# Evaluation and management of postpartum hemorrhage: consensus from an international expert panel

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**BACKGROUND:** Postpartum hemorrhage (PPH) remains one of the leading causes of maternal morbidity and mortality worldwide, although the lack of a precise definition precludes accurate data of the absolute prevalence of PPH.

**STUDY DESIGN AND METHODS:** An international expert panel in obstetrics, gynecology, hematology, transfusion, and anesthesiology undertook a comprehensive review of the literature. At a meeting in November 2011, the panel agreed on a definition of severe PPH that would identify those women who were at a high risk of adverse clinical outcomes.

**RESULTS:** The panel agreed on the following definition for severe persistent (ongoing) PPH: *"Active bleeding >1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage."* A treatment algorithm for severe persistent PPH was subsequently developed. Initial evaluations include measurement of blood loss and clinical assessments of PPH severity. Coagulation screens should be performed as soon as persistent (ongoing) PPH is diagnosed, to guide subsequent therapy. If initial measures fail to stop bleeding and uterine atony persists, second- and third-line (if required) interventions should be instated. These include mechanical or surgical maneuvers, i.e., intrauterine balloon tamponade or hemostatic brace sutures with hysterectomy as the final surgical option for uncontrollable PPH. Pharmacologic options include hemostatic agents (tranexamic acid), with timely transfusion of blood and plasma products playing an important role in persistent and severe PPH.

**CONCLUSION:** Early, aggressive, and coordinated intervention by health care professionals is critical in minimizing blood loss to ensure optimal clinical outcomes in management of women with severe, persistent PPH.

The United Nations has identified a 75% reduction of maternal mortality by 2015 as a millennium development goal.[1] Postpartum hemorrhage (PPH) continues to be a leading cause of maternal mortality globally with a case fatality rate of 1%.[2] This represents a significant disease burden, accounting for one-third of maternal deaths in some regions of the world,[3] although the exact incidence of

**ABBREVIATIONS:** POC = point of care; PPH = postpartum hemorrhage; rFVIIa = recombinant activated Factor VII; TXA = tranexamic acid.

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**TRANSFUSION** **,**:**-**.

**TABLE 1. Levels of evidence based on American Congress of Obstetricians and Gynecologists grading system[6]**

| | | |
|---|---|---|
| Level 1 | | |
| | I | Meta-analyses |
| | II | At least one randomized controlled trial |
| Level 2 | | |
| | I | At least one well-designed controlled study without randomization |
| | IIa | At least one well-designed cohort observational study |
| | IIb | At least one well-designed case-controlled observational study |
| | III | At least one well-designed cross-sectional, comparative, or correlation study |
| Level 3 | | |
| | I | Expert committee reports or opinions and well-designed descriptive studies |

PPH remains uncertain given the lack of both precise definition and diagnosis.[3]

Previously, members of this expert panel convened to develop guidelines for the evaluation and management of obstetric and gynecologic problems in women with underlying disorders of hemostasis[4] and for the evaluation and management of acute menorrhagia.[5] In November 2011, international experts in the field of obstetrics, gynecology, hematology, and anesthesiology met to discuss and debate issues surrounding the evaluation and management of PPH, with the aim of developing consensus recommendations to guide clinicians in treatment of the condition.

## METHODS

An extensive literature search was performed using PubMed to identify the relevant and important evidence to inform the consensus. Boolean text searches were performed using the term "postpartum hemorrhage" with the operator "AND" alongside the following terms: "transfusion," "management," "risk," "bleeding disorder," "prevention," "laboratory monitoring," "placenta," "anesthesia," "primary OR secondary," "tranexamic," "fibrinogen," "fresh frozen plasma," "fibrinolysis," "factor VIIa" "thromboelastometry OR ROTEM" and "uterotonic."

Studies considered to be most relevant for inclusion were graded according to the level of evidence they provided. These studies, alongside the clinical experience of the experts formed the basis on which consensus recommendations were made. Any points where full consensus was not achieved have been described, with the need for more compelling evidence highlighted.

Consensus recommendations have been assigned a grade and level of evidence; the use of American Congress of Obstetricians and Gynecologists grading system is summarized in Table 1.[6]

## DEFINITION OF PPH

No single satisfactory definition of PPH exists and a number of definitions are currently in use worldwide (Table 2).[7-10] While existing definitions allow comparison of rates of PPH among different countries, the clinical relevance of these volumes of blood loss in otherwise fit, healthy women is questionable. Determination of rates of clinically severe hemorrhage may be more useful. The severity of PPH will be influenced by the rate and the total volume of blood loss and also the response to treatment. The clinical impact of blood loss will be influenced by maternal health with existing anemia and other medical conditions, making women more vulnerable to decompensation with bleeding around delivery. The panel suggested that the following definition of PPH would identify women at high risk of adverse clinical outcomes and used this to determine its recommendations for management in this paper:

> "Persistent (ongoing) PPH is active bleeding >1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage."

