Identification and Management of Obstetric Hemorrhage

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INTRODUCTION

Obstetric hemorrhage remains the leading cause of maternal death and severe morbidity worldwide. In developing nations, including Africa and Asia, peripartum hemorrhage is responsible for 30% of all direct maternal mortality.\(^1\) Despite advances in obstetric and transfusion medicine, well-resourced countries are not impervious to this potentially catastrophic complication, with peripartum bleeding accounting for 3.4% and 11.8% of maternal deaths in the United Kingdom and United States, respectively.\(^2,3\)

Significant morbidity, in the form of loss of fertility, pituitary necrosis, renal insufficiency, coagulopathy, and respiratory failure, is also associated with severe peripartum bleeding.\(^4\)

Although uterine atony is the most common cause of hemorrhage, abnormal placentation, coagulation disorders, and genital tract trauma also contribute to significant morbidity and mortality. Despite the identification of many...
characteristics associated with obstetric hemorrhage, most parturients who subsequently experience significant bleeding have no recognizable risk factors. Given the inability to reliably predict patients at high risk for obstetric hemorrhage, all parturients should be considered susceptible, and extreme vigilance must be exercised in the assessment of blood loss and hemodynamic stability during the peripartum period. Obstetric-specific hemorrhage protocols, facilitating the integration and timely escalation of pharmacologic, radiological, surgical, and transfusion interventions, are critical to the successful management of peripartum bleeding.

**DEFINITION OF OBSTETRIC HEMORRHAGE**

The precise definition of obstetric hemorrhage remains nebulous, with numerous classification systems currently in use worldwide (Box 1). Given the dynamic changes in plasma volume commonly accompanying the peripartum period, the use of acute changes in hematocrit (Hct) is of limited utility in the timely diagnosis of significant bleeding. Most international guidelines rely on estimation of blood loss and/or hemodynamic instability to identify peripartum hemorrhage. In the United States, blood loss

<table>
<thead>
<tr>
<th>Box 1</th>
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</thead>
<tbody>
<tr>
<td><strong>Summary of international obstetric hemorrhage definitions currently in use</strong></td>
</tr>
<tr>
<td><strong>American Congress of Obstetricians and Gynecologists Guidelines</strong></td>
</tr>
</tbody>
</table>
| • “No single, satisfactory definition”
| • Conventional definition:
| • Blood loss greater than 500 mL following vaginal delivery
| • Blood loss greater than 1000 mL following cesarean delivery
| **Australian Guidelines** |
| • Blood loss greater than 500 mL following vaginal delivery
| • Blood loss greater than 750 mL following cesarean delivery
| **Austrian Society of Obstetrics and Gynaecology** |
| • Blood loss 500 to 1000 mL with clinical signs of hypovolemic shock
| • Blood loss greater than 1000 mL
| **German Society of Obstetrics and Gynaecology** |
| • Blood loss greater than 500 mL following vaginal delivery
| • Blood loss greater than 1000 mL following cesarean delivery
| **Royal College of Obstetricians and Gynaecologists** |
| • Blood loss 500 to 1000 mL
| • Severe obstetric hemorrhage
| • Blood loss greater than 1000 mL
| • Blood loss 500 to 1000 mL with clinical signs of hypovolemic shock
| **World Health Organization** |
| • Blood loss greater than 500 mL
| • Severe obstetric hemorrhage
| • Blood loss greater than 1000 mL

exceeding 500 mL for vaginal delivery and 1000 mL for cesarean delivery has traditionally been used in the classification of obstetric hemorrhage. These values are of questionable clinical significance given that they are only slightly higher than the average blood loss for each mode of delivery. Furthermore, the expansion of blood volume typically accompanying pregnancy confers a protective advantage, and blood losses of 1000 mL are generally well tolerated. Recently, an international panel of experts in the fields of obstetrics, gynecology, hematology, and anesthesiology proposed the following diagnostic criteria for the identification of women at increased risk of adverse outcomes from obstetric hemorrhage:

Active bleeding > 1000 mL within the 24 hours following birth that continues despite the use of initial measures, including first-line uterotonic agents and uterine massage.5

Although a unified definition will facilitate comparison of the incidence and outcomes of obstetric hemorrhage among different countries, the clinical significance of 1000 mL of blood loss in 24 hours is questionable.

CAUSES OF OBSTETRIC HEMORRHAGE

Obstetric hemorrhage is an all-inclusive term referring to several distinct pathways ultimately resulting in significant peripartum blood loss. Causes of obstetric hemorrhage have traditionally been classified as “antepartum” or “postpartum,” in reference to the timing of maternal bleeding in relation to the delivery of the fetus (Box 2). The presence of coagulation disorders, both congenital and acquired, can further contribute to the incidence and severity of obstetric hemorrhage. An understanding of the unique mechanisms, risk factors, and clinical manifestations of these distinct causes of peripartum bleeding is critical in the early identification and successful management of obstetric hemorrhage.

