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HIGH-RISK OBSTETRICS (T MCELRATH, SECTION EDITOR)

Postpartum Hemorrhage: What's New?

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Abstract

Purpose of Review Postpartum hemorrhage (PPH) remains an important cause of maternal morbidity and mortality in the USA and in particular worldwide. Recent epidemiological studies have enhanced our ability to identify risk factors for PPH. Novel diagnostic, surgical, and pharmaceutical techniques present opportunities for improving our care of patients with PPH.

Recent Findings This review aims to highlight recent primary research in the field of PPH. Large studies have refuted some assumed risk factors for PPH, including high body mass index and scheduled repeat cesarean delivery. Non-white race is an increasingly important risk factor for major maternal morbidity in the USA. New studies evaluated the role of tranexamic acid, point-of-care tests such as rotational thromboelastometry, uterotonic agents, and cell salvage in the management of PPH.

Summary Attention to and preparation for PPH, especially in patients with significant risk factors, may allow early intervention and improved patient outcomes. Obstetric units should have protocols that use uterotonic agents for PPH prevention and treatment, and tranexamic acid for treatment only. Centers treating the highest risk patients may benefit from having point-of-care testing and cell salvage available.

Keywords Postpartum hemorrhage · Obstetric hemorrhage · Quantitative blood loss · Cell salvage · Rotational thromboelastometry · Tranexamic acid

Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide and is a leading direct cause of maternal mortality in the USA [1]. A call-to-action was made in 2014 with the objective of reducing preventable forms of major maternal morbidity, with PPH included [2]. The National Partnership for Maternal Safety was created, and this organization subsequently published Safety Bundles for all obstetric providers to adopt. They focused on preparation, early recognition, systematic treatment, and education with regard to PPH as well as other major obstetric complications. Since that time, researchers have continued to clarify patient triaging, early identification, and best treatment practices with regard to obstetric hemorrhage. The latest research in this area is presented here.

Patient Identification: Risk Factors

In 2015, the National Partnership for Maternal Safety issued their Safety Bundle on Obstetric Hemorrhage. This included a recommendation that all patients should be evaluated for PPH risk, ideally in the antepartum, intrapartum, and postpartum periods. Such recognition may facilitate delivery planning, earlier recognition, and more aggressive intervention when major PPH occurs [3]. Many PPH risk factors have been evaluated in the obstetric literature, and after initial development and then validation, a list of "high-risk" hemorrhage criteria have been published that capture 85% of major PPHs [4]. These include placenta previa, suspicion for placenta accreta (or previa with a prior cesarean delivery (CD)), uterine rupture, severe anemia, thrombocytopenia or coagulopathy, active bleeding on admission, CD, antenatal hypertension, and preterm delivery. Recent publications have used larger databases to verify the results of earlier risk factor studies.

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One such population study in Australia was able to link data from women's successive pregnancies, showing that those receiving a blood transfusion in a first singleton pregnancy had a quadrupled risk of hemorrhage and severe morbidity in the subsequent pregnancy [5]. A separate California study used a statewide database to address conflicting research on maternal obesity and PPH risk. They controlled for a large number of maternal, obstetric, and socioeconomic variables, and found only a very modest relationship between high body mass index (BMI) and PPH, suggesting that risk stratification should focus on other factors [6]. Both of these risk factors had previously been listed as "moderate" risk factors for PPH, though an earlier work also failed to validate the role of high BMI [4]. Using these large databases helps to overcome bias and practice variation that can be introduced when patients are limited to individual academic research centers.

The absolute risk of major PPH is very low, at about 1–2%, and even with a 2- to 4-fold elevated risk, patients found to be at-risk will still have a low chance of requiring a major hemorrhage protocol. Alternatively, the use of risk factor triaging can miss 40% of patients who have a major hemorrhage but had no identified risk factors upon admission to the labor unit [3]. One group of researchers attempted to address this recently by building a prediction model for transfusion at CD [7]. They used a large national registry of CDs and examined a broad list of risk factors, with a goal of having only a 10% false positive rate. They furthermore developed two models, one including 17 antepartum risk factors that can be considered prior to delivery or at the time of admission, and the second including 20 antepartum plus intrapartum factors, which are identified in labor or at the time of delivery (Table 1). Their models had statistically good discrimination, though the highest risk patients in the two models still had transfusion rates of 10% and 13%, respectively. Notably, performance of these calculators was demonstrably better than using simple lists of risk factors to identify patients. To date, no widely accessible risk calculation tools have been made available.

