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Update on Obstetric Hemorrhage

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Abstract

Purpose of Review Postpartum hemorrhage is increasing in prevalence in the USA and continues to be an important cause of preventable maternal morbidity and mortality. This review provides the most recent epidemiologic data on postpartum hemorrhage in the USA, current nationwide initiatives for prevention, preparedness, and response to postpartum hemorrhage, and recent evidence-based advances in management.

Recent Findings The National Partnership for Maternal Safety consensus bundle on obstetric hemorrhage serves as a resource for postpartum hemorrhage–related clinical and research initiatives. Areas of focus include standardizing postpartum hemorrhage management with protocol use, massive transfusion protocols, early and enhanced risk assessment, accurate quantitation of blood loss, and refined transfusion strategies such as early fibrinogen replacement, tranexamic acid therapy, and point of care testing to detect and treat coagulopathy.

Summary Continued focus on improving the management of postpartum hemorrhage with available resources is imperative to minimize associated risks of morbidity and mortality.

Keywords Postpartum hemorrhage · Obstetric hemorrhage · Maternal morbidity · Transfusion medicine · Point-of-care testing · Quantitative blood loss measurement

Introduction

Postpartum hemorrhage (PPH) is a major source of morbidity and mortality in the USA, complicating approximately 3% of all deliveries [1]. The incidence of PPH in the USA and other countries is increasing, with uterine atony as the leading cause [1–3]. It is the fourth most common source of pregnancy-related US mortality, accounting for 11.4% of pregnancy-related deaths, and is the second most common source of obstetric-ICU admissions in a recent cohort [4••, 5]. Severe PPH requiring massive blood transfusion occurs at rate of approximately 6/10,000 deliveries, with cases seen at even the lowest volume delivery centers [6]. Intrapartum PPH was the leading cause of maternal cardiac arrest (MCA) during admission for labor and delivery in the USA between 1998 and 2011, an outcome that complicated 1 in 12,000 deliveries with a mortality rate of 53.2–55.1% [7]. A similar 13-year analysis in Canada reported a MCA incidence of 1 in 12,500 admissions, with both hemorrhage and conditions associated with PPH including morbidly adherent placenta (MAP), placenta previa, placental abruption, and polyhydramnios significantly associated with MCA [8•].

Recognizing morbidity from PPH, its widespread prevalence, and its largely preventable nature, national- and state-level quality improvement projects are focused on guidelines to enhance PPH management, including the National Partnership for Maternal Safety (NPMS) consensus bundle on obstetric hemorrhage [9••]. The NPMS hemorrhage bundle provides PPH management recommendations for

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implementation at every labor and delivery (L&D) unit in the USA. The bundle includes 13 elements within 4 domains: readiness, recognition and prevention, response, and systems learning [9••]. The California Maternal Quality Care Collaborative (CMQCC) implementation of the NPMS bundle in 99 collaborative hospitals statewide was associated with reductions in severe maternal morbidity from hemorrhage compared to 48 non-collaborative hospitals [10•]. Recent advances in PPH that we review in this chapter are represented in the NPMS hemorrhage bundle, reflecting the importance and widespread utility of these recommendations.

Preparation

General Management and Transfusion Protocols for PPH

The use of a *management protocol* for PPH is a key recommendation of the NPMS hemorrhage bundle. A 2012 survey of academic obstetric centers in the USA reported that approximately 20% of L&D units did not have a PPH protocol in place [11]. Centers with a delivery volume of > 3200 births per year were more likely to have an established protocol (OR 3.16, 95% CI 1.01–9.90) [11]. Implementation of a comprehensive PPH protocol including pre-delivery risk assessment and stepwise escalation of care at 29 L&D units resulted in a reduction of maternal morbidity related to transfusion [12•]. These established protocols are available on the internet (https://www.ajog.org/article/S0002-9378(14)00694-2/fulltext) and serve as resources for any L&D unit. Pre-existing protocols for PPH management can be modified, tailored, and updated to reflect the resources of a unit over time.