## PPH: CAUSES AND RISK FACTORS

The causes of PPH can be classified into four main groups: 1) uterine atony, 2) placental problems including retained placenta and abnormal placental implantation, 3) genital tract trauma, and 4) systemic medical disorders (including inherited and acquired coagulation defects).[2] Uterine atony is the major cause of PPH accounting for up to 80% of cases of primary PPH.[11]

A large proportion of women who develop PPH do not have identifiable risk factors, so all women must be considered to be at risk. However, antenatal screening is important to identify women who are at high risk of PPH, so that appropriate management plans can be developed and implemented. A summary of risk factors for primary PPH is presented in Table 3.[10-19]

## INHERITED BLEEDING DISORDERS

### von Willebrand disease

Women with von Willebrand disease (VWD) are at increased risk of both primary and secondary PPH (defined by the WHO as any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally[9]). Three case series, summarizing 92 deliveries in 51 women with VWD reported primary PPH in 16% to 29% and secondary PPH in 20% to 29%,[22-24] although selection bias may play a role in these retrospective studies. An analysis of the United States Nationwide Inpatient Sample involving 4067 deliveries among women with VWD (1 in 4000 deliveries) reported PPH in 6% of

**TABLE 2. Summary of primary PPH definitions in current use globally[7-10]**

| Guidelines | Definition |
|---|---|
| Australian 2008 | Blood loss of >500 mL after vaginal delivery and >750 mL after cesarean section |
| Austrian Guidelines 2008 | Blood loss of 500-1000 mL and clinical signs of hypovolemic shock or blood loss >1000 mL |
| German Guidelines 2008 | Blood loss of ≥500 mL within 24 hr after birth<br>Severe PPH is blood loss of ≥1000 mL within 24 hr |
| UK Royal College of Obstetricians and Gynaecologists 2009 | Primary PPH—estimated blood loss of 500-1000 mL in the absence of clinical signs of shock<br>Severe PPH—estimated blood loss of >1000 mL or clinical signs of shock or tachycardia with a smaller estimated loss |
| WHO definition | Blood loss of ≥500 mL within 24 hr after birth<br>Severe PPH is blood loss of ≥1000 mL within 24 hr |

**TABLE 3. Risk factors associated with PPH**

| | OR or range | |
|---|---|---|
| Category and risk factor | >500 mL EBL | >1000 mL EBL |
| Sociodemographic | | |
| Asian ethnicity[12] | 1.8-2 | |
| Hispanic ethnicity[15] | 1.7 | |
| Age ≥ 30 years[12,16] | 1.3-1.4 | 1.5 |
| Obstetric | | |
| Prolonged Stage 3 labor[15] | 7.6 | |
| Preeclampsia[15] | 5.0 | |
| Retained placenta[11,13,18,19] | 4.1-7.8 | 11.7-16.0 |
| Known placenta previa[17,19] | 4-13.1 | 15.9 |
| Previous PPH[15] | 3.0-3.6 | |
| Suspected or proven placental abruption[17,19] | 2.9-12.6 | 2.6 |
| Multiple gestation[12,20,21] | 2.3-4.5 | 2.6 |
| Fetal macrosomia[12,18,19] | 1.9-2.4 | |
| HELLP syndrome[12] | 1.9 | |
| Polyhydramnios[11] | 1.9 | |
| Oxytocin exposure[14] | 1.8 | |
| Induction of labor[12,18,19] | 1.3-2 | 2.1-2.4 |
| Prolonged labor[12,15] | 1.1-2 | |
| Surgical | | |
| Emergency cesarean delivery[12] | 3.6 | |
| Elective cesarean delivery[12] | 2.5 | |
| Forceps delivery[12] | 1.9 | |
| Vacuum delivery[12] | 1.8 | |
| Episiotomy[15,18,19] | 1.7-4.5 | |
| Perineal suture[18] | 1.7 | 2.5 |
| Systemic or medical | | |
| Antepartum hemorrhage[11] | 3.8 | |
| VWD[12] | 3.3 | |
| Anemia (<9 g/dL)[12] | 2.2 | |
| Pyrexia in labor[10] | 2 | |
| Obesity (BMI > 35)[19] | 1.6 | |
| Cardiac disease[12] | 1.5 | |

BMI = body mass index; EBL = estimated blood loss.

deliveries in women with VWD compared with 4% of control women (odds ratio [OR], 1.5; 95% confidence interval [CI] 1.1-2.0).[25] Women with VWD had almost a fivefold greater risk of being transfused (OR, 4.7; 95% CI, 3.2-7.0).

### Carriers of hemophilia

Women who are carriers of hemophilia appear more likely to experience primary and secondary PPH than noncarriers.[20] Hormonal changes during pregnancy induce increases in Factor (F) VIII levels in most carriers of hemophilia A but increases in F IX in carriers of hemophilia B are uncommon.[26] The risk of PPH in carriers of hemophilia is correlated with plasma clotting factor levels, with the most significant cases of PPH observed in women with levels below 50 IU/dL who received no hemostatic coverage during labor and postpartum.[20] The risk of secondary PPH is also increased when clotting factor levels return to normal after delivery.[21]

### Rare bleeding disorders

The limited available data regarding the rate of PPH in women with rare bleeding disorders show that PPH is a common obstetric complication, reported in 45% of the deliveries in 10 women with congenital hypofibrinogenemia[27] and 76% of deliveries in nine women with FV deficiency.[28] High rates of PPH have also been reported in women with FVII,[29] FX,[30] FXI,[23] and FXII[31] deficiencies.

