EXPERT REVIEWS

Advances in the treatment of postpartum hemorrhage

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Postpartum hemorrhage (PPH) is the largest contributor to maternal mortality, occurring in between 1 and 5% of deliveries. Prophylactic uterotonics are widely recommended to prevent atonic hemorrhage. Rapid recognition of PPH and identification of hemorrhage etiology is essential to reduce mortality and morbidity. Treatment is etiology-specific and comprises a range of medical, mechanical, temporizing and surgical procedures. Important developments from trauma and emergency medicine around massive hemorrhage protocols are newly implemented for PPH, and the evidence base for PPH medical management is expanding, with clinical trials ongoing. Improving the management of PPH in limited-resource settings will require continued attention to ensure the availability of low-cost accessible prevention and treatment options, in addition to a focus on skilled care providers.

Keywords: emergency obstetric care • hemostatic resuscitation • hypovolemic shock • postpartum hemorrhage

Epidemiology

Postpartum hemorrhage (PPH) is the leading contributor to maternal mortality globally, responsible for approximately 25% of the nearly 300,000 maternal deaths estimated to occur each year [1,2]. It is a major contributor to maternal morbidity, such as anemia [3]. While low-resource countries experience a much higher burden of PPH, it is also a significant cause of maternal death in the developed world [4]. Death from PPH occurs in about 1 per 1000 deliveries in low-resource countries compared with 1 in 100,000 deliveries in higher-resource countries [5]. PPH has traditionally been defined as blood loss ≥500ml within the 24 h following childbirth, with severe PPH defined as blood loss ≥1000ml [6]. Other definitions specified PPH as blood loss >15% of total blood volume, or 10% measured peripartum decline in hemoglobin levels [7]. Recent definitions pay greater attention to symptoms (e.g., lightheadedness, weakness, palpitations, diaphoresis, restlessness, confusion, air hunger and/or syncope) and signs of hypovolemia (e.g., hypotension, tachycardia, oliguria, low oxygen saturation). Most healthy women do not exhibit signs or symptoms of hemodynamic instability until blood loss of 1200 ml. However, some PPH may not be recognized prior to onset of hypovolemia because blood loss is often underestimated [8], bleeding may occur intra-abdominally [9] and less blood loss is sufficient for PPH development when women are compromised by anemia, preeclampsia or another co-morbidity. Provider awareness of blood loss and monitoring of vital signs is important to trigger the initiation of resuscitation measures and to determine response to resuscitation.

PPH is estimated to occur in between 1 and 5% of deliveries [10,11], but incidence estimates vary by definition. Globally, Calvert *et al.* reported PPH prevalence at 10.8% (95% CI: 9.6–12.1) in a recent systematic review and meta-analysis, with wide regional variation ranging from 7.2% (95% CI: 6.3–8.1) in Oceana to 25.7% (95% CI: 13.9–39.7) in Africa [12]. Severe PPH was lower, at 2.8% (95% CI: 2.4–3.2), with similar regional patterning from 1.9% (95% CI: 1.2–2.8) in Asia to 5.1% (95% CI: 0.3–15.3) in Africa. Variability in PPH prevalence was reported by blood loss measurement method (objective vs subjective), management of third stage of labor (active vs expectant), and region. Trend data from the past decade suggest an increasing prevalence of PPH, evidenced by research based in Australia, Canada, USA and UK [13]. Joseph *et al.* report the observed increase in Canada was mediated by an increase in uterine atony despite temporal adjustment for risk

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factors [14]. Wu *et al.* describe a temporal increase in the incidence of placenta accreta over the past several decades, concurrent with increases in cesarean delivery [15].

Etiologies of PPH are traditionally referred to as the '4 Ts': tone, trauma, tissue and thrombin. 'Tone' describes uterine atony, failure of the uterus to adequately contract. It is the primary cause of PPH, responsible for approximately 70% of cases [16]. Genital tract or uterine 'trauma' is responsible for about 20% of PPH, and comprises perineal, cervical and vaginal lacerations as well as spontaneous or iatrogenic uterine rupture due to surgical or instrumental delivery [16]. 'Tissue' etiologies including retained placenta and abnormal placentation are responsible for 10% of cases [16]. Such etiologies operate via three primary mechanisms of action: uterine atony due to retained tissue prohibiting the uterus from effectively contracting, placental misplacement in less contractile tissue of the lower uterus, or invasive placental implantation with varying levels of attachment to the myometrium and potential extension to other organs (e.g., rectum or bladder) [17]. 'Thrombin' refers to inherited or acquired coagulation disorders including dysfunctions of the clotting cascade or platelets, and disseminated intravascular coagulopathy (DIC), which cause approximately 1% of PPH [16,18].

Diagnosis of PPH

The majority of PPH occurs without warning; thus, consistent implementation of prevention measures, rapid PPH recognition and prompt identification and treatment of hemorrhage etiology are essential to reduce maternal mortality and morbidity [8]. Frequent monitoring of vital signs and palpation of the uterine fundus after delivery is recommended to identify PPH development, and providers should remain cognizant of blood loss and vital signs.