A *massive transfusion protocol* (MTP) is important for PPH preparedness. Activation of an MTP triggers the release of a pre-defined ratio of packed red blood cells, fresh frozen plasma, and platelets from an institution's blood bank. Ensuring immediate availability of an MTP for cases of major PPH can decrease the time to procurement of these products, facilitate early transfusion, and avoid morbidity from delayed resuscitation during obstetric hemorrhage [13•]. MTPs specific to obstetric hemorrhage that have a higher content of fibrinogen-rich sources including cryoprecipitate or fibrinogen concentrate may be warranted (Fig. 1), in conjunction with mechanisms to identify low-fibrinogen states during PPH [13•, 14•, 15].

Cell Salvage for PPH

Cell salvage for obstetric hemorrhage has become increasingly accepted as its safety has been established [16•, 17]. While the use of cell salvage for PPH was historically avoided due to the theoretical risk of maternal alloimmunization and amniotic fluid embolism, recent literature indicates that risks of cell salvage in obstetric patients are similar to that of the general population. The use of leukocyte depletion filters reduces fetal cell content in cell-salvaged blood to levels comparable to that of maternal blood at the time of placental separation. A report of 7 peer-reviewed studies including 299 cases of reinfused salvaged blood during PPH revealed no definitive cases of amniotic fluid embolism or other adverse outcomes [16•].

Cell salvage requires trained personnel and preparation of the appropriate equipment, and cases with the highest likelihood to benefit from cell salvage should be identified for optimal allocation of resources. A report of cell salvage utilized for 884 cases of PPH during an 8.5-year period identified that only 21% of patients achieved adequate volume of salvaged blood to receive intraoperative shed blood reinfusion, and those who did receive cell-salvaged blood received a mean of 1.2 units. Patients who underwent a cesarean hysterectomy had the highest rate of reinfusion (75 of 103 cases, 73%), while patients undergoing cesarean delivery with a perceived clinical risk for PPH had the lowest rate of reinfusion (94 of 748 cases, 13%) [17]. Patients with active PPH after cesarean or vaginal delivery had intermediate rates of reinfusion (69 and 53%, respectively). A separate study examining the cost effectiveness of cell salvage in obstetrics found that it is beneficial for patients with risk factors for hemorrhage such as placenta previa, suspected MAP, repeat cesarean delivery, multiparity, chorioamnionitis, placental abruption, hypertensive disorders, or uterine rupture, though not for routine cesarean deliveries [18••]. Taken together, these reports confirm the safety of cell salvage as a way to lower maternal exposure to allogeneic blood transfusions during PPH, and advocate reserving its use for high-risk cases to optimize its cost-benefit ratio.

Recognition and Prevention

Delayed recognition of PPH and "too little done too late" continues to be an area of focus to reduce preventable morbidity [19–21]. The NPMS hemorrhage bundle emphasizes pre-delivery assessment of hemorrhage risk, measurement of blood loss as quantitatively as possible, and active management of the third stage of labor [9••].

Identification of Risk Factors for PPH

Identification of PPH risk factors is essential in the antepartum, intrapartum, and postpartum periods [10•, 12•]. Patients should be systematically screened by their obstetrician prior to admission for L&D. Patients at high risk for PPH such as those with suspected MAP should deliver at a tertiary center that has resources to manage major PPH. Multidisciplinary management of patients at high risk for