### Severe inherited platelet function defects

Severe platelet (PLT) function defects are also rare. In women with Glanzmann thrombasthenia (GT), primary and secondary PPH was seen in 34 and 24% of pregnancies, respectively.[32] Primary and secondary PPH was reported in 33 and 40%, respectively, of 30 pregnancies among 18 women with Bernard-Soulier syndrome.[33] Women in 15 pregnancies required blood transfusion and two women underwent obstetric hysterectomy.[33]

### Recommendations for prevention of PPH in women with inherited bleeding disorders

Table 4[34] outlines the recommended hemostatic coverage for women with different bleeding disorders. Clotting factor concentrates that are currently available for the treatment of inherited bleeding disorders are listed in Table 5.[5] Management plans for labor and delivery should be individualized after multidisciplinary antenatal risk assessment (obstetric, anesthetic, and hematologic) during the third trimester of pregnancy (Grade 3-I[35]). The

**TABLE 4. Recommendations for the prophylactic treatment of women with inherited bleeding disorders***

| Deficiency | Management |
|---|---|
| VWD | |
| Type 1 | TXA, DDAVP |
| Type 2 | TXA, VWF concentrates, DDAVP in responders |
| Type 3 | TXA, VWF concentrates |
| Afibrinogenemia and hypofibrinogenemia | Replacement therapy according to availability (fibrinogen concentrate, cryoprecipitate, FFP†) and volume status |
| Dysfibrinogenemia | Women with dysfibrinogenemia are also at risk of both postpartum thrombosis and PPH. Postpartum management of these women should be individualized based on their fibrinogen level as well as personal and family history of bleeding and thrombosis. Postpartum thromboprophylaxis in these patients also requires individualized management. |
| FII | PCCs to maintain FII level >20%-30% |
| FV | FFP† (increase FV level to >15%-25%) |
| FV plus FVIII | FV >15%-25%; FVIII >50% (combination of DDAVP or FVIII concentrate and FFP†) |
| FVII | rFVIIa or nonactivated plasma-derived FVII concentrate (15-30 μg/kg) for women with FVII level of <10%-20% hemostatic level for uterine bleeding OR surgery may be higher (clinical observation) |
| FX | Replacement therapy during labor and delivery (FX concentrate or PCC as available) in women with FX levels of <10%-20%. In women with FX level >10%-20% and no significant bleeding history, a conservative approach could be adopted. |
| FXI | Prophylactic treatment with TXA should be considered after delivery up to 2 weeks. For those with a bleeding phenotype and severe deficiency of FXI should receive FXI concentrate if available, otherwise FFP†. Prophylactic treatment with TXA should be considered after delivery for up to 2 weeks. The concomitant use of TXA and FXI concentrates should be avoided due to increased thrombogenicity. |
| FXIII | The incidence of PPH in women with FXIII deficiency is not known. Successful pregnancy in women with FXIII subunit A deficiency is generally only achieved with replacement therapy throughout pregnancy (using FXIII concentrate); a level >10%-20% during pregnancy should be considered. |
| Carriers of hemophilia | FVIII carrier: TXA, DDAVP, FVIII replacement (recombinant or plasma derived)<br>F IX carrier: TXA, F IX replacement (recombinant or plasma derived) |

* It is possible that a patient may deliver where no products but standard blood products are immediately available for an unexpected bleed. In such cases, FFP is used as a second choice. Cryoprecipitate can also be used as a second choice in carriers of hemophilia, VWD, and fibrinogen and FXIII deficiency. Adapted from Peyvandi et al.,[34] Grade 3-I.
† Virus inactivated when available.
DDAVP = desmopressin; PCC = prothrombin complex concentrate.

**TABLE 5. Commercially available clotting factor concentrates for the treatment of inherited bleeding disorders**

| Factor | Brand | Company |
|---|---|---|
| Fibrinogen | Clottafact | LFB |
| | Fibrinogen HT | Benesis |
| | FIBRORAAS | Shangai RAAS |
| | Haemocomplettan P/RiaSTAP | CSL Behring |
| FVII | FVII | Baxter BioScience |
| | NovoSeven (rFVIIa) | Novo Nordisk |
| FX | FX P Behring | CSL Behring |
| FXI | FXI | BPL |
| | Hemoleven | LFB |
| FXIII | Fibrogammin P | CSL Behring |
| | rFXIII-A2† | Novo Nordisk |
| Four-factor PCCs | Beriplex P/N | CSL Behring |
| | Octaplex | Octapharma |
| | Prothromplex Total/S-TIM 4 Immuno | Baxter |

* Adapted from James et al.[5]
† Currently on Phase III clinical trial as hemostatic agent.
PCC = prothrombin complex concentrate.

assessment should consider additional risk factors for PPH, including bleeding history, clotting factor level, and pregnancy-induced changes of factor levels. A plan for hemostatic coverage (including the type, dose, and duration of hemostatic agent) for labor and postpartum should be formulated. Current recommendations for postpartum factor replacement suggest treatment duration of at least 3 to 5 days (Grade 3-I[29]) extended up to 2 weeks or even longer to maintain clotting factors at or above the recommended hemostatic level, especially after cesarean section or in women with other risk factors. Women should be kept under clinical surveillance for up to 4 weeks postpartum. Treatment with hemostatic agents such as antifibrinolytics should continue until the lochia is minimal.