Clinical track and trigger systems including defined threshold values for hemodynamic instability are used to indicate patients at impending risk of an adverse event. The California Maternity Quality Care Collaborative (CMQCC) has proposed designated values for alert and action lines (e.g., heart rate ≥110 bpm, blood pressure (BP) ≤85/45 mmHg and oxygen saturation <95%), and the UK Confidential Enquiry into Maternal and Child Health (CEMACH) developed an 'Obstetric Early Warning Chart' to alert providers to numeric and visual cues for action, used in the National Health System [19,20]. The CEMACH chart triggers a provider to urgent medical assessment when a patient demonstrates either one markedly abnormal observation or a combination of two mildly abnormal observations for the vital signs being tracked (e.g., respiratory rate, O_2 saturation, temperature, heart rate, BP). Validation of this chart reported high sensitivity and reasonable specificity, but called for further refinement of low blood pressure threshold values [21]. The Royal College of Obstetricians and Gynecologists (RCOG) recommends the use of an obstetric early-warning score system such as this for early identification of continuous bleeding [22]. The shock index, a combined measure of pulse and systolic blood pressure (pulse/systolic bp), was found to have clinical utility for early diagnosis of hemorrhage in a recent systematic review by Pacagnella *et al.*; however, further research among the obstetric population is necessary [23]. The evidence base on the effectiveness of trigger tools for reducing intensive care admissions or poor health outcomes is not well-established.

Timely recognition of PPH through accurate monitoring of blood loss at delivery and postpartum is critical in resource-poor settings, in particular, but is also useful in the developed world. The gold standard for blood loss estimation, photospectrometry or colorimetric measurement of alkaline hematin, is impractical for many clinical settings [24]. Visual estimation is the most common method of quantifying blood loss worldwide; however, this method underestimates blood loss between 30 and 50%, with greater inaccuracy as blood loss increases [8]. Dedicated clinical training improves the accuracy of visual blood loss estimation, and use of written and pictorial guidelines may assist labor ward staff [8]. Devices to assist measurement such as an under-buttocks, plastic, closed-ended, calibrated blood-collection drape (Figure 1) also improve valid estimation [24]. Clinicians may soon be able to utilize mobile phones to estimate blood loss using the camera of the phone and a built in algorithm; such a low-cost application that provides real-time blood loss monitoring via scanning is in development [25].

Prevention of atonic PPH

As uterine atony is the leading cause of PPH, agents that improve uterine tone and increase uterine smooth muscle contractility are most beneficial for overall prevention and treatment of PPH. The WHO recommends prophylactic uterotonic administration during the third stage of labor, with oxytocin (IM/IV, 10 IU) the preferred drug [6]. Where oxytocin is unavailable, WHO recommends the use of other injectable uterotonics (e.g., ergometrine/methlergometrine or oxytocin/ergometrine) or oral misoprostol (600 μg) [6]. Updated evidence regarding other common components of active AMTSL prompted the WHO to change recommendations around controlled cord traction (CCT). It is considered optional in the presence of skilled birth attendants, but not recommended in the absence of a skilled provider. NICE and International Federation of Gynecology and Obstetrics (FIGO) also support AMTSL, though the individual components vary by recommending body [26,27]. Early cord clamping and cutting was favored by NICE while fundal massage following placental delivery was recommended by FIGO [26,27]. Recent WHO recommendations suggest performing delayed cord clamping (1–3 min after birth) and intermittent uterine tone assessment [6]. AMTSL requires a trained healthcare provider for implementation; the risks of AMTSL performed by unskilled birth attendants, particularly CCT, are not well studied [6].

A number of other pharmacologic agents have been evaluated for PPH prophylaxis. Recent literature suggests carbetocin may soon play a greater role in PPH prevention given demonstrated equal efficacy as oxytocin and decreased need for

subsequent uterotonic administration at cesarean section, less blood loss and fewer adverse effects than Syntometrine for vaginal deliveries and greater cost–effectiveness over oxytocin among cesarean deliveries [28,29].

Medical management of atonic PPH

Pharmacologic management of atonic PPH includes the use of oxytocin, ergometrine and prostaglandins. Intravenous oxytocin is the preferred initial agent in PPH treatment, regardless of whether a prophylactic dose was administered [6]. If bleeding continues after oxytocin administration or if oxytocin is unavailable, IV ergometrine, ergometrine-oxytocin fixed dose (Syntometrine) or a prostaglandin such as misoprostol 800 µg sublingual can be administered [6]. Simultaneous administration of misoprostol with treatment doses of oxytocin is not recommended [6]. Carboprost is may be useful when bleeding is resistant to other agents [30].

If bleeding proves unresponsive to uterotonics, consideration may be given to tranexamic acid (TXA), a synthetic derivative of lysine with antifibrinolytic properties, or recombinant activated factor VII (rvFIIa), the latter of which is discussed later. A 2010 Cochrane Review of TXA reported decreased blood loss after vaginal and cesarean birth but called for further investigation around efficacy and safety [31]. Two more recent randomized controlled trials (RCT) concurred, yet were underpowered to evaluate safety concerns such as thrombolytic events [32,33]. The WOMAN Trial is currently evaluating TXA for PPH treatment [34]. WHO provides a weak recommendation for TXA where oxytocin and prostaglandins fail to control atonic PPH [6]; however, RCOG reports that fibrinolytic inhibitors seldom have a place in PPH management [22].