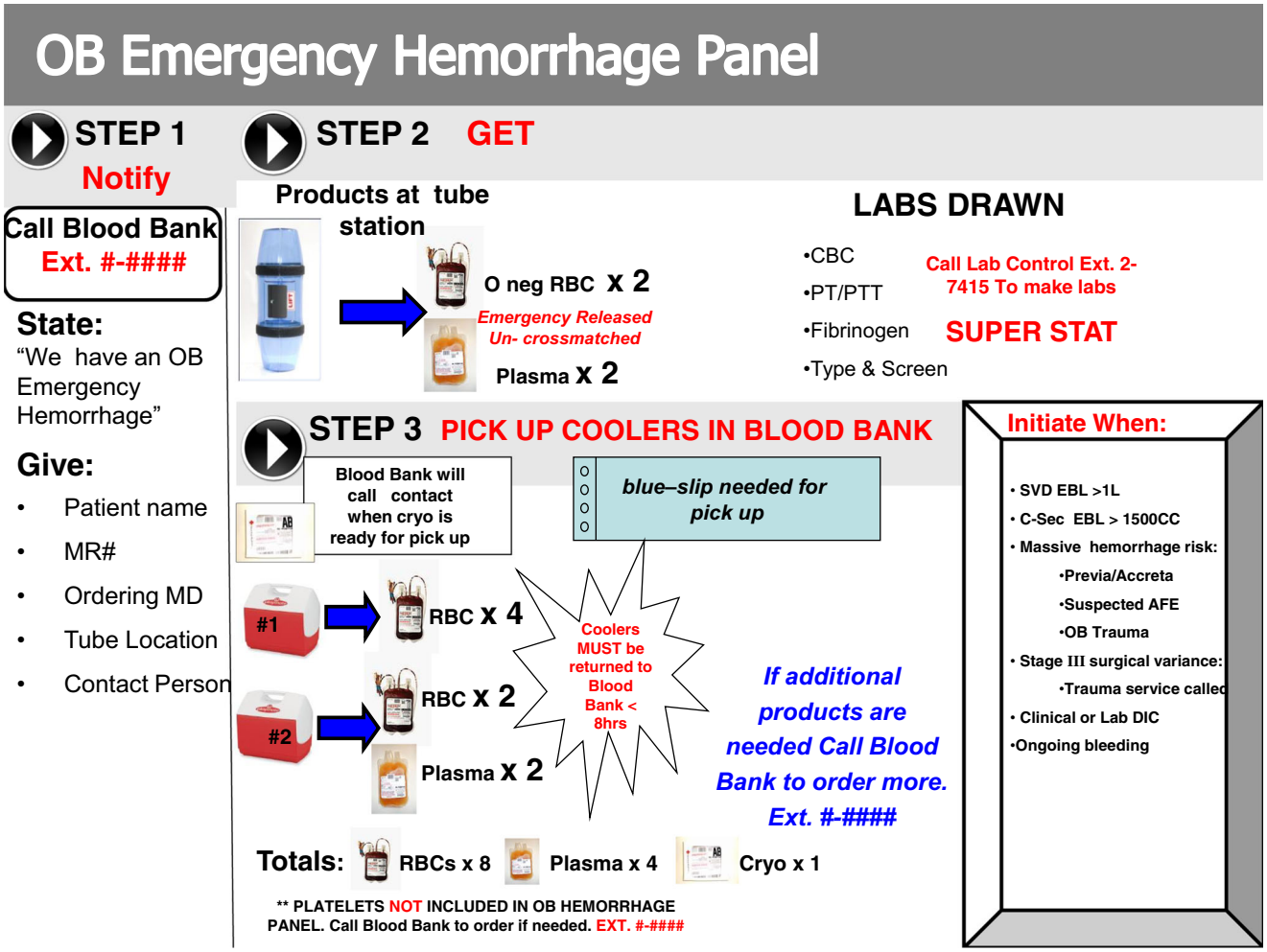

Fig. 1 Transfusion algorithm for obstetric hemorrhage. Used with permission, R.M. Kaufman MD and A.D. Miller MD

bleeding can facilitate pre-delivery planning for resources such as specialized obstetric anesthesia management, blood product availability, procoagulant therapy, interventional radiology, urology, general surgery, and intensive care [22•]. Upon admission for L&D, providers in the hospital can review pre-determined risk factors and continuously re-evaluate for new risks through the course of L&D. Risk factors for severe PPH after cesarean delivery (> 1500 mL blood loss or blood transfusion within 48 h of delivery) were compared among women who required intrapartum cesarean delivery vs. elective cesarean delivery [23••]. Shared risk factors for severe PPH included general anesthesia and multiple gestation, while placenta previa and pre-delivery anemia were unique risks for scheduled vs. unscheduled cases, respectively [23••].