### Women with inherited PLT function disorders

For women with mild disorders, such as PLT secretion and activation defects, tranexamic acid (TXA; 1 g four times daily until lochia is minimal) is generally sufficient (Grade 3-I). In women with moderate bleeding risk and who are not at risk for fluid retention, DDAVP (one to two doses) during the immediate postpartum period can be used in addition to TXA. PLT transfusion should be available in case of hemorrhage with recombinant activated FVII (rFVIIa) on standby. For women with severe PLT function disorders (such as Glanzmann thrombasthenia and Bernard-Soulier syndrome), TXA with or without rFVIIa is used in cases of uncomplicated vaginal delivery (Grade

3-I).[36] In case of operative delivery or in the presence of other risk factors for PPH, PLT transfusion at a dose targeted to achieve a hemostatic response is recommended (Grade 3-I).[37] When available, for women who have had previous transfusion or pregnancy, PLT antibody testing should be performed to detect alloimmunization to human leukocyte antigen and human PLT antigen. If alloimmunization is present, matched PLTs negative for the antigens are required. Leukoreduction of PLT transfusion is required as the preferred method of alloimmunization prophylaxis and to ameliorate other adverse reactions (Grade 2-IIa[38]).

### Can PPH be an indicator of an unidentified bleeding disorder?

PPH is multifactorial in nature and the prevalence of undiagnosed bleeding disorders in women presenting with PPH is unknown. In a study of 50 women with primary PPH screened for underlying bleeding disorders (VWD and FXI deficiency) 3 to 9 months after delivery, only one woman was diagnosed with VWD, suggesting that primary PPH is not a helpful discriminator to screen for these bleeding disorders.[39] Further larger studies are required to fully answer this question. Bleeding assessment tools,[40-42] which catalog the bleeding history of patients to evaluate the likelihood of an underlying bleeding disorder have not yet been validated in women who have experienced PPH.

### Recommendation: bleeding history assessment after PPH

Women with PPH with no obvious obstetric cause should be investigated using bleeding assessment tools, and those who have high scores should be referred for full laboratory hemostatic assessment for underlying bleeding disorders (Grade 3-I).

## MANAGEMENT OF LABOR AND PREVENTION OF PPH

### Active versus expectant management of the third stage of labor

A recent systematic review of five studies all conducted in high-income countries compared active management with expectant or mixed management strategies. Active management was associated with a reduced risk of both severe PPH (>1000 mL) and anemia (maternal hemoglobin after delivery <9 g/dL) compared with other strategies.[26] Active management protocols generally included a uterotonic agent, early cord clamping, and cord traction to facilitate the delivery of the placenta,[26] but the optimal uterotonic agent and protocol have not been determined. Expectant management strategies typically involve no uterotonic administration, no cord clamping or traction, and spontaneous delivery of the placenta.[26] A Cochrane review showed that, compared with no uterotonic therapy, prophylactic oxytocin treatment reduced the risk of PPH by approximately 60% and the need for therapeutic oxytocics by approximately 50%.[43] No statistical difference was observed in the effect of oxytocin (Syntocinon) compared with oxytocin-ergometrine (Syntometrine) in preventing PPH episodes of more than 1000 mL, although oxytocin-only treatment had fewer side effects.[44]

### Recommendation: management of the third stage of labor

Active management of the third stage of labor by skilled attendants is recommended using uterotonic agents (Grade 1-I[26,44]).

## MANAGEMENT OF PERSISTENT PPH

Early assessment and aggressive treatment of PPH are important for reducing morbidity and mortality rates.[45] A critical first step in managing persistent PPH is rapid recognition that clinically significant bleeding (unresponsive to initial measures) has occurred, with effective communication of the situation to the appropriate team members, both clinical and laboratory staff. Subsequent measures include immediate resuscitation with definitive action to arrest the bleeding (obstetric, surgical, and/or hematologic) and ongoing assessment and monitoring of the response to treatment.[10] Persistent severe PPH requires early involvement of the most experienced members of the team.

### Assessment of PPH severity: estimation of blood loss and clinical assessment

The accurate assessment of blood loss during PPH facilitates timely transfusion and reduces the severity of hemorrhagic shock.

### Recommendation: measurement of blood loss

Training regarding the measurement or estimation of blood loss is given to anyone undertaking midwifery or obstetric practice. Accurate monitoring of blood loss volume is recommended using widely available pictorial guidelines (described by Bose et al.[46]) or physical collection where possible (Grade 1-II/3-I[46,47]).