Box 2
Common causes of and/or contributors to obstetric hemorrhage

Antepartum Hemorrhage
- Placenta previa
- Uterine rupture
- Placental abruption

Postpartum Hemorrhage
- Uterine atony
- Placenta accreta
- Genital trauma

Congenital Coagulation Disorders
- von Willebrand disease
- Hemophilia A
- Hemophilia B
- Glanzmann thrombasthenia
- Bernard-Soulier syndrome
Antepartum Obstetric Hemorrhage

Placenta previa
Placenta previa, complicating 1 in 200 pregnancies, is characterized by the presence of the placenta overlying the endocervical os (Fig. 1). Risk factors include previous uterine surgery and a history of placenta previa. Disruption of the placental attachment from the uterine decidua can lead to significant bleeding and uteroplacental insufficiency. The classic presentation is “painless vaginal bleeding,” but abdominal pain and/or contractions may also occur. Diagnosis is confirmed with the use transabdominal and/or transvaginal ultrasound to delineate the relationship of placenta to the endocervical os. Placenta previa is an indication for cesarean delivery.

Uterine rupture
Uterine rupture, defined as a full-thickness separation of the uterine wall and the overlying serosa, occurs in approximately 1 in 100 parturients with a prior uterine surgery. Factors compromising the integrity of the uterine wall, including grand multiparity, fetal malpresentation, and oxytocin augmentation of labor, can further increase the risk of uterine rupture. Clinical manifestations include a non-reassuring fetal heart rate, abdominal pain, hypotension, cessation of labor, and palpation of fetal parts in the abdomen. Urgent cesarean delivery is indicated.

Placental abruption
Placental abruption develops in 1 in 150 pregnancies. Antepartum separation of the placenta from the decidua basalis may lead to significant blood loss and compromised placental blood flow. Hypertension, preeclampsia, cocaine use, tobacco use, and abdominal trauma have been associated with an increased risk of placenta abruption. Classic findings include painful vaginal bleeding, abdominal tenderness, and irritable uterine contraction pattern. Delivery is generally indicated unless the fetus is premature and the abruption is small with minimal maternal and fetal hemodynamic sequel.

Postpartum Obstetric Hemorrhage

Uterine atony
Uterine atony is responsible for approximately 80% of postpartum hemorrhages. At term gestation, blood flow to the uterus is approximately 700 mL/min. Following

Fig. 1. Placenta previa describes a condition whereby the placenta partially or completely covers the cervix.
placental delivery, contraction of the uterus leads to compression of the spiral arteries supplying the placental bed. Inadequate myometrial tone allows continued maternal perfusion of the unoccupied placental bed, resulting in significant postpartum blood loss. Several antepartum characteristics have been associated with the subsequent development of uterine atony (Box 3). Unfortunately, predicting the occurrence of postpartum hemorrhage is challenging given that less than 40% of parturients with uterine atony resulting in transfusion had an identifiable risk factor. Management of uterine atony involves administration of uterotonic agents (discussed later), uterine massage, and manual removal of retained placental tissue. Invasive methods for controlling blood loss associated with uterine atony unresponsive to more conservation measures include the Bakri balloon, B-Lynch compression sutures, and hysterectomy (discussed later).

Placenta accreta

Accreta refers to a spectrum of abnormal placentation, characterized by the aberrant attachment of the placenta to the uterus. Placenta accreta is further classified based on the depth of placental uterine invasion (Fig. 2). Placenta accreta vera describes placental attachment directly to the myometrium, without an intervening decidua basalis layer. Placental infiltration into the uterine myometrium is designated increta, whereas percreta describes placental invasion through the uterine serosa, and potentially into surrounding pelvic structures. Regardless of the degree of uterine invasion, all variations of placenta accreta are associated with postpartum hemorrhage given the significant challenge in removing the placenta following delivery.

The incidence of placenta accreta has risen exponentially over the past 50 years, with recent estimates suggesting a rate of approximately 1 in 500 pregnancies. The increased occurrence of abnormal placentation parallels the increase in invasive maternal obstetric and gynecologic interventions, including cesarean delivery, uterine embolization, and myomectomy. Because placenta accreta is generally asymptomatic before delivery, antenatal diagnosis is dependent on noninvasive imaging techniques. When performed by an experienced sonographer, ultrasound combined with color Doppler has a diagnostic sensitivity, specificity, and negative predictive value of approximately 80%, 90%, and 98%, respectively. Ultrasound findings