This large study was able to evaluate many risk factors simultaneously and showed some unexpected findings [7]. First, they supported the California study's finding that high BMI is a minor contributor to PPH risk [6]. In fact, low BMI was significantly associated with transfusion in the CD cohort. Second, while "history of prior cesarean delivery" has been included in hemorrhage risk triaging tools [4], this study showed that the first CD has a significantly higher risk of PPH than repeat procedures. This finding is supported by data published by the Centers for Disease Control and Prevention, which showed that primary CDs have the highest risk of transfusion when compared with both repeat CDs and vaginal deliveries [8]. This likely reflects the fact that most repeat CDs are scheduled, while first CDs often occur after a labor that can be prolonged, obstructed, or complicated by infection.

Risk factor studies are intrinsically limited by the variables included. The role of in vitro fertilization (IVF) in maternal morbidity, and specifically PPH, has come to light in the past decade, but is not generally considered in studies evaluating multiple risk factors. A 2010 study used a large Australian database to show that IVF patients had higher rates of PPH than the general population [9]. Multiple subsequent studies have supported the association with both PPH and peripartum hysterectomy using large databases [10, 11]. Recent studies have attempted to elucidate the specific IVF components that are contributing to this risk, supporting IVF as a risk factor while factoring out the role of multiple gestations and placenta previa [12, 13]. Only one study has supported the role of IVF by evaluating multiple PPH risk factors [14]; increased awareness of this factor is needed in order to understand its relative contribution to hemorrhage.

Racial disparities have gained attention in many areas of healthcare, and PPH has not been overlooked. The National Inpatient Sample (NIS) has been recently used to show that women in every racial and ethnic minority category had a higher rate of severe maternal morbidity than non-Hispanic white women [15]. Another study looked at a cohort of NIS patients with PPH and found that black women had a significantly higher rate of severe maternal morbidity after controlling for comorbidities, and were at higher risk of death [16•]. Asian and Pacific Islander women in this study had the highest risk of hysterectomy. A separate NIS-based study found that black women over 40 years old had the highest morbidity at both the beginning and end of the study period, and also showed the largest increase in risk for transfusion and hysterectomy. Furthermore, both black and Hispanic women had a higher overall risk of death than white women [17]. While the contributors to this morbidity are likely multifactorial and complex, this represents an important area for decreasing preventable sources of morbidity.

Diagnosis: Blood Loss and Maternal Vital Signs

Underrecognition of major blood loss has been cited as a significant contributor to hemorrhagic morbidity. Therefore, the National Partnership for Maternal Safety recommended using quantitative blood loss (QBL) measurement in place of visual blood loss estimations (EBL) [3]. This can come in the form of volumetric assessment, with which conical, graduated patient drapes or suction canisters are used to collect and measure blood; gravimetric systems, with which blood-soaked sponges, drapes, and other items are weighed; or a combination of the two.

Recent studies have clinically evaluated the success of QBL systems. One study compared QBL and EBL estimates with calculated blood loss based on changes in maternal

hemoglobin [18]. They found that the two were not significantly different in their predictions, though they were missing data for many patients. A recent Cochrane review attempted to compare different methods of blood loss estimation with a focus on maternal morbidity outcomes. They found no significant difference when comparing volumetric estimates (calibrated drapes) to visual EBL, and no difference when comparing volumetric to gravimetric systems [19].

A separate study looked at clinical risk factors for unrecognized PPH at vaginal delivery [20]. They used changes in maternal hemoglobin to identify women with both recognized and unrecognized PPH and found that unrecognized PPH was uniquely associated with Asian race, previous CD, and episiotomy. Primiparity, prolonged labor, instrumental delivery, and retained placenta were associated with both recognized and unrecognized PPH. Use of intrapartum risk factors such as these can help to focus attention on the highest concern patients, which may make a resource-intense QBL system more manageable.