### Recommendation: clinical assessments of the severity of PPH

In otherwise fit and healthy women, development of tachycardia and hypotension are relatively late events in PPH, only occurring after loss of significant blood volume.

**TABLE 6. Commercially available POC assays**

| Assay | Content | Information |
|---|---|---|
| ROTEM[49] | | |
| INTEM | Contact activator | Clotting factors, fibrin polymerization, high sensitivity for heparin, fibrinolysis |
| EXTEM | Tissue factor | Coagulation factors, fibrin polymerization, PLT function |
| FIBTEM | Cytochalasin D, $Ca^{2+}$ | Fibrin status |
| APTEM | Aprotinin, $Ca^{2+}$ | In vitro fibrinolysis inhibition when compared with EXTEM |
| HEPTEM | Heparinase | Like INTEM without heparin influence |
| NATEM | Recalcification only; classical TEM | Very sensitive assessment of the equilibrium of coagulation activation or inhibition |
| TEG[50] | | |
| Native | None | Nonactivated assay |
| Kaolin | Kaolin | General coagulation assessment including PLT function |
| Heparinase | Kaolin and heparinase | Detection of heparin |
| PLT mapping | Adenosine diphosphate arachidonic acid | PLT function monitoring during anti-PLT therapy |
| r-TEG | RapidTEG reagent | Analysis of comprehensive thrombostatic function, including both enzymatic and PLT components of thrombus formation[51,52] |
| Functional fibrinogen test | Functional fibrinogen test reagent | Functional fibrinogen contribution to clot strength, as well as general coagulation assessment |

ROTEM, Tem Innovations GmbH, Munich, Germany. RapidTEG, Haemonetics, Braintree, MA.
TEG = thrombelastography; TEM = thromboelastometry.

Regular clinical assessment (every 30 min) of pulse, blood pressure, and respiratory rate can provide an indication of clinical compromise especially if recorded on a modified obstetric early warning chart (Grade 2-IIa).[48]

### Assessment of coagulation

Coagulopathy is frequently an early feature of PPH even before the development of dilutional coagulopathy that results from massive transfusion. An early assessment of coagulation status is recommended to identify unanticipated coagulopathy. The role of point-of-care (POC) testing such as thromboelastometry and thrombelastography as an adjunct to conventional coagulation studies is being actively explored and these tests are increasingly used (Table 6[49-52]), since they have the advantage of providing rapid results and may provide additional information to guide hemostatic therapy during PPH.[53,54] However, there are limited published data assessing their utility in the obstetric setting and future clinical studies of management of PPH should assess the role of POC testing and other coagulation variables.

### Recommendation: coagulation screening

Coagulation screens should be performed as soon as persistent (ongoing) PPH is declared to guide subsequent therapy. Standard tests should include PLT count, prothrombin time, activated partial thromboplastin time, and fibrinogen concentration. Where available, POC testing can be performed in addition to standard tests of coagulation. Coagulation status assessment should be repeated every 45 to 60 minutes until the bleeding is controlled and coagulation abnormalities are corrected.

### Treatment of persistent (ongoing) PPH

The immediate resuscitation of women with PPH includes assessment of the airway and breathing and the administration of oxygen by mask at 10 to 15 L/min. The woman should be kept flat and kept warm using appropriate available measures. Intravenous (IV) access with two 14-gauge cannulas should be obtained and an infusion of warmed crystalloid should be commenced until blood is available. The maximum volume of infused clear fluids should, ideally, not exceed a total of 3.5 L (up to 2 L of warmed crystalloid solution as rapidly as possible, followed by up to an additional 1.5 L if blood is still not available) while awaiting compatible blood.[55]

### Recommendations: first-line measures

First-line measures should be directed to the treatment of atony, which is the most common cause of PPH: primarily, uterine massage to stimulate uterine muscle contractions and a trial of therapy with a uterotonic agent (Table 7[10,35,56]; Grade 1-I). The choice and dosing of uterotonic agents as a first-line therapy should be administered according to local guidelines (Table 7[10,35,56]). The bladder should be emptied and an indwelling catheter should be inserted. An obstetric review to identify and manage other causes for PPH, that is, retained placenta or genital tract trauma, should be performed.

### Recommendations: second-line measures

If initial measures fail to stop bleeding and uterine atony persists, other pharmacologic (uterotonics and hemostatic agents) and mechanical or surgical measures should be instituted (Table 7[10,35,56]). Progression to secondary