Diagnosis of hemorrhage etiology & management of non-atonic PPH

Treatment of PPH is specific to cause of bleeding, and appropriate etiologic management must be implemented. Identification of bleeding source and subsequent repair can rectify bleeding attributable to genital tract lacerations [35]. If bleeding is so severe, hematoma formation so rapid or vaginal tissue so friable that suturing is not feasible, mechanical and conservative surgical intervention may be warranted.

Manual removal of retained placenta is the definitive treatment, and should be performed after attempting gentle CCT with counter pressure upwards on the uterus (skilled provider only), and administration of IM or IV oxytocin but avoidance of ergometrine and prostaglandin E2 alpha (dinoprostone or sulprostone) [6]. A Cochrane review of nine trials suggested that intraumbilical vein injection of prostaglandins or plasma expander may reduce the need for manual removal of placenta; however, further research is necessary to determine the effect on requirement for blood transfusion or therapeutic uterotonics [36].

Abnormal placentation (i.e., placenta accreta, increta, and percreta) should be suspected if manual extraction of retained placenta is unsuccessful. Antenatal diagnosis via ultrasonography, supplemented by magnetic resonance imagery (MRI), will

Figure 1. Calibrated blood drape.
Figure courtesy of Suellen Miller.

minimize maternal and neonatal mortality and morbidity and is particularly important among women with prior cesarean section [22,37]. Lower blood loss and fewer complications are observed in planned versus emergent cesarean hysterectomies; thus, planned cesarean delivery is favorable [38]. Scheduled cesarean at 34–35 weeks balances the increased risks associated with an emergency cesarean section with advancing gestational age while maximizing fetal maturity [39]. Optimal delivery management includes antenatal optimization of maternal hemoglobin level, early assessment by anesthesiologist, placement of pneumatic compression stockings, administration of prophylactic antibiotics, performance of pre-operative cystoscopy, alerting the blood bank for potential massive hemorrhage and ensuring availability of blood products in the operating theater [37]. Where women strongly desire future fertility, conservative approaches to the management of placenta accreta have been attempted such as ligation, suturing, uterine artery embolization (UAE) and methotrexate to accelerate placental regression; however, the evidence base is low for these methods [40-42].

Uterine rupture and uterine inversion are rare yet serious obstetrical complications, which may result in PPH. The most common etiology of uterine rupture is a prior uterine scar from a cesarean section or other uterine surgery [43]; however, it is often due to prolonged obstructed labor or use of herbal preparations to induce or augment labor in low-resource countries [44]. Rupture may extend superiorly toward the uterine fundus, inferiorly toward the bladder and vagina or laterally toward the broad ligaments thus increasing the risk of substantial blood loss and associated maternal morbidity and mortality. Labor induction/augmentation is implicated in uterine rupture,

Figure 2. Intrauterine balloon tamponade.
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with greater evidence for prostaglandins than for oxytocin [45]. The American College of Obstetricians and Gynecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) acknowledge the potential increased risk of uterine rupture with induction, but support its rational use in conjunction with appropriate patient counseling [46]. ACOG and RCOG recommend vaginal birth after cesarean (VBAC) be undertaken in a suitably staffed and equipped delivery facility capable of providing emergency care. SOGC indicates that laparotomy be available within 30 minutes. Signs and symptoms of rupture include abdominal pain and tenderness, vaginal or intra-abdominal bleeding, chest pain, fetal de-oxygenation, cessation of uterine contractions and palpation of the fetus outside of the uterus. Early recognition or suspicion of rupture allows for timely surgical evaluation, fetal delivery and surgical repair of the uterus. Delays in diagnosis or management may otherwise result in fetal and/or maternal death [43]. Uterine inversion may result from forceful placental cord traction at placental delivery, especially where the uterus is not well contracted, or spontaneously with Valsalva maneuver [43]. Manual return of the uterus to its proper anatomical position will correct the inversion and the resulting PPH [43]. Tocolytics, halogenated anesthetics or nitroglycerine may be administered to relax the uterus and aid in reversal [47]. If the inversion is resistant to manual efforts, surgical intervention may be required [47].

Bleeding due to inherited or acquired coagulopathy is an uncommon cause of PPH; however, it should be considered with a family history of bleeding defects or personal history of menorrhagia [48]. More common is development of DIC, a consumptive coagulopathy caused by severe PPH. In DIC, the clotting cascade is activated and fibrin-rich thrombi are deposited intra-vascularly. This process causes rapid depletion of platelets and clotting factors, and severe bleeding develops due to the body's inability to continue forming clots as factors V and VII, platelets, prothrombin and fibrinogen quickly become depleted [49]. The hemorrhage that ensues from factor depletion is managed by factor replacement and transfusion of blood products [50]. Treatment with fibrinogen concentrate within the obstetric population suggests rapid and efficient treatment of hypofibrinogenemia in the absence of severe adverse effects [51,52]. Clinical trials of fibrinogen concentrate conducted among elective and cardiac surgery patients have found improved hemostasis and reduced need for other blood products [53]; however, the first RCT focusing specifically PPH is still underway [54].