Uterine atony is the leading cause of PPH, accounting for 79% of cases in a recent US database analysis [1]. For patients with uterine atony requiring blood transfusion, risk factors were identified in only 40% of cases [1]; early detection of uterine atony and timely administration of methylergonovine or carboprost is important, even in the absence of risk factors for uterine atony. A recent multicenter database analysis evaluated outcomes from uterine atony–related PPH to identify risk factors. Morbidity occurred in 10.6% of cases and included blood transfusion, cesarean hysterectomy, arterial ligation, or intensive care unit admission. Risk of morbidity was highest among African-Americans, Hispanics, women with multiple gestation, placenta previa, American Society of Anesthesiology (ASA) classes III and IV, exposure to general anesthesia or combined general and neuraxial anesthesia, or two or more prior cesarean deliveries [24]. Prompt recognition of these risks for increased morbidity from PPH enables focus on modifiable, patient-specific factors to optimize safety.

Advances in the Quantitation of Blood Loss After Delivery

Interventions for PPH are typically triggered when the observed or measured blood loss exceeds 500 mL after vaginal delivery or 1000 mL after cesarean delivery [25]. The 2017 Practice Bulletin from the American College of Obstetricians and Gynecologists (ACOG) defines PPH as any cumulative blood loss greater than or equal to 1000 mL, or blood loss

accompanied by symptoms or signs of hypovolemia within 24 h of delivery regardless of route of delivery [26••]. However, visual estimation of blood loss (EBL) is plagued with inaccuracy due to blood concealed in the uterus itself (placental abruption, uterine atony) or under surgical drapes, inevitable admixture of blood with amniotic fluid or irrigation fluid, and physician or nurse denial when a patient without any risk factors has abnormal bleeding. Even during cesarean delivery, a controlled surgical setting with the constant presence of an obstetrician and anesthesiologist, blood loss underestimation can occur and may prohibit timely resuscitation [27]. Urgent delivery, general anesthesia, greater surgeon experience, and higher patient BMI are risk factors for major blood loss underestimation [28•]. As such, objective measures of blood loss are increasingly being employed for timely diagnosis and more accurate quantification of PPH.

Gravimetry

Quantitation of blood loss (QBL) by gravimetry, in which 1 g of a blood-saturated sponge minus the sponge's dry weight is equivalent to 1 mL blood loss, is recommended as standard of care for all deliveries by the ACOG Patient Safety and Quality Improvement, the CMQCC hemorrhage bundle, the NPMS hemorrhage bundle, and the AWHONN Practice Brief [9••, 29–31]. In a simulated PPH scenario with known volumes of blood, QBL by gravimetric analysis yielded 4.0% error compared to 34.7% error by visual estimation of blood volume [32]. Clinical use of gravimetry for PPH correlated to corrected fall in hemoglobin (correlation coefficient 0.77) and requires only basic equipment, is easy to perform, and enhances accuracy of blood loss detection during PPH.

Calibrated Drapes

Toledo and colleagues demonstrated that the accuracy of visual EBL worsens with increased volumes (up to 41% underestimation at 2000 mL) and that the use of calibrated drapes reduces inaccuracy to < 15% error at all volumes measured in a simulated vaginal delivery environment [33]. However, a cluster-randomized trial of 25,831 vaginal deliveries in 13 European countries reported no change in severe maternal morbidity or blood transfusion with use of calibrated drapes compared to visual EBL [34]. A randomized controlled trial of 900 deliveries comparing calibrated drapes to gravimetry demonstrated that use of a calibrated drape was superior for the detection of blood loss greater than 500 mL [35•]. Taken together, these studies affirm that the use of calibrated drapes for QBL during PPH is more accurate than visual EBL in simulated environments, may be superior to gravimetry, but yielded no benefit over visual EBL in the clinical setting. Of note, neither of these clinical trials reported on maternal anemia nor infection and the latter study did not report severe maternal morbidity, outcomes that facilitate meaningful clinical comparisons between methods for QBL [36].