**TABLE 7. Approaches to prevention and management of PPH**

| Stage | Patient status | Treatment |
|---|---|---|
| Prevention of PPH | Woman with high risk of PPH (Grade 1-I) *(bleeding disorder, placenta previa, twins, antepartum hemorrhage)* | Germany:[35] oxytocin—3 IU bolus IV following cord clamp. Second bolus of 3 IU oxytocin if required<br>France:[56] oxytocin—5 IU IV following cord clamp<br>United Kingdom:[10] oxytocin—5 IU IM (vaginal delivery) or 5 IU IV (cesarean delivery) NB. Some centers have reverted to using Syntometrine after observing an increase in the prevalence of PPH<br>Misoprostol*—800 μg PR<br>TXA (according to national guidelines) |
| | Woman not at high risk or with no evidence of bleeding (Grade 1-I) | Uterotonic therapy according to country-specific guidelines, e.g., Syntometrine<br>France:[56] oxytocin—5 IU IV following cord clamp, with 10 IU IV infusion (maximum 30 IU in 30 min) |
| First-line treatment | All women who develop hemorrhage postpartum (Grade 1-I) | Assess clinical response with uterotonic agents (Grade 1-I)<br>IV infusion and IM bolus of oxytocin (combination with prostaglandins considered dependent on local practice†): e.g., Syntocinon (40 IU over 4 hr); ergometrine (500 mg IV): misoprostol (800 μg PR)<br>*Country-specific guidelines:*<br>France:[56] oxytocin infusion (30 IU/30 min) followed by initial Sulprostone infusion (500 μg/1 hr) then 500 μg/6-12 hr depending on the rate of bleeding<br>Germany:[35] oxytocin infusion (10-40 IU oxytocin/500-1000 mL crystalloid solution) depending on uterine tone<br>Persistent bleeding: stop oxytocin infusion. Begin Sulprostone (500 μg/500 mL crystalloid solution) IV 1.7 μg/min (max rate 8.3 μg/min, max dose 1500 μg in 24 hr) |
| Second-line treatment | Failure to stop bleeding with uterotonics | *Nonsurgical measures:*<br>Coagulation screen<br>TXA (Grade 1-II)<br>Fibrinogen supplementation (Grade 3-I)<br>Blood product transfusion<br>*Obstetric assessment and surgical intervention:*<br>Bimanual compression<br>Balloon tamponade/B-Lynch sutures (the choice depends on the mode of delivery)<br>Packing the uterus<br>Uterine artery embolization |
| Third-line treatment | Failure to stop bleeding with first operative procedure | B-Lynch sutures if not yet performed<br>Hysterectomy<br>*Nonsurgical:*<br>rFVIIa‡ (Grade 3-I) |

* The consensus panel agrees that when considering the benefits safety profile of misoprostol alongside the benefits of its physiologic effects it is reasonable to administer prophylactically in women at high risk of PPH.
† Route of administration and dose varies between countries.
‡ Administration is off-label and the group did not reach consensus regarding its role in management of PPH.
IU = international unit; IM = intramuscular; PR = per rectal; U = unit.

measures should ideally trigger the initiation of a predefined management algorithm for the aggressive treatment of persistent PPH. Escalation of mechanical or conservative surgical interventions in cases of ongoing uterine atony will depend on the availability of expertise. Options include intrauterine balloon tamponade or hemostatic brace sutures (such as B-Lynch or modified B-Lynch suture) surgical ligation of the uterine arteries and radiologic uterine artery embolization (Table 7[10,35,56] and Fig. 1). Surgical interventions should be performed by the most experienced obstetrician available.

### Recommendations: third-line measures

The final surgical option for PPH is hysterectomy. Although early recourse to hysterectomy is recommended in cases of placenta accreta or uterine rupture (Grade 3-I) in other cases the decision may be influenced by a woman's circumstances and future reproductive wishes but a potentially lifesaving intervention should not be delayed. The decision should be made by the most experienced obstetrician and preferably supported by a second experienced clinician. Subtotal hysterectomy has lower surgical morbidity and is the operation of choice, unless there is trauma to the cervix or lower segment (Grade 2-IIb/2-III). rFVIIa is a third-line nonsurgical option[57,58] and its use is discussed below.

## ADMINISTRATION OF HEMOSTATIC AGENTS AND BLOOD PRODUCTS

### Antifibrinolytics

The role of antifibrinolytic therapy in the treatment of massive hemorrhage has been the subject of recent trials