Mechanical procedures for PPH management

Mechanical procedures used to treat atonic and non-atonic PPH include uterine massage, uterine packing and tamponade [6]. WHO and FIGO strongly recommend the use of uterine massage for treatment of PPH immediately upon diagnosis [6,27]. Uterine packing is no longer recommended by the WHO due to concerns around potential harms [6]. The WHO does recommend intrauterine balloon tamponade (IUB) (Figure 2) for atonic PPH unresponsive to uterotonics or when uterotonics are unavailable [6]. IUB placement may reduce the need for invasive procedures; however, the evidence base is solely comprised of case-reports [55]. Uterine balloons such as the Sengstaken tube, Bakri and Rüsch balloons are available in higher-resource countries but are prohibitively expensive for use in low-resource areas. Concerns around increased infection rates with IUB use are not supported by the literature [56]. Intra-vaginal tamponade has been suggested for management of vaginal lacerations, but this has not been adequately explored [57]. IUB also serves as a diagnostic tool to indicate whether laparotomy is required [58]. Finally, use of IUB in conjunction with B-lynch or other compression sutures is a technique referred to as the 'uterine sandwich'; this joint method has been successful at avoiding hysterectomy in all reported cases with no postpartum morbidity and warrants further exploration [59]. Chemical tamponade agents are also being explored for PPH [60].

Temporizing measures & other procedures for PPH

Temporizing measures recommended for intractable atonic and non-atonic PPH include external aortic compression, bimanual uterine compression and the non-pneumatic anti-shock garment (NASG) [6]. External aortic compression significantly reduces blood flow to the pelvic organs while preserving blood supply to surrounding organs [61]. It has traditionally been accomplished manually, with a provider applying pressure with a closed fist on the abdominal aorta slightly to the patient's left and immediately above the umbilicus [62]. Recently, the external aortic compression device (EACD), a hand-made spring device held in place by a leather belt, was used as a first aid temporizing intervention. EACD use was associated with significantly reduced time to cessation of uterine bleeding in one study; however, additional research is necessary to determine the effectiveness of this device [61].

The NASG (Figure 4) is a low-technology first-aid device for stabilizing women suffering hypovolemic shock secondary to

obstetric hemorrhage (OH). It is a lightweight, re-usable lower-body compression garment made of neoprene and Velcro™. The NASG plays a unique role in hemorrhage and shock management by reversing shock and decreasing blood loss; thereby stabilizing the woman until definitive care is accessed. The NASG increases blood pressure by decreasing the vascular volume and increasing vascular resistance within the compressed region of the body, but does not exert pressure sufficient for tissue ischemia like its predecessors. It can be used for OH of any etiology, applied by individuals with minimal training, and does not compete with the use of other PPH management interventions. Quasi-experimental studies at the tertiary care facility level have shown significantly reduced measured blood loss, more rapid recovery from shock and decreased mortality [63–65]. The NASG is recommended as a temporizing measure for PPH by the WHO and FIGO [6,27], and RCOG indicates that NASG may be useful in UK settings during transfer from midwife-led to consultant-led units [22]. It also may have a role during transport of hemorrhaging women from rural areas to urban treatment centers, or while awaiting procedures or surgery.

Figure 3. Blood collection mat.
Reproduced with permission from [113].

Arterial balloon occlusion and UAE are procedures that can prevent major blood loss, obviating the need for blood transfusion and hysterectomy, and are recommended for trial prior to surgical intervention [66]. These procedures are performed by an experienced interventional radiology team. Occlusion is often prophylactic for known placenta accreta by placement of occlusive balloons in the internal iliac or uterine arteries, which are inflated in the event of PPH [67]. If bleeding continues despite inflation, embolization can be performed via the balloon catheters, or via dedicated catheters by placement of microparticles, polyvinyl alcohol, gel foam or coils, which occlude blood flow to the uterine arteries [68]. UAE is recommended as a conservative management alternative for multiple hemorrhage etiologies where resources are available [6]. It is not widely used despite case studies demonstrating high clinical success rates (95%), low complication rates (4.5%) and preliminary evidence of fertility preservation [69]. Other research reports a comparative advantage of shorter operating time for UAE, lower operating blood loss and higher success rate in placenta accreta when compared with other hemostatic surgeries [70]. Complications such as uterine necrosis, thromboembolic events or fistula have been reported; thus, these techniques require sufficient expertise [71].

Surgical management of PPH

Failed medical and mechanical approaches to management of PPH warrant surgical exploration [72]. The surgical approach differs by delivery method, suspected etiology and clinical status [73]. The surgeon must decide if a dilation and curettage, laparotomy (or re-laparotomy after cesarean section), with exploration and/or hysterectomy is indicated.