Studies to evaluate clinical accuracy of QBL by gravimetry or calibrated drapes rely on pre- and post-delivery hemoglobin which is challenging due to other variables such as fluid, uterotonic, and blood product administration. As the accuracy of QBL using gravimetry or calibrated drape measurement has been demonstrated in simulated environments, future studies are needed to evaluate other outcomes such as whether QBL enhances team recognition of faster rates or acuity of blood loss or leads to faster treatment by uterotonic administration or surgical intervention.

Innovation in EBL Performance

The Triton System (Gauss Surgical, Inc., Los Altos, CA) is a novel, US Food and Drug Administration–approved mobile application on a tablet computer (iPad, Apple Inc., Cupertino, CA) that utilizes the tablet camera's image capture to measure the mass of hemoglobin on surgical sponges using feature extraction technology (FET). FET uses colorimetric correction and analysis and cloud-based models with machine-learning capabilities. With similar technology, hemoglobin content of fluid in suction canisters can be extracted. QBL using the Triton System has been compared to hemoglobin concentration obtained by soaking blood-containing sponges in heparinized saline, rinsing them by manual compression or centrifugation, and analysis by a hemoglobin analyze. Triton QBL correlated well with both in vitro and in vivo hemoglobin measurements from manual rinsing, and was more accurate than gravimetry in the in vitro comparison [37, 38]. Among 50 women having cesarean delivery, QBL determined by the colorimetric system was compared to visual EBL and gravimetry using hemoglobin extraction from surgical sponges as the reference standard [39]. By Bland-Altman comparison between measures, the FET colorimetric method was more accurate than gravimetry or visual EBL, which systematically overestimated blood loss. Of interest, blood loss by extraction in this study was a mean of 470 mL, a volume less than commonly estimated for cesarean delivery, pre- and post-delivery hemoglobin was not reported, and blood loss on surgical drapes was not accounted for by any method compared. A second study comparing blood loss measurements after cesarean delivery by visual EBL, gravimetry, and the colorimetric system revealed only weak correlation between any measuring modality and the postpartum hemoglobin values [40••]. This study was under conditions of low blood loss and suggests that visual EBL during cesarean delivery is not inferior to gravimetry or more sophisticated measurements under low blood loss conditions. The greater accuracy of the colorimetric technique demonstrated in the first study but not the second study may be due to different methods utilized for determining hemoglobin: hemoglobin extraction vs. early

postpartum hemoglobin change, respectively. Further studies are warranted to assess the utility of this platform under higher blood loss conditions, understanding the challenge that we lack a gold standard for direct calculation of blood loss. Ongoing refinement of methods for hemoglobin measurement and cumulative gravimetric QBL may also facilitate future PPH intervention studies in which blood loss is a primary or secondary endpoint.

Response to PPH

Recent advances in PPH interventions include the use of tranexamic acid (TXA) to decrease morbidity or mortality, prioritizing treatment of low-fibrinogen states and fibrinogen replacement, the use of point-of-care coagulation devices such as rotational thromboelastometry (ROTEM®) and thromboelastography (TEG®), and novel approaches for the management of suspected morbidly adherent placenta (MAP).

Tranexamic Acid

The WOMAN trial was a landmark randomized controlled trial comparing TXA 1 g intravenous (IV) at the time of PPH to placebo, with the primary endpoint of maternal death from PPH. Over 20,000 women were enrolled in this multicenter study, which showed the risk of death from PPH was significantly reduced after TXA therapy (RR = 0.78; 95% CI 0.62–0.98, $p = 0.03$). Significantly, TXA therapy yielded no reported increase in pulmonary embolism or other thromboembolic sequelae. The recommendation that emerged from this study was to administer TXA after maternal bleeding onset, but within 3 h of delivery [41]. The number needed to treat to prevent death from PPH with TXA was 1 in 250. However, a large proportion of study subjects in the trial delivered in low-resource environments, and the comparative number needed to treat in high-resource settings is likely to be substantially higher [42].

In a multicenter, double-blinded, randomized controlled trial of 3891 women in labor who had spontaneous vaginal deliveries, prophylactic TXA 1 g IV with prophylactic oxytocin did not lower the rate of PPH defined as at least 500 mL in a graduated collector bag. Patients in the TXA group had a higher incidence of nausea and vomiting, but no increase in thromboembolic events within 3 months of treatment [43]. Further study of prophylactic TXA after instrumented or traumatic vaginal delivery is warranted before it becomes standard of care.

