complications after delivery. Immediately after delivery, if the bleeding risk is still considered elevated, mechanical prophylaxis devices should be used. As soon as considered safe, pharmacologic prophylaxis should be instituted.

Not infrequently, oliguria and hypotension persist after massive resuscitation. The typical approach to the latter clinical situation is administration of more intravenous fluids. Although in most cases fluid therapy may be the answer, abdominal compartment syndrome must always be considered. Both crystalloid and colloid administration lead to third spacing of fluid (crystalloid will third space earlier than colloid). Consequently, bowel edema and ascites may ensue. Extensive surgical procedures are commonly associated with ileus, which may also favor intraabdominal hypertension. Put together, all these factors may increase the intraabdominal pressure to a point where compression of the abdominal and retroperitoneal vessels will compromise preload to the heart, leading to a drop in cardiac output and, consequently, in blood pressure. Another important component of this syndrome is oliguria, as the kidney is poorly perfused secondarily to compromised cardiac output and the kidney venous system is also compressed by increased extravascular pressure, leading to a decrease in the gradient of perfusion. Cephalad displacement of the diaphragm leads to bivalve atelectasies, with more right-to-left shunt and consequent hypoxemia. Patients on mechanical ventilators will display sudden increases in airway pressures. Central vascular pres-
DVT, deep venous thrombosis; EPO, erythropoietin; Fe, iron; MRI, magnetic resonance imaging; TEG, thromboelastograph.

sures (central venous pressures or pulmonary pressures recorded by means of a pulmonary artery catheter) will also be elevated as the intrathoracic pressure rises secondarily to the upward displacement of the diaphragm.

Obstetricians need to be familiar with this complication, as the administration of more fluid in an attempt to increase blood pressure and urine output will only worsen intraabdominal pressures and hemodynamics. If the condition is suspected, a bladder pressure should be obtained at the bedside as a surrogate for abdominal pressure.37 Bladder pressure should be measured with the patient in the supine position and the bladder distended with 25 mL saline after the urinary catheter has been clamped.37 Normal abdominal pressures are 0-10 mm Hg. Abdominal hypertension is defined as an intracavitary pressure >12 mm Hg. Finally, abdominal compartment syndrome includes a pressure >20 mm Hg and at least 1 organ compromised.37

Normal values of intraabdominal pressure in the postpartum period are not known. A recent publication involving women after a cesarean section found mean intraabdominal pressures of 6.4 ± 5.2 mm Hg. Interestingly, and likely because of higher risk of third spacing, patients with preeclampsia who underwent a cesarean section had mean values of 11 ± 9 mm Hg.38

Once the diagnosis is established, most patients will require surgical decompression, and the open abdomen may be managed with a vacuum-assisted closure or a Bogota bag or silo.37 Enteral feeding and limitation of fluid therapy are beneficial. If fluids are required, the use of colloids (eg, albumin) is recommended over crystalloids. Limited evidence suggests that temporal use of paralytic agents while the abdomen is open may help achieve primary fascial closure.39

Figure 3 summarizes the key aspects involved in the medical management of the parturient at risk of massive hemorrhage.

Summary

Obstetric hemorrhage is one of the most common causes of maternal morbidity and mortality worldwide. Placental accretism, just like the patient described in the vignette, is becoming increasingly frequent and is responsible for most cases of peripartum hysterectomy. Interventions that may limit transfusion requirements include normovolemic hemodilution, use of rFVIIa, selective embolization of pelvic vessels by interventional radiology, and the use of the cell saver intraoperatively. The use of techniques like hypotensive resuscitation and the TEG should be limited to centers with vast experience in the management of these complex patients. Current understanding of the mechanisms of acute coagulopathy calls into question the current transfusion guidelines in favor of massive transfusion protocols based on hemostatic resuscitation. Prospective trials are required to validate the efficacy of this approach. Obstetricians should be familiar with current transfusion protocols.

REFERENCES