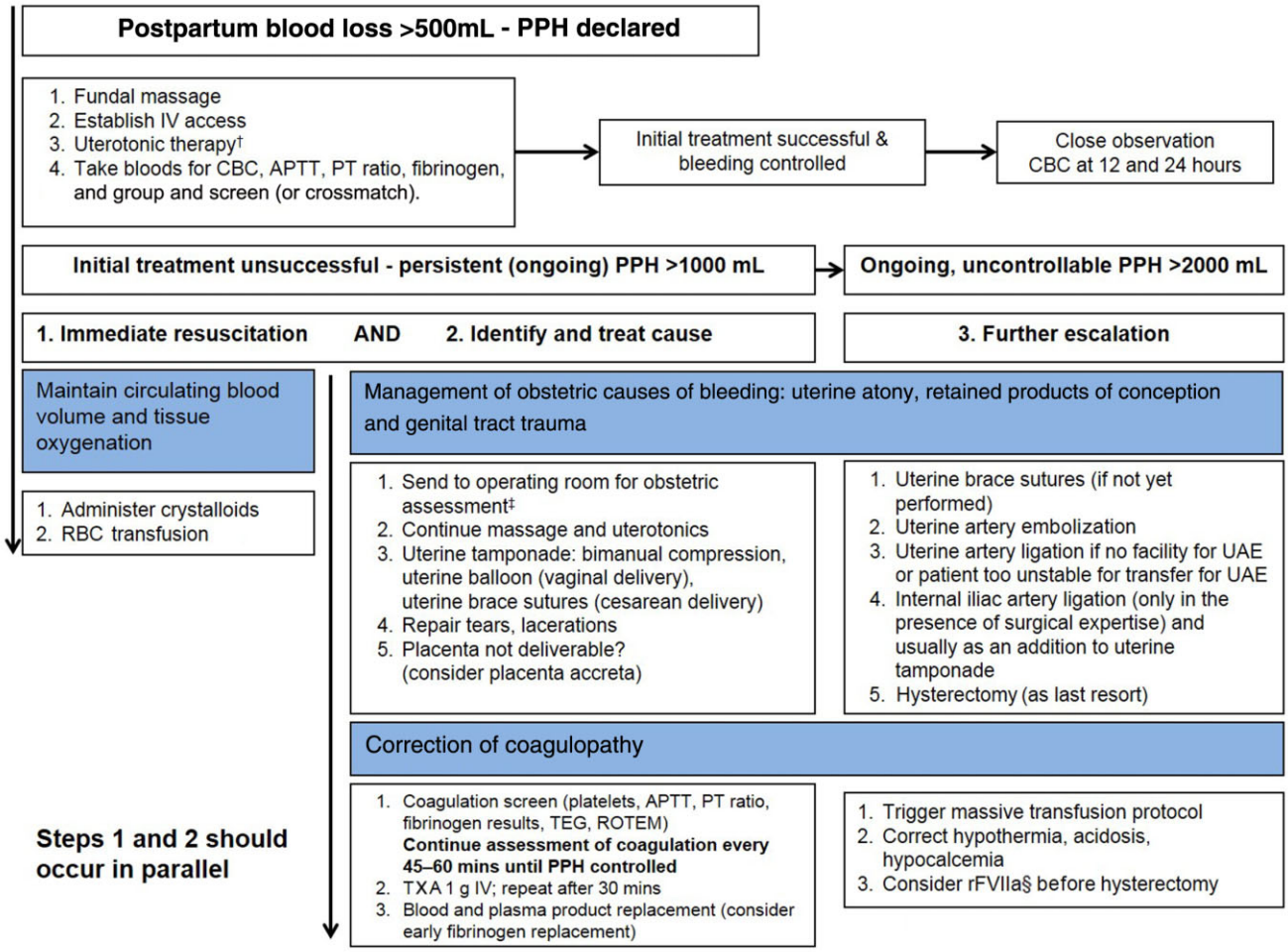


**Fig. 1. Recommended treatment algorithm for the treatment of PPH. *Declaration of PPH. The loss of more than a normal volume of blood in the immediate postpartum period should lead to prompt response to control the bleeding. †Uterotonics used may vary between institutions and should be patient specific; typical uterotonic administration will include IV infusion of Syntocinon, intramuscular Syntometrine, or prostaglandin analogs, for example, misoprostol, carboprost, or sulprostone. ‡Surgical and obstetric measures used to manage PPH will depend initially on the mode of delivery. Early recourse to B-Lynch or other compression suture may be more appropriate after cesarean section than after vaginal delivery. §The use of rFVIIa is off-label and must be considered carefully. Published case series have reported efficacy in this setting with some authors suggesting that in selected cases it may be appropriate to consider before hysterectomy. Hysterectomy should be a last resort. aPTT = activated partial thromboplastin time; CBC = complete blood count; PT = prothrombin time; ROTEM = rotational thromboelastometry; TEG = thrombelastography.**

in trauma-related bleeding[59] and severe PPH.[45] A randomized, controlled, prospective, open-label, multicenter study (n = 144) investigated the effect of TXA (loading dose 4 g [in 50 mL of saline] IV over 1 hr, followed by maintenance IV infusion of 1 g/hr for 6 hr) in women experiencing PPH (>800 mL after vaginal delivery) compared with no TXA administration.[45] The observed blood loss between enrolment and 6 hours was significantly lower in women who received TXA compared with the control group ($p = 0.041$). In addition, bleeding duration, red blood cell (RBC) transfusion requirement, and progression to severe PPH were also significantly reduced ($p < 0.03$). The authors of the study concluded that high-dose TXA administration is able to reduce blood loss and maternal morbidity significantly in women experiencing PPH.[45] A further, large multinational randomized trial is currently enrolling (World Maternal Antifibrinolytic [WOMAN] Trial[60]), which will investigate the impact of TXA administration (maximum dose 2 g IV) on the rate of hysterectomy and mortality in women with PPH. Breast-feeding during TXA administration should not be discouraged, since milk concentration 1 hour after the last dose is approximately 1% of the peak serum concentration.[61]

### Recommendations: antifibrinolytics

TXA should be administrated early in the treatment of women with severe PPH and before fibrinogen supplementation (Grade 1-II[45]) with an initial dose of 1 g of TXA IV; the same dose is repeated after 30 minutes and can be followed by an infusion of 1 g/hr.