<table>
<thead>
<tr>
<th>Box 3 Conditions associated with uterine atony</th>
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</thead>
<tbody>
<tr>
<td>Uterine distension</td>
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<tr>
<td>• High parity</td>
</tr>
<tr>
<td>• Multiple gestations</td>
</tr>
<tr>
<td>• Polyhydramnios</td>
</tr>
<tr>
<td>• Macrosomia</td>
</tr>
<tr>
<td>Oxytocin desensitization</td>
</tr>
<tr>
<td>• Induced or prolonged labor</td>
</tr>
<tr>
<td>Impaired uterine involution</td>
</tr>
<tr>
<td>• Retained placenta</td>
</tr>
<tr>
<td>• Placenta accreta</td>
</tr>
<tr>
<td>Decreased myometrial tone</td>
</tr>
<tr>
<td>• Volatile halogenated anesthetic agents</td>
</tr>
<tr>
<td>• Magnesium</td>
</tr>
<tr>
<td>• Tocolytic agents</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
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</table>
suggestive of placenta accreta include loss of the normal retroplacental-myometrial hypoechoic zone, increased vascularity within the uterine wall, and the presence of multiple vascular lacunae (creating a “moth-eaten or Swiss cheese” appearance). Early identification of placenta accreta facilitates the coordination of multidisciplinary postpartum management, which frequently involves massive transfusion in conjunction with a combined cesarean delivery–hysterectomy.

**Genital trauma**

Vaginal delivery is associated with varying degrees of injury to the vagina, vulva, and/or cervix. Risk factors associated with lower genital tract trauma during childbirth include nulliparity, macrosomia, precipitous delivery, forceps- or vacuum-assisted delivery, and/or episiotomy. Although cervical laceration complicates 50% of vaginal deliveries, most injuries are superficial with minimal hematologic consequences. Lacerations extending into the lower uterine segment, uterine artery, and/or retroperitoneum can be associated with significant blood loss and hemodynamic perturbations, requiring pharmacologic, hematological, and/or surgical intervention.

**Coagulation Disorders**

Pregnancy is characterized as a hypercoagulable state, with an increase in many coagulation factors and a decrease in the activity of anticoagulant and fibrinolytic pathways (Fig. 3). Inherited coagulation disorders can disrupt these protective prohemostatic changes. Parturients with hereditary hematologic disorders, most frequently von Willebrand disease, hemophilia, and platelet disorders, are at an increased risk of significant obstetric bleeding. Recommendations for the prophylactic treatment of parturients with inherited bleeding disorders are included in Table 1.

**MANAGEMENT OF OBSTETRIC HEMORRHAGE**

**Obstetric Hemorrhage Protocol**

Most fatalities associated with obstetric hemorrhage are preventable, with “substandard care” contributing to approximately 70% of maternal mortality. Adverse outcomes have been attributed to several avoidable factors, including underestimation of blood loss, lack of blood product availability, insufficient interdisciplinary communication, and delayed escalation of invasive interventions. Obstetric-specific massive transfusion algorithms have been associated with a decrease in maternal morbidity. Despite the proven success of obstetric hemorrhage protocols, a recent survey
Table 1
Recommendations for the prophylactic treatment of women with inherited bleeding disorders

<table>
<thead>
<tr>
<th>Coagulation Disorder</th>
<th>Characteristics</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 vWF deficiency</td>
<td></td>
<td>TXA, DDAVP</td>
</tr>
<tr>
<td>Type 2 vWF dysfunction</td>
<td></td>
<td>TXA, vWF concentrates</td>
</tr>
<tr>
<td>Type 3 vWF absent</td>
<td></td>
<td>TXA, vWF concentrates</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>Fibrinogen deficiency</td>
<td>Fibrinogen concentrate, cryoprecipitate, FFP</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>Fibrinogen dysfunction</td>
<td>Treatment individualized based on risk of bleeding vs thrombosis</td>
</tr>
<tr>
<td>FII</td>
<td>Factor II deficiency</td>
<td>PCC</td>
</tr>
<tr>
<td>FV</td>
<td>Factor V deficiency</td>
<td>FFP</td>
</tr>
<tr>
<td>FVII</td>
<td>Factor VII deficiency</td>
<td>rFVIIa</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Factor VIII deficiency</td>
<td>TXA, DDAVP, FVIII replacement</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Factor IX deficiency</td>
<td>TXA, Factor IX replacement</td>
</tr>
<tr>
<td>FX</td>
<td>Factor X deficiency</td>
<td>FX concentrate, PCC</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>Platelet dysfunction</td>
<td>TXA, Factor VIIa, platelets</td>
</tr>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>Platelet dysfunction and deficiency</td>
<td>TXA, Factor VIIa, platelets</td>
</tr>
</tbody>
</table>

Abbreviations: DDAVP, desmopressin; PCC, prothrombin complex concentrate.