Placement of uterine compression sutures in a suspender fashion to promote uterine contractility may be a useful initial attempt at bleeding cessation while preserving fertility. Similar to manual compression and balloon tamponade, compression sutures should be used as a first step in surgical management when hemorrhage is a result of atony. This technique, referred to as a B-Lynch procedure or Cho suture if a hysterotomy has been performed (delivery via cesarean section) and Hayman suture in the absence of a hysterotomy (vaginal delivery), is technically less challenging than vessel ligation and results in less morbidity than a hysterectomy [72]. Alternatively, the uterine or the internal iliac arteries can be ligated bilaterally to temporarily decrease blood perfusion to the uterus. While ligation of the internal iliac arteries was once more common, uterine artery ligation is now favored for ease of identification and higher success rates (80–96%) [74].

While the aforementioned surgical procedures are often attempted in succession, combining surgical techniques may maximize hemostasis while maintaining fertility. Shahin *et al.* combined compression sutures and uterine artery ligation on patients with atonic PPH secondary to adherent placenta accreta [75]. While the study sample was small (n = 26), this approach may be a safe and effective option for surgical management of atonic PPH in the future. In the event that compression sutures, vessel ligation and stepwise de-vascularization fail, definitive management of PPH is hysterectomy.

Transfusion protocols for PPH

The WHO recommends that health facilities have a formal protocol in place for PPH management [6]. Recent resuscitation

algorithms of PPH are modeled after trauma, and massive transfusion protocols demonstrate improved patient outcomes [76]. Such protocols focus on the creation of a multidisciplinary team for patient care, initiation of appropriate laboratory studies, restoration of fluid volume, correction of a coagulopathy with blood components and factors, appropriate responses to laboratory and hemodynamic assessments and correction of the primary cause of bleeding. Conventional resuscitation follows a stepwise approach starting with intravenous fluids, followed by red blood cells (RBCs) and clotting factors or platelets [77]. While this approach corrects hypovolemia, it worsens existing dilutional coagulopathy, enhances fibrinolysis and contributes to acidemia and hypothermia [78,79]. Recent advances from trauma medicine suggest that increasing the ratio of fresh frozen plasma (FFP) to RBCs from 1:3 and 1:4 to 1:1 or 1:2 improves survival [80].

The fibrinogen decrease seen in severe PPH is of great concern and considered an early predictor of hemorrhage severity [49,81]. Treatment of hypofibrinogenemia involves cryoprecipitate transfusion to maintain fibrinogen levels (100–200 mg/dl) [49,81]. While not approved for PPH treatment, fibrinogen concentrate is available in the US, Canada and Europe for other indications and may be an advantageous alternative. Fibrinogen concentrate is stable at room temperature and can be rapidly administered, unlike cryoprecipitate, which must be kept frozen and then thawed prior to administration. Fibrinogen concentrate also contains a greater concentration of fibrinogen and more reliably increases fibrinogen levels [49]. Widespread belief in benefits of early fibrinogen substitution for PPH spurred this off-label usage; the first RCT (FIB-PPH) is currently in progress [82].

Rapid blood product selection may benefit from the use of a thromboelastograph, a point-of-care device that examines clot formation and dissolution in whole blood, and provides faster results than laboratory testing [49,83]. An observational study of thromboelastograph measurements found that clot amplitude and maximum clot firmness were strongly correlated with fibrinogen levels [84]. Availability of the thromboelastograph in the labor ward could be an important tool for managing PPH.

In obstetrical practice, as in other surgical specialties, patients may refuse transfusion of blood products. Worldwide, members of the Jehovah's Witness faith most commonly decline blood transfusions, even for life-saving purposes, posing unique challenges [85]. Advanced planning regarding alternative management options is critical for Jehovah's Witnesses and for patients with rare antibodies. This is especially true where cesarean section is anticipated [72]. Autologous blood donations can be alternatives to donated blood products, and provide a practical alternative for patients who prefer to avoid allogenic blood transfusions. Pre-operative donation has been successful for managing patients with placenta accreta or previa and appears to be well tolerated by women in the third trimester of pregnancy; however, it requires an operating blood bank for storage, and depends upon accurate prediction of an individual patient's risk of hemorrhage [86,87]. Intra-operative blood collection is accomplished via cell salvage systems; however, there are theoretical risks of contamination with amniotic fluid or fetal cells that can result in amniotic fluid embolism or isoimmunization (in an Rh negative patient), respectively [88]. While data to support these concerns is sparse, precautions such as washing and/or filtration of blood prior to re-administration can be implemented and Rh negative patients should receive Rhogam (Rho (D) immune globulin) following auto transfusion [88]. ACOG and NICE support intra-operative cell saver technology as a safe and feasible option during cesarean sections [72,89].