Given the additional work and cost involved with QBL systems, some have advocated for focusing on maternal vital signs instead as an indicator of significant blood loss. Some have advocated for use of the maternal shock index, which is the maternal heart rate divided by systolic blood pressure at a single time point. One case-control study found significantly higher shock index values at 30 min and 2 h for women undergoing vaginal deliveries [21]. A subsequent study found that a shock index cutoff of 0.9 had high sensitivity (94%) but poor specificity (31–51%) for predicting massive transfusion or invasive procedures [22]. If easily implemented in clinical practice, this tool could act as an alert for patients who need more careful assessment and monitoring for PPH.

Diagnosis: Point-of-Care Tests

Point-of-care viscoelastic tests allow for rapid evaluation of overall hemostasis, representing an alternative to the standard coagulation tests of platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level. One type of viscoelastic test, rotational thromboelastometry (ROTEM) has shown promise as a point-of-care test aiding resuscitation in PPH. In order to understand the contribution of the hypercoagulable state of pregnancy, a number of groups have evaluated ROTEM baseline values at different points in pregnancy [23] and at term [24, 25]. Adding to these data, Lee et al. report the largest study to date of baseline ROTEM values of healthy term pregnant patients [26]. This study measured multiple parameters and calculated reference ranges for 132 patients presenting for elective CD. Their findings, compared with those of previous studies reporting obstetric ROTEM data, will allow better interpretation of baseline abnormalities

Table 1 Risk factors retained in two multivariate prediction models for transfusion at the time of cesarean delivery [7]

Model 1: antepartum risk factors only	Model 2: antepartum and intrapartum risk factors
Maternal age < 21 or > 36 years	Maternal age < 21 or > 36 years
BMI at delivery[a]	BMI at delivery[a]
3+ prior term deliveries	3+ prior term deliveries
Gestational age < 37 weeks	Government vs private insurance
African-American Race	No vs private insurance
Government vs private insurance	Thrombocytopenia
No vs private insurance	Hematocrit < 32%
Thrombocytopenia	Primary CD
Hematocrit < 32%	Two prior CD
Primary CD	Three or more prior CD
Two prior CD	History of cardiac disease
Three or more prior CD	Gestational hypertension or preeclampsia
History of asthma	Non-elective repeat CD
History of cardiac disease	General anesthesia
Gestational hypertension or preeclampsia	Abruption identified at delivery
HELLP syndrome	Multiple gestations
Antepartum abruption	Failure to progress in labor
	Eclampsia or HELLP in labor
	Placenta accreta spectrum identified at delivery
	Antibiotic use in labor

BMI, body mass index; *CD*, cesarean delivery; *HELLP*, hemolysis, elevated liver enzymes, low platelets

[a] BMI was inversely associated with transfusion risk in both models

[23–25]. Further studies are needed to assess baseline ROTEM values in obstetric patients with pregnancy-related diseases such as pre-eclampsia and thrombocytopenia.

One of the advantages of ROTEM analysis is that clinical data can be obtained within tens of minutes of test initiation. In order to determine if even earlier time points can potentially provide clinically useful data, a retrospective study using ROTEM data from PPH patients demonstrated a strong correlation between 2- and 10-min result interpretations for certain parameters [27]. These data provide evidence that values obtained within minutes of ROTEM analysis can potentially and usefully guide management of PPH; however, further prospective studies are needed to demonstrate clinical utility.

In 2015, Mallaiah et al. reported their before-after study in which an algorithm for ROTEM-guided fibrinogen concentrate use replaced a standard (empiric) blood product transfusion protocol for PPH resuscitation [28]. These authors extend their findings and report a reduction in the total number of units (from median 6 to 3 units) and total volume transfused (from median 1.7 to 0.8 L) and a reduction in incidence of transfusion-associated circulatory overload (from 7.7 to 0%) with the introduction of the ROTEM-guided fibrinogen administration algorithm [29]. In a similarly designed study utilizing ROTEM-guided blood product replacement for severe PPH, use of the ROTEM device and an algorithm was associated with a higher rate of those receiving no packed red blood cell (PRBC) transfusion (from 5 to 39%), a higher rate of those receiving no fresh frozen plasma transfusion (from 28 to 89%), lower EBL (from 3 to 2 L), and lower rates of other markers of maternal morbidity [30].