Fig. 3. Changes in coagulation cascade and fibrinolytic pathway during pregnancy.
suggested that they are in practice in less than 70% of labor and delivery units within the United States. In response to the alarming increase in obstetric hemorrhage and associated morbidity and mortality, the National Partnership for Maternal Safety (NPMS) has developed a safety bundle, outlining critical clinical practices that should be implemented in every maternity unit (Box 4). The obstetric safety bundle emphasizes the basic tenets of crisis management, namely readiness, recognition and prevention, response, and reporting and systems learning. Application of obstetric-specific protocols, facilitating the integration and timely escalation of pharmacologic, radiological, surgical, and transfusion interventions, is critical to reducing maternal morbidity and mortality associated with peripartum bleeding. Successful implementation of the NPMS recommendations requires multidisciplinary collaboration, ongoing resource assessment and allocation, unwavering provider vigilance, and a commitment to system processes improvement. Although initial application and continued maintenance of the NPMS recommendations require an investment of both personnel and financial resources, it will unquestionably contribute to improve maternal outcomes in the setting of obstetric hemorrhage.

**Box 4**

**Obstetric hemorrhage safety bundle from the National Partnership for Maternal Safety, Council on Patient Safety in Women’s Health Care**

**Readiness (Every Unit)**
- Hemorrhage cart with supplies, checklist, and instruction cards for intrauterine balloons and compression stitches
- Immediate access to hemorrhage medications (kit or equivalent)
- Establish a response team: who to call when help is needed (blood bank, advanced gynecologic surgery, other support and tertiary services)
- Establish massive and emergency-release transfusion protocols (type O–negative or un-cross-matched RBC, FFP, platelets, cryoprecipitate)
- Unit education or protocols, unit-based drills (with post-drill debriefs)

**Recognition and Prevention (Every Patient)**
- Assessment of hemorrhage risk (prenatal, intrapartum, postpartum)
- Measurement of cumulative blood loss (formal, as quantitative as possible)
- Active management of the third stage of labor (department-wide protocol)

**Response (Every Hemorrhage)**
- Unit-standard, stage-based obstetric hemorrhage emergency management plan with checklists
- Support program for patients, families, and staff for all significant hemorrhage

**Reporting and Systems Learning (Every Unit)**
- Establish a culture of huddles for high-risk patients and postevent debriefs to identify successes and opportunities
- Multidisciplinary review of serious hemorrhages for systems issues
- Monitor outcomes and process metrics in perinatal quality improvement committee

**Estimation of Blood Loss**

The most common trigger for initiation of obstetric hemorrhage protocols is blood loss exceeding 1500 mL. Timely identification of hemorrhage is complicated by inherent inaccuracies in visual estimation of blood loss and the lack of early hemodynamic changes. Several studies have indicated that visual assessment of blood loss is grossly unreliable, with actual losses frequently exceeding twice the reported visual estimations.\(^3\) Physiologic perturbations are often late signs of hypovolemia in young, healthy parturients (Table 2). Peripheral and splanchnic vasoconstriction facilitates the relocation of blood from venous capacitance vessels to the central circulation, allowing the blood pressure and heart rate to remain near normal until blood loss exceeds 1500 mL in most parturients. Laboratory evaluation is generally too slow to meaningfully reflect dynamic changes in Hct and coagulation status during an obstetric hemorrhage. Precision in blood loss assessment is improved with the use of widely available pictorial guidelines and/or meticulous physical collection systems.\(^3\)\(^\text{2}\) Given the challenges in the accurate estimation of blood loss during delivery, extreme vigilance is necessary to assure the early recognition and treatment of obstetric hemorrhage.

**Pharmacologic Treatment**

Because uterine atony is the primary cause of obstetric hemorrhage, the early administration of uterotonic agents should be considered in the setting of significant postpartum bleeding. Uterotonic medications decrease blood loss by directly stimulating uterine contractions, thus compressing the spiral arteries supplying the vacant placental bed. Oxytocin is generally regarded as the “first-line” pharmacologic intervention for postpartum hemorrhage. Previous studies have demonstrated that prophylactic use of oxytocin during the third stage of labor decreases the incidence of obstetric hemorrhage.\(^3\)\(^\text{3}\) Other classes of uterotonic agents should be considered if uterine atony is unresponsive to oxytocin. The specific “second-line” pharmacologic intervention is dependent on the presence of maternal comorbidities. Administration guidelines and contraindications of commonly used uterotonic agents are included in Table 3.