The Role of Fibrinogen During PPH

Interest in fibrinogen during PPH has been prioritized since Charbit and colleagues demonstrated that a maternal serum fibrinogen < 200 mg/dL at the onset of PPH has a positive predictive value of 100% for progression to severe PPH. Fibrinogen, factor I, is the most abundant procoagulant factor by molecular weight, and thus is most susceptible to hemodilutional decrease below normal pregnancy range (350–600 mg/dL at term gestation) during resuscitation. Furthermore, certain maternal bleeding etiologies such as placental abruption and amniotic fluid embolism induce a hyperfibrinolytic state in which profound coagulopathy including low fibrinogen can cause and compound PPH.

Recent work has evaluated timing, triggers and the impact of fibrinogen replacement during PPH. In a randomized controlled trial of 249 patients diagnosed with PPH, 2 g of prophylactic fibrinogen concentrate did not lower the need for red blood cell transfusion [44•]. Patients in this study had a mean serum fibrinogen level of 450 mg/dL prior to fibrinogen therapy, and the identification of patients with low-fibrinogen states may be more efficacious as a trigger for targeted fibrinogen therapy. In a study administering fibrinogen concentrate 1 g IV during PPH if ROTEM® Fibtem A5 was < 15 mm, there was no benefit compared to those who received placebo [45]. A pre-specified subgroup analysis in this study suggests that fibrinogen supplementation may benefit patients with a ROTEM® Fibtem A5 < 12 mm, and further studies using this ROTEM® threshold are warranted.

In a before-and-after study, introduction of a novel algorithm utilizing ROTEM®-based fibrinogen administration during PPH (51 patients) was compared to the use of MTP "shock packs" during PPH (42 patients). Patients with PPH managed with ROTEM®-based fibrinogen therapy had lower numbers of blood products transfused, more fibrinogen concentrate, and a lower incidence of transfusion-associated circulatory overload [14•]. An algorithm for PPH that titrates fibrinogen concentrate administration based on prothrombin time and serum fibrinogen levels was evaluated in 19 patients and 19 historical controls, and demonstrated increased fibrinogen infusion, decreased fresh frozen plasma infusion, and lower blood loss after initiation of fibrinogen therapy (229 vs. 1110 mL) [15].

Point-of-Care Coagulation Testing

POC coagulation testing with ROTEM® or TEG® to guide transfusion during PPH is encouraged by the ASA Task Force on Perioperative Blood Management and the European Society of Anesthesiologists [46, 47], and high-quality algorithms exist to manage coagulopathy during PPH (Fig. 2). De Lloyd and colleagues demonstrated that in PPH, serum fibrinogen measurement best correlated with the severity of the bleed, and standard coagulation tests (activated partial thromboplastin time, aPTT, and prothrombin time, PT) remained within normal range of most