Reporting of the pre-clinical use of the ROTEM*sigma* device continues. The cartridge-based sigma device is an update to the ROTEM*delta* device which requires manual pipetting of the sample and reagents. While the authors specifically excluded pregnant patients, a comparison study found values between *sigma* devices and between a *sigma* and *delta* device to be highly precise ($R > 0.99$) and strongly correlated ($R > 0.8$) [31].

Prevention: Uterotonic Agents

Uterine atony remains a common cause of PPH [32]. The efficacy of uterotonic medications is well known; however, the preferred route of oxytocin administration was not well studied. To address this, Adnan et al. completed a double-blind, placebo-controlled, randomized trial of prophylactic oxytocin administration comparing the intravenous (IV) and intramuscular (IM) routes [33]. While these authors found no significant difference in the rate of PPH (≥ 500 mL EBL) between the IV and IM routes (19 vs 23%), they found a significant reduction in cases of severe (≥ 1000 mL EBL) PPH (5 vs 8%) and a reduction in the number of patients transfused (1.5 vs 4.4%), with no difference in side effects (4.1 vs 5.2%) using the IV route. In another trial, the effects on PPH of administration of oxytocin 10 international units (IU) via the IM route, the IV bolus (over 1 min) route, and the IV infusion (diluted in 500 mL and administered by gravity) route were measured [34]. The IV bolus route was found to be the most effective at minimizing QBL, and the IV infusion route was found to be the most effective at minimizing the percentage of patients with QBL ≥ 500 mL. Taken together, these studies advocate for IV administration of oxytocin over IM.

While oxytocin administration is the standard of care for PPH prevention, the requirement of cold storage for this medication poses a barrier to its use in low-resource settings. The use of carbetocin, a synthetic oxytocin analogue with a heat-stable formulation, has been evaluated for PPH prevention recently. In a large, randomized, double-blind, non-inferiority trial, carbetocin 100 μg IM and oxytocin 10 IU IM were compared using the primary outcomes of (1) QBL of ≥ 500 mL or the use of additional uterotonic agents and (2) QBL ≥ 1000 mL [35]. These authors found that the percentage of patients with the first primary outcome was similar between the carbetocin group (14.5%) and the oxytocin group (14.4%), consistent with non-inferiority. Regarding the second primary outcome, the carbetocin group (1.51%) did not meet criteria for non-inferiority compared with the oxytocin group (1.45%); however, the low event rate reduced the power of the trial for this outcome.

In a series of meta-analyses, the use of uterotonics for prevention of PPH has been reviewed. In general, uterotonic agents were found to be effective for preventing PPH when compared with placebo or no treatment [36, 37]. Oxytocin probably reduces the need for additional uterotonic agents; however, it is not associated with reduced need for blood transfusion compared with placebo or no treatment [37]. When compared with oxytocin, three medication regimens may have additional PPH benefits: (1) ergometrine plus oxytocin, (2) carbetocin, and (3) misoprostol plus oxytocin [36]. However, the addition of misoprostol was beneficial only for prevention of PPH between 500 and 1000 mL, and had a significant risk of fever. Finally, carbetocin was found to be superior to misoprostol regarding PPH prevention, need for additional uterotonic agents, length of third stage of labor, and side effects [38].

Treatment: Cell Salvage

The main finding of the 2017 multicentered pragmatic randomized controlled trial of routine cell salvage use for CD in patients at risk for PPH (the SALVO trial) was a non-significant decrease in allogeneic blood transfusion in the cell salvage group [39]. In a similar sized study, but using an

interrupted time series analysis, Yan et al. also analyzed routine cell salvage for CD in patients at high risk for PPH [40]. Similar to the SALVO trial, these authors report a non-significant overall decrease in blood transfusion rate and PRBC units transfused after implementing routine cell salvage. Also like the SALVO trial, approximately 50% of patients in which cell salvage blood was collected received transfusion of the salvaged blood; likewise, there were no amniotic fluid embolism events reported.