**Invasive Obstetric Management**

Obstetric hemorrhage unresponsive to uterotonic agents may require mechanical or surgical interventions to control blood loss. Uterine massage stimulates myometrial contractions, although the benefit in the setting of ongoing uterotonic administration is questionable.\(^3\)\(^\text{4}\)\(^,\)\(^3\)\(^\text{5}\) Internal uterine tamponade decreases blood loss by compressing

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### Table 2

<table>
<thead>
<tr>
<th>Blood Loss (mL)</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Heart Rate (bpm)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>Palpitations, lightheadedness</td>
</tr>
<tr>
<td>1500</td>
<td>90–100</td>
<td>100–120</td>
<td>Weakness, diaphoresis</td>
</tr>
<tr>
<td>2000</td>
<td>70–80</td>
<td>120–140</td>
<td>Restlessness, confusion, pallor</td>
</tr>
<tr>
<td>3000</td>
<td>50–70</td>
<td>&gt;140</td>
<td>Lethargy, air hunger</td>
</tr>
</tbody>
</table>

intrauterine vessels and bleeding surfaces. Intrauterine placement of a Foley catheter or Bakri balloon allows simultaneous compression of uterine surfaces with cavity drainage for monitoring of ongoing blood loss (Fig. 4). External uterine compression can be accomplished with the use of circumferential (B-Lynch) uterine sutures (Fig. 5). Retrospective studies have demonstrated decreases in blood loss and postpartum hysterectomy rates with the use of internal uterine tamponade and/or external compression sutures in the setting of obstetric hemorrhage.\textsuperscript{36} Blood flow to the uterus can be restricted further with surgical ligation or embolization of the uterine arteries. When escalating mechanical and fertility-preserving surgical/radiological interventions are ineffective, hysterectomy should be considered for the definitive management of obstetric hemorrhage.

**Resuscitation**

There is currently no consensus on the optimal pathway for resuscitation of massive bleeding in the obstetric patient. Given the unique changes in the coagulation and

<table>
<thead>
<tr>
<th>Uterotonic Agent</th>
<th>Route/Dose</th>
<th>Frequency</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin (Pitocin)</td>
<td>Intravenous (IV): 10–40 U/L</td>
<td>Infusion</td>
<td>None</td>
<td>Hypotension, Nausea/vomiting, Free water retention</td>
</tr>
<tr>
<td></td>
<td>Intramuscular (IM): 10 U</td>
<td>Once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylergonovine</td>
<td>IM: 0.2 mg</td>
<td>Every 2–4 h</td>
<td>Hypertension, Coronary disease, Raynaud</td>
<td>Nausea/vomiting, Hypertension</td>
</tr>
<tr>
<td>(Methergin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-methyl PGF\textsubscript{2\alpha} (Hemabate, Carboprost)</td>
<td>IM: 0.25 mg</td>
<td>Every 15–90 min (8 doses maximum)</td>
<td>Reactive airway, Pulmonary hypertension</td>
<td>Bronchoconstriction, Shivering, Diarrhea, $\uparrow$ Temperature</td>
</tr>
<tr>
<td>Misoprostol (Cytotec)</td>
<td>Buccal: 400 µg, Rectal: 1000 µg</td>
<td>Once, Once</td>
<td>None</td>
<td>Nausea/vomiting, Shivering, Diarrhea, $\uparrow$ Temperature</td>
</tr>
</tbody>
</table>

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Fig. 4. Intrauterine balloon tamponade exerts pressure against the uterine wall to reduce venous bleeding from the endometrium and myometrium. A central drainage catheter helps quantitate ongoing uterine bleeding.
fibrinolytic systems accompanying pregnancy, most obstetric-specific massive transfusion protocols suggest resuscitation with the early administration of red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate, and platelets. In the setting of hemorrhage unresponsive to blood component therapy, consideration should be given to prohemostatic and antifibrinolytic agents. Furthermore, the use of cell salvage techniques offers the ability to recycle blood lost from the surgical field, potentially minimizing heterologous transfusion and associated complications.

**Crystalloid and colloids**

Rapid restoration of intravascular volume is generally initiated with the use of warmed, non-dextrose-containing crystalloid, including lactated Ringer solution and normal saline. Crystalloid is typically administered in a ratio of 3:1 in relation to estimated blood loss. Although crystalloid is useful for initial resuscitation and/or mild hemorrhage, previous studies have demonstrated that only 20% of the crystalloid volume remains intravascular an hour after infusion.\(^{15}\) Re-equilibration of large crystalloid volumes can lead to interstitial edema and impairment of microcirculation.

Given the transient intravascular effect of crystalloid resuscitation, volume expansion with synthetic colloid solutions had been previously proposed. Although synthetic colloids are effective in prolonged restoration of circulating volume, they have been associated with inhibition of platelet aggregation, impaired clot formation, and increased blood loss.\(^{37,38}\) Furthermore, recent studies in nonpregnant patients have demonstrated that colloid resuscitation is associated with a significant increase in cost but no benefit in outcomes.\(^{39,40}\) Synthetic colloid administration is therefore not indicated in the management of obstetric hemorrhage.