rFVIIa is an effective, yet expensive, synthetic agent initially FDA-approved to control bleeding among patients with hemophilia and factor VII deficiency and is now used for trauma, surgical and severe PPH patients [50,72]. The effectiveness of rFVIIa is dependent upon adequate fibrinogen and platelets. Thus, where clinical response to rFVIIa is sub-optimal, evaluation and treatment with cryoprecipitate, fibrinogen concentrate or platelet transfusion should be initiated [90]. rFVIIa assists hemostasis in PPH patients with bleeding refractory to pharmacologic management and uterus sparing surgical techniques (e.g., uterine and hypogastric artery ligation) [90]. rFVIIa use in the obstetrical population is controversial due to concern around increased thromboembolic events [91]. Multiple case reports synthesized in a review by Franchini *et al.* support the use of rFVIIa for severe bleeding following conventional treatment failure [92]. In these cases, rFVIIa was most often administered as a means to avert an emergency hysterectomy or prevent additional interventions where hysterectomy was already performed. No thromboembolic events were reported in the review. Recommended administration of rFVIIa is 90 μg/kg rFVIIa as IV bolus over 3–5 min, per RCOG and Franchini *et al.* [92,93]. While RCTs are lacking, significant blood loss reductions have been noted in the available literature, suggesting that rFVIIa may have a place in severe PPH management [94].

Staying prepared

Ensuring that obstetric care providers are adequately prepared for handling hemorrhagic emergencies should be accomplished through high quality medical, nursing and midwifery education, with ample opportunities to practice managing rare events and by verifying that all tools and materials required for PPH intervention are readily available. It is also important that standardized protocols and/or guidelines be adopted and monitored to ensure that facility-level practices are evidence-based.

The California Maternal Quality Care Collaborative (CMQCC) established evidence-based guidelines in 2010 to improve the treatment of OH by both identifying women who may be at higher risk of developing OH and producing a set of best practice steps to guide clinicians through OH management, beginning with prenatal assessment and planning through severe OH presentation [95]. This model supplies materials for a quality improvement-team to conduct a needs assessment and develop a facility-specific OH care guideline. These standards are in place for all California facilities, have been adopted by several other states, and are freely available [202]. Peripartum risk stratification, defined by maternal characteristics and conditions clinically associated with OH, is an

important component of these guidelines and is used to determine prenatal pre-transfusion testing recommendations. A recent validation of the risk stratification supported assessment of peripartum risk upon delivery admission [96]. Results recommended typing and screening high-risk women at admission to improve preparedness. Other states have implemented similar guidelines.

Simulation-based team training (drills) to ensure preparedness for obstetric emergencies can be used to train providers to be prepared for clinical situations, which are infrequent but that have a high potential for morbidity or mortality, such as PPH. Obstetric emergencies are characterized by significant time challenges and the need to manage both mother and child simultaneously. Drills allow for the identification of system weaknesses and strengths, provide the opportunity to test policies and procedures for hemorrhage management and help improve teamwork among staff. RCTs of teamwork training via simulation for acute obstetric situations report increases in knowledge, practical skills, communication and team performance; but have not adequately assessed effectiveness on maternal and neonatal outcomes [97]. Recent developments include birth simulators such as PartoPants™ and Mama Natalie™ to improve fidelity to real-life situations [98].

The establishment and maintenance of obstetrical hemorrhage 'carts' or 'boxes' can improve preparedness through rapid access to supplies, medications and surgical instruments designed to treat PPH [99]. The supply cart/box contains all equipment and instruments used to treat PPH prior to consideration of hysterectomy, including equipment for IV administration, laceration repair and tamponade. Carts/boxes should include job aids such as flow charts or management algorithms. Maintenance of an OH medication kit in an accessible refrigerated storage location and a PPH surgery tray in the operating room is also recommended [99]. Case studies suggest easy access to treatment tools may reduce delays in surgical management of PPH, and need for blood transfusion and hysterectomy [100]. The UK Haemostatis and Thrombosis Task Force recommends maintaining sample tubes for cross-matching, full blood count and clotting studies within labor ward refrigerators so that they are rapidly available [101].

A number of international and national organizations such as WHO, FIGO, CMQCC, RCOG and ACOG have developed and distributed updated guidelines for the management of PPH over the past few years [6,27,72,93,95]. These guidelines reflect the current state of knowledge around best practices for prevention and treatment of PPH and should be integrated into facility and community practices with local modifications as necessary. The WHO recommends the adoption of standardized protocols, as they are considered useful and unlikely to be harmful [6]. Evidence-based recommendations have recently been assembled by the multi-center Safe Childbirth Checklist Collaboration, which is currently evaluating the effectiveness of the checklist on provision of minimum care standards during childbirth. Previous research has demonstrated the difficulty of sustainable behavior change interventions; however, information access, use of role models, skill development and improved resources may be effective ways to overcome barriers to changing obstetric care [102].

Particular concerns in the developing world

A major challenge to reducing the global burden of PPH is the failure to prevent PPH or rapidly connect patients to treatment in low-resource settings. A series of delays in receiving definitive PPH treatment is associated with much higher mortality rates in such settings. Long transport times from communities or primary healthcare facilities, lack of transport or fuel, shortage of skilled providers and lack of basic medical supplies (e.g., medications, intravenous fluids, safe blood) contribute to these delays. Strategies to reduce PPH in low-resource areas must emphasize community-level prevention and first-aid while broadly improving healthcare capacity and access, and will benefit from novel methods designed to overcome the specific challenges of this clinical context [103].