While clearly beneficial in some cases, cell salvage confers equipment and personnel costs. Two studies sought to evaluate the cost-effectiveness of routine cell salvage for CDs with a high risk of PPH. The authors of the SALVO trial have reported the findings of a simultaneous analysis that evaluated the cost-effectiveness of cell salvage and reported a minimal cost difference between routine cell salvage and non-routine cell salvage [41]. These findings contrast the conclusion made by Lim et al. in which they found via a modeling method that routine cell salvage was cost-effective in patients at a high risk of PPH undergoing CD [42]. The difference in conclusions of these two studies is likely due to differences in study design. Though the benefit of cell salvage for average-risk CD patients has yet to be established, the safety profile of the technique in obstetric patients is reinforced as these larger studies become available.

Treatment: Tranexamic Acid

Tranexamic acid (TXA) is a small-molecule competitive inhibitor of plasminogen activation to plasmin, the enzyme that degrades fibrin clots. Since the 2017 WOMAN trial that demonstrated a reduction in maternal mortality due to hemorrhage with early (within 3 h of delivery) TXA administration [43••], the efficacy of TXA administration for treatment of PPH was confirmed in a Cochrane review [44] and treatment is now recommended by the World Health Organization [45] and the California Maternal Quality Care Collaborative [46].

One concern of the WOMAN trial was that early maternal mortality events may have diluted the effect of TXA administration because death in these patients may have been imminent and inevitable at the time of randomization regardless of treatment. This effect may have biased the study toward the null hypothesis, that is, that TXA administration had no effect. To address this possibility, a secondary analysis of WOMAN trial was performed in which only those that received TXA within 3 h of delivery were included [47•]. When early maternal morality events were excluded through repeated analyses, the risk ratio of death continued to decline from 0.69 (no exclusion) to 0.41 at 9 h postrandomization. These data likely demonstrate a more profound effect of TXA for prevention of maternal mortality due to hemorrhage than the original WOMAN trial. Of note, this effect was not observed with hysterectomy events, the other primary outcome of the WOMAN trial.

The data are less supportive of prophylactic treatment of PPH with TXA. Prophylactic administration of TXA after vaginal delivery did not show a reduction in PPH (≥ 500 mL QBL) compared with placebo [47•], but has shown benefit for reducing PPH at CD for placenta previa when combined with bilateral uterine artery ligation [48]. A study underway (WOMAN-2 trial) aims to randomize 10,000 patients with hemoglobin level < 10 g/dL to receive 1 g TXA IV or placebo immediately after vaginal delivery and compare the groups with regard to PPH and maternal hemodynamic instability [49].

Two recent randomized studies compared TXA with uterotonic agents for its effect on PPH. In one, a regimen of prophylactic TXA 1 g oral combined with misoprostol 600 mg buccal was found to be as effective at preventing PPH for vaginal delivery as oxytocin 10 IU IV [50]. In another study, patients with uterine atony during vaginal or CD were administered oxytocin 10 IU IV and either carboprost 250 μg intrauterine every 15–90 min for a maximum of 8 doses or TXA 4 g IV over 1 h followed by 1 g over 6 h [51]. There were no differences between the carboprost and TXA groups regarding intraoperative QBL, postoperative QBL, transfusion requirement, or hysterectomy requirement. These studies imply that TXA administration should be considered if certain uterotonic agents are unavailable or contraindicated.

Conclusions

All obstetric facilities should have systems in place for PPH risk stratification, rapid identification, and treatment. Understanding risk factors may allow more intensive patient surveillance and faster hemorrhage treatment in the postpartum period. However, it is important to remember that a significant proportion of PPH patients have no identified risk factors. Algorithms using QBL systems or intensive vital sign monitoring may help in the surveillance process, though these likely do not outweigh vigilance and early suspicion of hemorrhage. Viscoelastic tests such as ROTEM have been successfully incorporated into obstetric hemorrhage algorithms that have led to reductions in transfusion requirements. Uterotonic agents remain a mainstay of PPH prevention and data continue to guide the dose, route, and alternatives to these important medications. Finally, the role of routine cell salvage does not seem to be supported by recent studies, and the role of TXA for treatment, but not necessarily prevention, of PPH continues to evolve.

Compliance with Ethical Standards

Conflict of Interest John C. Markley, MD, PhD, and Daneila A. Carusi, MD, MSc, declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- •• Of major importance

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