**Red blood cells**

Although crystalloid can restore intravascular volume, RBC are needed to ensure adequate oxygen-carrying capacity of blood and avoid acidosis. The transfusion of 1 unit of RBC is expected to increase the Hct by 3% to 5%.\(^{15}\) The threshold at which RBC replacement should be initiated depends on the presence of comorbidities, hemodynamic parameters, and anticipated additional blood loss. Although an Hct of 18% to 25% may be well tolerated in an otherwise healthy parturient, most experts agree that RBC transfusion is warranted with an Hct less than 25% in the setting of ongoing hemorrhage.\(^{15}\) A higher Hct during active bleeding not only maintains tissue and organ perfusion but also improves overall coagulation.\(^{41}\)

Coagulation involves the intimate interplay between RBC, plasma coagulation factors, platelets, and the endothelium. Adequate RBC mass is essential in coordinating
the interactions between platelets and the vessel wall. A reduction in RBC mass (anemia) leads to marked decreases in both blood viscosity and resistance to blood flow. The resulting fast transit of platelets through central luminal flow causes a reduction in crucial platelet and endothelial cell interactions necessary for primary hemostasis. Timely RBC transfusion is critical in the maintenance of adequate intravascular volume, tissue oxygenation, and effective coagulation.

**Fresh frozen plasma**

The development of an acquired coagulopathy, from consumptive and dilutional effects, frequently complicates obstetric hemorrhage. Although pregnancy is associated with an increase in procoagulant activity and a decrease in fibrinolytic pathways, these protective mechanisms are overwhelmed in the setting of massive blood loss. Effective hemostasis is generally maintained if the concentration of coagulation factors does not decrease beyond 30% of normal levels. The brisk bleeding characteristic of obstetric hemorrhage can lead to the rapid consumption of clotting proteins and platelets, exceeding the normal surplus of coagulation factors. Critical levels of prothrombin, factor V (FV), FVII, and platelets are reached after a loss of greater than 200% of calculated blood volume, whereas life-threatening levels of fibrinogen are reached after a loss of only 140%. Aggressive replacement of intravascular volume with crystalloid and RBC can lead to dilution of coagulation factors and platelets, further impeding hemostatic mechanisms.

The prompt implementation of prohemostatic interventions is critical in preventing complications from uncontrolled coagulopathy. Each unit of FFP increases coagulation factor levels by approximately 8%. Although traditional guidelines suggest FFP should be used only in the setting of an elevated prothrombin time or activated partial thromboplastin time, recent data emerging from the trauma and obstetric literature endorse a more aggressive repletion of coagulation factors. The trauma literature suggests 1:1 FFP:RBC resuscitation ratio is associated with faster reversal of coagulopathy, decreased blood loss, and lower mortality. Although the parturient population is distinctly different from that encountered in military and civilian trauma, preliminary obstetric hemorrhage research corroborate the findings of improved outcomes with more aggressive procoagulant transfusion strategies. A recent, large retrospective study of transfusion in postpartum hemorrhage found an association between a higher FFP:RBC ratio and lower odds of requiring an advanced interventional procedure, including uterine artery embolization and/or hysterectomy. Given the significant risk of coagulopathy with massive bleeding, FFP should be considered early in the resuscitation of obstetric hemorrhage.

**Fibrinogen**

Fibrinogen, the final factor in the coagulation cascade, may play a unique role in the diagnosis and management of obstetric hemorrhage. Fibrinogen concentration substantially increases during the third trimester, with term parturients having fibrinogen levels of approximately 4.5 to 5.8 g/L compared with nonpregnant control levels of 2.0 to 4.5 g/L. Several studies have identified decreased fibrinogen levels as an important predictor of severe obstetric hemorrhage. Charbit and colleagues reported the risk of severe postpartum bleeding increased by a factor of 2.6 for each 1 g/L decrease in fibrinogen level. Baseline plasma fibrinogen level less than 2 g/L at the time of bleeding onset had a positive predictive value of 100% for subsequent evolution to severe hemorrhage, whereas plasma fibrinogen level greater than 4 g/L had a 79% negative predictive value for significant blood loss. It is unclear whether decreased
fibrinogen levels simply reflect the severity of blood loss or if it is an independent and measurable risk factor that could potentially be used as a diagnostic tool in the early identification of obstetric hemorrhage.