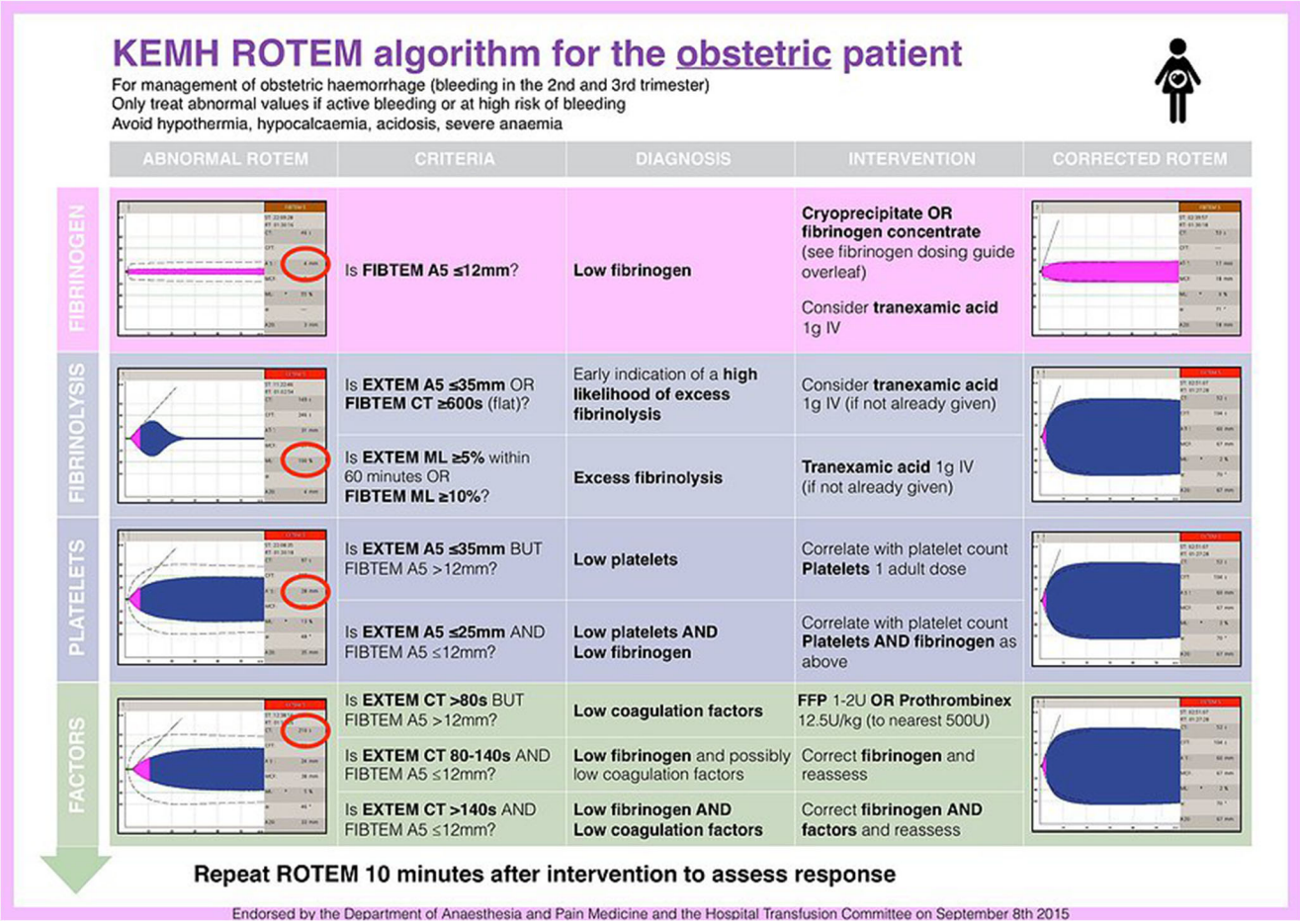

Fig. 2 Point-of-care testing for obstetric hemorrhage. Used with permission, R. Browning MD (https://www.obsgynaecritcare.org/)

women with PPH until 4-5 L blood loss. Therefore, the standard coagulation tests do not serve as clinically useful triggers for PPH transfusion therapy [48]. POC testing can evaluate serum fibrinogen level, overall clot strength, and fibrinolysis within 10 min. POC references ranges in pregnancy are well defined and reflect the hypercoagulable changes of pregnancy [49, 50]. Serum fibrinogen levels can be correlated with ROTEM FIBTEM amplitude at 5 and 15 min and FIBTEM maximum clot firmness ($r = 0.82$, $p < 0.001$) [51].

The use of ROTEM-based algorithms to guide transfusion for PPH has been shown to lower overall blood product transfusion [14•, 52], lower the transfusion of fresh frozen plasma [15], lower the incidence of transfusion-associated circulatory overload [14•], and potentially decrease costs [52]. POC-guided transfusion may decrease the reliance upon fixed-ratio transfusions that may not be appropriate in the obstetric setting [52]. However, comparative data on the relative benefits of different POC tests (i.e., TEG® vs. ROTEM®) are lacking and much of the current body of literature is based on elective cardiac surgical patients rather than on obstetric patients [53].