Prenatal evaluation of anemia is important globally; however, diagnosis and treatment of nutritional factors, hemoglobinopathy, malaria and helminth infection is even more important in low-resource countries due to the higher burden of anemia among this population [104].

Despite the fact that oxytocin is the recommended uterotonic for prevention and treatment of PPH, its availability in the developing world is limited due to the requirement for temperature-regulated storage and administration by skilled health provider. The WHO supports oral misoprostol (600 μg) for PPH prevention by community and lay health workers in resource-limited settings where oxytocin use is not feasible [6]. FIGO also recommends community-based misoprostol distribution in conjunction with health worker training [27]. Optimal strategies for community-level distribution of misoprostol for PPH prevention should be considered to maximize limited resources and handle potential side effects of misoprostol. A recent review of community-based distribution suggests that high coverage of universal primary prophylaxis can be achieved through home visit or community-based personnel distribution, with low incidence of erroneous administration [105]. Evaluation of a secondary prevention strategy, selectively offering misoprostol to women who appear to be bleeding more than average, is underway and will inform service delivery programming on clinical outcomes, program feasibility, cost and acceptability of these two community models of PPH care [106].

Development of oxytocin in modes that can surmount low-resource delivery challenges in underway. Oxytocin in a Uniject system, an easy-to-use single-dose injection format, was considered safe and feasible for active management of the third stage of labor in Guatemala and Mali pilot evaluations [107,109]. A recent cluster-randomized trial of Uniject oxytocin administered by peripheral health workers without midwifery skills in Ghana reported a 51% reduction in postpartum blood loss $\leq$500 ml with no safety concerns, providing preliminary evidence that community health workers can safely administer injected oxytocin at home births in rural areas [110]. Pharmaceutical development of powdered, heat-stable oxytocin that can be inhaled is also being developed for an aerosol delivery system to remove the need for cold supply chain, sterile conditions and trained health workers [111].

Community mobilization and engagement strategies play an important role in improving the success of PPH-prevention

Figure 4. Non-pneumatic anti shock garment.
Figure courtesy of Suellen Miller.

programs. Greater community ownership and support of projects has been achieved by establishing rapport with key opinion leaders, and involving community members in the design and implementation of project activities [112,113]. FIGO recommends that community members be taught home-based life-saving skills (HLBSS), community-based obstetric first aid including uterine massage and emergency preparedness [27]. Field tests suggest that HBLSS may be a useful adjunct for a comprehensive PPH prevention and treatment program, and its utility around increasing community support for emergency preparedness is particularly important for ensuring women's access to healthcare where they have less decision-making power [114].

Several low-cost strategies have been devised to improve accurate blood loss estimation in low-resource settings [8]. Prata *et al.* recognized the utility of using household items such as the 'kanga' cloth, a locally produced standard size cotton fabric, for postpartum blood loss assessment in Tanzania [115]. Use of the kanga for recognizing excessive blood loss (soaking 2 kangas = PPH) enabled the development of community-level guidance for early recognition of PPH in Tanzania. This method may translate to similar items throughout the developing world (e.g., chitengis, saris, longis). A dedicated absorbent delivery mat, which holds a maximum of 500 ml of blood, and visually depicts quantity of blood loss has also been effectively used by traditional birth attendants to recognize PPH in Bangladesh (Figure 3) [116]. In 2006, Patel *et al.* validated blood measurement in an under-buttocks, plastic, closed-ended, calibrated blood-collection drape [24]. Blood collection drapes (Figure 1) have subsequently been used in studies in sub-Saharan Africa, Asia and Latin America [63,117].

Given the long delays women in low-resource settings often face obtaining transport, during transport and awaiting definitive treatment, the NASG described previously is particularly suited to these settings (Figure 4). A cluster randomized trial of the NASG applied at the primary healthcare level prior to transfer to the RH was recently completed and suggested a promising trend for mortality reduction. The NASG has been recommended as a temporizing measure for PPH by the WHO and FIGO, and is cost effective [6,27,118].

While the IUB devices currently available are prohibitively expensive for use in low-resource areas, PATH is working to develop an affordable dedicated balloon tamponade [119]. In the meantime, point-of-care assembly of a condom-catheter device is able to achieve the same objective at low cost using commonly available materials [120]. Other low-cost technologies in development that may impact prevention and treatment of PPH include a novel blood pressure device equipped with traffic light early warning systems to indicate that a woman should be referred to care for hyper or hypotension [121].

Finally, one of the largest contributors to PPH and other causes of maternal mortality and morbidity in low-resource settings is the lack of skilled healthcare providers [122]. Increased production of and ability to retain a well-educated health workforce is crucial, but a challenge for many countries. Recent global discussions have focused on task-shifting to provide a greater mix of skilled providers and thus broader access to skilled care and lifesaving procedures. The WHO has made recommendations on key maternal health capacities with respect to each particular cadre of healthcare worker and context including lay health workers, auxiliary nurses, auxiliary nurse midwives, nurses, associate clinicians, advanced level associate clinicians and non-specialist doctors [123]. Countries should work to implement these recommendations into their health worker training programs and staffing.