Given the correlation between hypofibrinogenemia and severe obstetric bleeding, fibrinogen has emerged as a potential therapeutic target for the management of postpartum hemorrhage. Fibrinogen, which is essential for clot strength and speed of clot formation, is one of the first coagulation factors to decrease beyond critical levels during massive blood loss.46,50 Although transfusion guidelines historically recommended fibrinogen replacement with levels less than 1 g/L, a recent in vitro study suggests that fibrinogen levels of 2.5 g/L are associated with optimal clot formation.42 The elevated levels of fibrinogen in pregnancy and the observed progression to severe bleeding in parturients with levels less than 2 g/L further support the maintenance of higher fibrinogen concentrations.5 In addition, the rapid restoration of normal peripartum fibrinogen levels (4–6 g/L) has been shown to effectively reduce or arrest blood loss.51-53

Although FFP, cryoprecipitate, and fibrinogen concentrates can all be used to increase fibrinogen levels, the optimal strategy for managing hypofibrinogenemia in obstetric hemorrhage is unclear. The relatively low concentration of fibrinogen in FFP limits its usefulness in the treatment of significant hypofibrinogenemia.54 To increase fibrinogen plasma level by 1 g/L, 30 mL/kg of FFP is necessary, increasing the risk of pulmonary edema and other hypervolemic complications.55 Cryoprecipitate, which is a concentrated source of fibrinogen, factor VIII, fibronectin, von Willebrand factor (vWF), and factor XIII, will increase fibrinogen levels by ~0.7 to 1 g/L for every 100 mL given.56 Although cryoprecipitate is associated with a lower transfusion volume, the standard “dose” (10 U) is typically prepared by pooling concentrates from multiple donors.29 Given the risk of infectious disease transmission and/or an immunologic reaction from exposure to multiple donors, several countries preferentially use purified, pasteurized fibrinogen concentrate for the treatment of congenital and/or acquired hypofibrinogenemia. Fibrinogen concentrates are also prepared from large donor pools, but subsequent processing removes or inactivates potentially contaminating viruses, antibodies, and antigens. Studies comparing cryoprecipitate and fibrinogen concentrates utilization in hemorrhage resuscitation suggest fibrinogen concentrates are associated with lower blood loss, decreased RBC transfusion, and greater increases in plasma fibrinogen levels.51,57 Although the most appropriate method of fibrinogen replacement is somewhat controversial, the critical role of fibrinogen in reversing the coagulopathy accompanying obstetric hemorrhage is clear. As such, close monitoring and replacement of fibrinogen are crucial in the management of the bleeding parturient.

**Platelets**

Platelets are another essential component of coagulation, with quantitative and qualitative platelet deficiencies contributing to inadequate hemostasis. Fibrinogen degradation products and anemia are commonly associated with obstetric hemorrhage and can inhibit platelet function. Initial resuscitation with crystalloid, RBC, and FFP can lead to a dilutional thrombocytopenia, further impeding adequate platelet activity. A platelet count of at least 50,000/mm³ should be maintained in the setting of active bleeding to optimize adequate clot formation. One unit of platelets, which is typically compiled from 6 donors, will generally increase levels by 25,000 to 30,000/mm³.29 Although not required, ABO compatibility increases the lifespan of transfused platelets. Of note, rhesus (Rh) sensitivity can occur in an Rh-negative recipient due to the presence of a few red cells in Rh-positive unit.
**Procoagulation Agents**

In the setting of intractable obstetric hemorrhage, procoagulation agent recombinant activated factor VII (rFVIIa) may be considered. rFVIIa is a synthetic vitamin K–dependent glycoprotein that aids in hemostasis via activation of the extrinsic pathway of the coagulation cascade. Although currently approved only for use in hemophilia, factor VII deficiency, and Glanzmann thrombasthenia, several groups have reported the successful treatment of obstetric hemorrhage with rFVIIa. Retrospective studies investigating the use of rFVIIa in the management of obstetric hemorrhage unresponsive to conventional therapies have suggested rFVIIa is associated with decreased blood loss, reduced RBC transfusion, and lower maternal mortality. Although preliminary reports are certainly encouraging, there is some concern that use of rFVIIa may contribute to subsequent thrombotic complications. Given the paucity of randomized controlled trials (RCTs) to unequivocally define the efficacy and safety profile of its administration, rFVIIa should be used only after failure of conventional therapies, including invasive treatment (such as uterine embolization) but before obstetric hysterectomy.

The effectiveness of rFVIIa depends on an optimal hemostatic environment. rFVIIa is an enzyme, with temperature, acid-base status (pH), and substrate availability significantly influencing its function. Previous studies have demonstrated rFVIIa is maximally effective when the following parameters are achieved: temperature greater than 34°C, arterial pH greater than 7.20, normocalcemia, Hct greater than 30%, platelet count greater than 50,000/mm³, and fibrinogen greater than 1 g/L. Although the optimal rFVIIa dose for the parturient is not well defined, 60 to 90 µg/kg is commonly used. Given the short half-life of rFVIIa (2 hours), the dose may be repeated within 30 to 60 minutes if there is insufficient improvement in hemostasis and ongoing nonarterial bleeding.