Advances in Management of Morbidly Adherent Placenta

Prior cesarean delivery is a well understood risk factor for MAP, particularly in the context of current placenta previa [54•]. With the increasing rate of cesarean delivery in the USA, defining best practice for patients with suspected MAP is warranted. There is a greater than fourfold risk for severe maternal morbidity associated with placenta accreta, with substantial risk for PPH and need for blood transfusion [55••, 56]. A key, life-saving recommendation is that all patients with suspected MAP or multiple risk factors for MAP be delivered at a tertiary care center well equipped for major PPH resuscitation. Panigrahi et al. recently published a protocol for the management of MAP that includes multidisciplinary planning, use of obstetric MTPs, and POC testing to guide transfusion management [22•]. Preoperative planning ideally incorporates the anesthesia plan, obstetric plan, and anticipated nursing care. Though general anesthesia was previously the anesthetic of choice, neuraxial anesthesia has been increasingly reported. One single center, retrospective analysis of anesthesia for cesarean delivery in 129 patients with placenta

previa and suspected MAP demonstrated that neuraxial anesthesia was utilized as the primary anesthetic in 95% of cases, with 21% requiring intraoperative conversion rate to general anesthesia. Patients requiring conversion to general anesthesia had higher rates of packed red blood cell transfusion, longer surgical duration, and history of ≥ 3 previous cesarean deliveries [57]. Thus, neuraxial anesthesia should likely be considered a reasonable option for cases of suspected MAP, with an understanding of the risk factors that increase the likelihood of conversion to general anesthesia.

An advance in the use of interventional radiology for the management of PPH involves balloon occlusion of the lower abdominal aorta to control bleeding for patients with suspected MAP. A retrospective analysis of 45 patients who received a prophylactic abdominal aortic balloon for cesarean delivery with suspected MAP reported a 24.4% red blood cell transfusion rate and a mean estimated blood loss of 835 mL. These patients had very high risk of suspicion for MAP and confirmed placenta accreta ($n = 22$), placenta increta ($n = 20$), and placenta percreta ($n = 3$) at the time of delivery. Two of 45 patients (4.4%) experienced complications from aortic balloon occlusion including one case of lower extremity arterial thrombosis and one case of femoral nerve ischemic injury [58]. A before-and-after study in which internal iliac balloon catheters were introduced for patients having repeat cesarean delivery with suspected MAP demonstrated no reduction in blood loss and an increased rate of cesarean hysterectomy with use of internal iliac balloons. Furthermore, patients in the intervention period were more likely to have general anesthesia (100% vs. 54%), attributed to heparinization for vascular cannulation and inability to flex the leg for spinal placement anesthesia [59]. Given the lack of value from iliac arterial occlusion reported in this study, aortic occlusion may be superior, though further studies are warranted to confirm this and to determine optimal timing and patient selection for the lowest risk and highest benefit interventions.

Systems Learning

In order to assess compliance with hemorrhage bundle elements on an L&D unit, initial identification of deficient elements and determination of potential barriers to implementation are an effective way to gather group consensus for systems improvement [60]. These assessments should ideally be performed by a multidisciplinary task force representing the entire L&D unit, including obstetricians, anesthesiologists, surgical technicians, and nursing teams. Defining priorities and barriers to change is a constructive way to initiate implementation of any bundle elements found to be deficient. Establishing a culture of preoperative/preprocedural team huddles and post-event debriefing is important for identifying and tracking systems improvement initiatives.

Conclusions

PPH continues to be an important global health concern. The NPMS consensus bundle on obstetric hemorrhage with its four key domains—preparation, recognition, management, and systems improvement—has shaped and impacted modern research and advances in PPH management. Continued focus on enhanced risk assessment, QBL, and refined transfusion strategies is justified, with the goal of improving maternal outcomes when PPH occurs.

Compliance with Ethical Standards

Conflict of Interest Sharon C. Reale, Lisa R. Leffert, and Michaela K. Farber declare 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 any of the authors.

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