Conclusion

Broad global access to oxytocin, other uterotonics and oral misoprostol for PPH prevention and treatment is an important strategy to reduce PPH-related mortality. Continued institutionalization of PPH management protocols, and simulation efforts will help ensure preparedness for obstetric emergencies when they occur. Higher FFP to RBC ratios are suggested within resuscitation guidelines for better patient outcomes. Research in progress will inform optimal transfusion protocols, and use of TXA and fibrinogen concentrate for the PPH patient. Low-resource areas must focus on development of health workers and task-shifting.

Expert commentary

The evidence base around PPH prevention and treatment has rapidly expanded over the past decade. Randomized trials evaluating the effectiveness of TXA and fibrinogen concentrate are underway and should provide strengthened treatment guidance over the next few years. The field has benefited from focused efforts on the development of lower cost methods to improve blood loss estimation and temporizing measures targeted for use in low-resource settings such as anti-shock garments.

Hemorrhage preparedness through drills and standardized hemorrhage management guidelines are among the most promising measures for PPH. Algorithms for hypovolemic shock resuscitation have benefited from trauma research, and massive transfusion protocols are now being implemented on obstetric wards. These steps improve patient care and prevent severe anemia and coagulopathy. Broader implementation of higher FFP to RBC transfusion ratios (1:1 or

1:2) noted to improve patient outcomes in the trauma literature should optimize transfusion protocols for PPH in the near future.

While adequate therapeutic options are available for PPH in developed countries, reducing the global burden of PPH requires focused attention on prevention, early identification and access to care. However, delays in making the decision to seek medical care, reaching a facility where care is available and in obtaining quality care at the facility are all significant contributors to preventable maternal death in low-resource settings.

Five-year view

Contemporary resuscitation approaches for PPH are not evidence-based, and recent research suggests that while volume resuscitation followed by RBC transfusion corrects hypovolemia, this approach worsens dilutional coagulopathy and enhances fibrinolysis, leading to poor patient outcomes. Trauma literature reports improved outcomes with increased FFP to RBC ratios, and research is underway to improve the evidence base for defining optimal blood transfusion protocols, particularly among the obstetric population. Mass transfusion protocols are beginning to be developed in the community hospital setting, which will improve treatment capacity and patient outcomes in these settings. Similarly, more rapid selection of blood products, normally a multi-hour process, is enabled by a greater capacity of point-of-care monitoring via thromboelastometry-based machines housed in the labor ward.

Randomized trials are currently ongoing around the administration and timing of fibrinogen concentrate, and the role of TXA for PPH. Results will be available within the next few years and will provide valuable guidance for including these agents in broad recommendations for treatment of PPH.

Greater attention is being paid to the development and implementation of low-cost health technologies to improve access to medical and first-aid devices in low-resource areas such as an IUB and the NASG, and low-technology blood pressure devices designed to trigger the process for referral by community health workers.

Medical education focusing on improving obstetrics and gynecology trainee knowledge and incorporating PPH teaching and drills into residency, nursing and midwifery curricula will improve provider and team preparedness for managing PPH. Greater use of obstetric warning systems and more precise identification of warning thresholds such as the shock index to trigger focused medical attention should expand across facilities. Similarly, evidence-based algorithms have recently been developed for risk prediction of PPH; there may be a future role for individualized medicine, including risk assessment and practice of anticipatory medicine in this field, though the evidence base is undeveloped.

Globally, task shifting for maternal health functions is necessary to improve broad access to lifesaving technologies. Emphasis on training to improve the capacity and effectiveness of non-clinicians and non-physician clinicians is crucial.

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Key issues

- Postpartum hemorrhage (PPH) is the leading contributor to maternal mortality, occurring in 1–5% of deliveries.
- Prophylactic uterotonic administration during the third stage of labor is critical for reducing the incidence of PPH.
- Oxytocin is the preferred uterotonic for prevention and treatment of PPH. Where oxytocin is not available or feasible, administration of other injectable uterotonics or oral misoprostol is recommended for prevention; and ergometrine, oxytocin-ergometrine or a prostaglandin (including misoprostol) is recommended for treatment.
- Treatment for PPH is etiology-specific; prompt identification of cause of bleeding is necessary and appropriate and appropriate definitive treatment should be initiated as soon as possible. Conservative treatment measures should be attempted prior to surgical intervention to reduce the need for hysterectomy.
- Guidelines around resuscitation are changing due to trauma and critical care research suggesting better patient outcomes with higher fresh frozen plasma to red blood cells ratios.
- Randomized controlled trials evaluating the effectiveness of tranexemic acid and fibrinogen concentrate on PPH are currently underway, with results expected within the next few years.
- Institutionalization of standard PPH management protocols combined with a checklist approach and facility preparedness for obstetric emergencies may improve timely implementation of evidence-based PPH management.
- High-fidelity simulations (drills) of acute, severe hemorrhage improve team performance and communication for treatment of PPH.
- Research is needed on the community-level distribution or self-administration of uterotonics, particularly misoprostol, and other management options for PPH where skilled attendants are not available.
- Greater attention to the development of health personnel and task-shifting is required in low-resource areas to ensure adequate availability of health personnel.

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