**Antifibrinolytic Therapy**

Antifibrinolytics, which inhibit the enzymatic degradation of fibrin clots, may play a unique role in the prophylaxis against and management of obstetric hemorrhage. Although fibrinolytic capacity decreases during the last trimester of pregnancy, fibrinolysis increases in the postpartum period. Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effects by blocking lysine binding sites on plasminogen molecules, inhibiting the activation of plasmin. TXA in nonobstetric populations has shown a significant reduction in perioperative blood loss and RBC transfusion without an increase in thrombotic events. Studies exploring antifibrinolytic treatment of menorrhagia suggest that TXA can reduce nonsurgical, low-volume, uterine blood loss. Several small RCTs and meta-analyses investigating TXA use in the postpartum period demonstrate that antifibrinolytic therapy is associated with a reduction in blood loss, decreased need for additional uterotonic agents, and higher hemoglobin levels at 24 hours. There is currently no consensus on the optimal dosing or timing of TXA administration. In addition, further studies addressing neonatal safety are indicated given that TXA crosses the placenta. It is hoped that a large, randomized, double-blind controlled trial, the World Maternal Antifibrinolytic Trial (WOMAN), currently underway in Europe and Africa, will provide insight into the efficacy and safety of TXA in the prevention and/or treatment of obstetric hemorrhage. The WOMAN trial is designed to measure the effect of early TXA administration on maternal outcomes, including blood transfusion, surgical intervention, nonfatal vascular events, hysterectomy, and death.
Cell Salvage

Intraoperative blood salvage techniques decrease transfusion requirements with minimal additional risk. Blood collected from the surgical field is centrifuged, washed, and filtered to yield RBC with a high Hct (60%–80%). The favorable physiologic profile, including pH, morphology, osmotic stability, and 2,3 diphosphoglycerate content, contribute to increased oxygen carrying capacity and survival of salvaged blood compared with its stored counterpart. Furthermore, use of recycled, autologous blood minimizes the risk of alloimmunization, viral transmission, and hemolytic transfusion reactions. Because processing of scavenged blood removes platelets and activated clotting factors, a dilutional coagulopathy can develop with exclusive transfusion of salvaged blood. In addition, bacterial contamination can complicate processing, although there are no reports of sepsis or infection with the use of cell salvage. Finally, administration of salvaged blood through a leukocyte depletion filter can (rarely) lead to disruption of leukocytes with release of cytokines and transient hypotension. Given the nominal risk of adverse effects and the potential to significantly reduce heterologous transfusion requirements, cell salvage techniques are increasingly used for operative procedures.

Although the benefits of intraoperative blood salvage in nonobstetric surgery are well established, universal acceptance of this technique in parturients has been plagued by concerns over amniotic fluid embolism (AFE) and induction of maternal alloimmunization. AFE is an anaphylactoid syndrome presumed to be caused by an unknown fetal antigen. Leukocyte depletion filters have been shown to reduce levels of fetal contaminants, such as lamellar bodies, phospholipids, squamous cells, and amniotic fluid–derived tissue factor, with postwashed, postfiltered salvaged blood containing similar levels of impurities to that found in the maternal circulation. A retrospective, multicenter study of 139 parturients receiving autologous blood transfusion from cell salvage reported no cases of AFE or acute respiratory distress. Maternal alloimmunization is a valid concern given that blood salvage techniques are unable to discriminate between maternal and fetal erythrocytes. Rh antigen discordance is the more significant risk because ABO antigens in the fetus are not well developed. Transfused salvaged blood containing Rh-positive fetal blood could immunize an Rh-negative mother. Thus, after autologous transfusion, the Kleihauer-Betke test is indicated to quantify exposure and calculate the appropriate Rho (D) immune globulin dose to prevent maternal alloimmunization. Provided appropriate precautionary measures are taken to prevent maternal Rh alloimmunization, blood salvage techniques may be especially useful in specific obstetric populations, including rare blood types, Jehovah’s Witnesses, and/or limited blood product availability. Several peer-reviewed studies have collectively reported no significant complications to the more than 300 obstetric patients who have received cell-salvaged autologous blood.

SUMMARY

Obstetric hemorrhage remains a significant cause of maternal morbidity and mortality worldwide. Uterine atony, abnormal placentation, genital tract trauma, and coagulation disturbances frequently contribute to massive bleeding in the peripartum period. Given that most obstetric hemorrhage cases occur in the absence of any identifiable risk factor, vigilance is required for the early identification of significant bleeding and hemodynamic instability. Successful management frequently involves stepwise, escalating pharmacologic, hematological, radiological, and/or surgical interventions. It is hoped that universal implementation of obstetric hemorrhage protocols will decrease the frequency of significant adverse outcomes.
REFERENCES