### Transfusion of blood and plasma products

Alterations in hemostasis in pregnant and postpartum women[62] may mean that transfusion protocols developed for massive hemorrhage in other clinical settings are not applicable in the management of severe PPH. Discussion of the appropriate ratios of RBCs to plasma product has been driven by observational studies.[63-65] While such studies are hypothesis generating, wholesale changes to transfusion strategies are not recommended in the absence of prospective clinical trials.

### Fibrinogen

Studies of women with PPH have reported lower mean plasma fibrinogen levels (≤2 g/L) in women who go on to develop more severe PPH.[66,67] It is unclear, however, whether decreased fibrinogen is simply a measure of the severity of the blood loss or if it could potentially be an independent and measurable risk factor for development of severe PPH that could be a therapeutic target in early management of major hemorrhage.[68] The low fibrinogen concentrations in fresh-frozen plasma (FFP) limit its utility as a source of fibrinogen in transfusion.[69] Cryoprecipitate has higher concentrations of fibrinogen[70,71] but does not undergo viral inactivation procedures and carries the potential risk of patient exposure to blood-borne pathogens.[70] Fibrinogen concentrate is an alternative to cryoprecipitate and FFP for fibrinogen supplementation. Its use in obstetrics dates back to 1948[72] and it has been used in many countries in the management of PPH. Although a number of national guidelines suggest fibrinogen concentrate as choice of hemostatic therapy for ongoing bleeding in PPH,[73,74] there is a paucity of evidence from clinical trials to demonstrate the efficacy and safety of any one product for fibrinogen supplementation in this setting. There is a difference in the availability and licensure status of fibrinogen concentrates across different countries, for example, Haemocomplettan (CSL Behring) has full market authorization for use in PPH in several countries including Austria, Brazil, Germany, the Netherlands, Portugal, and Switzerland.[75] Off-label use of a fibrinogen concentrate has been reported.[76,77]

### Recommendations: fibrinogen supplementation

Randomized controlled trials are required to assess the safety and efficacy of early transfusion of fibrinogen in PPH before wholesale changes to transfusion protocols can be advised (Grade 3-I). Either fibrinogen concentrate or cryoprecipitate can be used for fibrinogen supplementation.

Given the elevated levels of fibrinogen in pregnancy and the observed prediction of progression to severe PPH in bleeding women with levels of less than 2.0 g/L,[66] fibrinogen should be maintained above 2.0 g/L (Grade 3-I).

### rFVIIa

The off-label use of rFVIIa, which was originally developed for the treatment of hemophilia, has been reported for the management of PPH.[78-80] Existing data are retrospective but cessation of bleeding is reported in some women with major hemorrhage.[57,58,78-82] The Australian and New Zealand Haemostasis Registry[58] reported improvement (cessation or significant slowing) in bleeding in 76% of women (n = 71/94) who were administered rFVIIa (median dose, 92 μg/kg) for the treatment of acute PPH and a Northern European registry[57] reported improvements in 80% of women with major PPH (n = 92). Venous thromboembolic events were reported in four and two women, respectively.

### Recommendations: rFVIIa

In life-threatening PPH, rFVIIa may be used as an adjunct to other surgical treatments but there are no data to support the optimal timing of its use or recommended dose (Grade 3-I). A commonly used dose is 90 μg/kg, repeated once if no clinical response within 15 to 30 minutes. Adequate levels of PLT and fibrinogen are essential for rFVIIa to be effective[83] and these variables should be checked and corrected before administration of rFVIIa aiming for PLT count higher than $50 \times 10^9$/L and fibrinogen level >2 g/L.

## TREATMENT ALGORITHM

A summary of the panel's treatment recommendations for management of severe, persistent PPH is presented in Fig. 1. The algorithm has been developed after the literature review and panel discussions at the consensus meeting with the aim of developing a practical approach to obstetric, surgical, and transfusion management of women with severe persistent PPH.

## MANAGEMENT AFTER PPH

Massive transfusion and PPH are recognized to be risk factors for development of postpartum venous thromboembolism[84-86] but clinical trial data are absent

to specify recommendations for thromboprophylaxis after this complication.

### Recommendations: management after PPH

Thromboprophylaxis should only be started once bleeding is controlled. Options for women at high risk of thromboembolism include unfractionated heparin or intermittent pneumatic compression devices with low-molecular-weight heparin reserved until the risk of bleeding has reduced.[87] Risk assessment protocols for the initiation of postpartum prophylaxis have been published.[10,88]

## CONCLUSIONS

Early and aggressive treatment of PPH is a key factor in reducing the morbidity and mortality associated with this global health problem. The numerous risk factors for and causes of PPH necessitate a well-established and multidisciplinary approach to management. The recommendations and treatment algorithm presented here are intended as a guide for clinicians in development of such a management plan. The consensus panel recognizes that the evidence and grade for the recommendations made in this document are of relatively low level. There is an urgent need for research in many areas relating to PPH, in particular, the hemostatic evaluation and the use of hemostatic agents for women with persistent PPH unresponsive to initial clinical maneuvers.

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#### CONFLICT OF INTEREST

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