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Peripartum Haemorrhage: Haemostatic Aspects of the Updated Peripartum Haemorrhage Guideline of the German-Speaking Countries

Heiko Lier[a] Thorsten Annecke[b] Thierry Girard[c] Georg Pfanner[d] Wolfgang Korte[e] Oliver Tiebel[f] Dietmar Schlembach[g] Christian von Heymann[h]

[a]Faculty of Medicine and University Hospital Cologne, Clinic for Anaesthesiology and Intensive Care Medicine, University of Cologne, Cologne, Germany; [b]Department of Anaesthesiology and Intensive Care Medicine, Merheim Medical Center, University Witten/Herdecke, Cologne, Germany; [c]Anaesthesiology, University Hospital Basel, Basel, Switzerland; [d]Anaesthesiology and Intensive Care Medicine, Landeskrankenhaus Feldkirch, Feldkirch, Austria; [e]Center for Laboratory Medicine and Haemostasis and Haemophilia Center, St. Gallen, Switzerland; [f]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Dresden, Dresden, Germany; [g]Clinic of Obstetric Medicine, Vivantes Clinicum Neukoelln, Berlin, Germany; [h]Department of Anaesthesia, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Vivantes Klinikum im Friedrichshain, Berlin, Germany

Keywords

Peripartum haemorrhage · Standard operating procedures · Uterotonics · Haemostasis · Tranexamic acid · Coagulation factor concentrates · Blood conservation · Viscoelastic haemostatic assays

Abstract

Background: Peripartum haemorrhage (PPH) is a potentially life-threatening complication. Although still rare, the incidence of peripartal haemorrhage is rising in industrialised countries and refractory bleeding remains among the leading causes of death in the peripartal period. Summary: The interdisciplinary German, Austrian, and Swiss guideline on "Peripartum Haemorrhage: Diagnostics and Therapies" has reviewed the evidence for the diagnostics and medical, angiographic, haemostatic, and surgical treatment and published an update in September 2022 . This article reviews the updated recommendations regarding the early diagnosis and haemostatic treatment of PPH. Keystones of the guideline recommendations are the early diagnosis of the bleeding by measuring blood loss using calibrated collector bags, the development of a multidisciplinary treatment algorithm adapted to the severity of bleeding, and the given infrastructural conditions of each obstetric unit, the early and escalating use of uterotonics, the therapeutic, instead of preventative, use of tranexamic acid, the early diagnostics of progressive deficiencies of coagulation factors or platelets to facilitate a tailored and guided haemostatic treatment with coagulation factors, platelets as well as packed red blood cells and fresh frozen plasma when a massive transfusion is required. Key Messages: Essential for the effective and safe treatment of PPH is the timely diagnosis. The diagnosis of PPH requires the measurement rather than estimation of blood loss. Successful treatment of PPH consists of a multidisciplinary approach involving surgical and haemostatic treatments to stop the bleeding. Haemostatic treatment of PPH starts early after diagnosis and combines tranexamic acid, an initially ratio-driven transfusion with RBC:plasma:PC = 4:4:1 (when using pooled or apheresis PC) and finally a goal-directed substitution with coagulation factor concentrates for proven deficiencies. Early monitoring of coagulation either by standard parameters or viscoelastic methods facilitates goal-directed haemostatic treatment.

karger@karger.com
www.karger.com/tmh

Correspondence to:
Heiko Lier, heiko.lier@uk-koeln.de

Background

Peripartum haemorrhage (PPH) remains the leading cause of maternal morbidity and mortality in most countries around the world and the leading preventable cause of maternal illness and death [1, 2]. Regarding its incidence, major differences exist. While the case fatality rate is 3% in Africa, it is (almost) 0% in Europe; without addressing logistical and structural issues in health care systems in low- and middle-income countries, maternal death rates comparable to those in high-income settings will not be achievable [3]. However, the rate of PPH is actually increasing in industrial countries, possibly caused by an increasing frequency of labour induction or augmentation with oxytocin as well as a growing number of caesarean deliveries within the past decades [4]. Maternal mortality differs significantly even between the so-called developed countries; e.g., for 2018, 1.7 deaths per 100,000 live births were reported in New Zealand, 3.2 in Germany, 6.5 in the UK, and 17.4 in the USA [5]. Of note, if a standardised, quantitative measurement of blood loss (BL) is systematically applied, an increased incidence of PPH of about 160% compared to before the initiative is found [6].

In Germany, the Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF]) advises on matters and tasks of fundamental and interdisciplinary interest in medicine and develops evidence-based recommendations and resolutions. About every 5 years, an update of each published guideline is recommended. As the AWMF's 2016 guideline registry number 015-063 on "Peripartum Haemorrhages: Diagnostics and Treatment" required an update, a committee with representatives of 17 medical specialist societies was formed in August 2020. While the 2016 guideline was published by delegates of the Austrian, Swiss' and German Societies of Gynaecology and Obstetrics, the German and European Midwifes' Societies, the Society of Thrombosis and Haemostasis Research, and the German Society of Anaesthesiology and Intensive Care Medicine, the new version included the Austrian and Swiss Societies of Anaesthesiology and Intensive Care Medicine. Therefore, this 2022 update [1] might be regarded as the first PPH guideline of all the German-speaking countries.

A systematic PubMed search using the query "postpartum haemorrhage, RCT, humans, 2016/2020" achieved 192 hits. Focusing on articles published since 2016, PubMed was queried with specific search terms related to each of the respective topics. Additionally, references of the original articles and articles known by the working group's members were considered. Although these articles were the basis for this guideline, the publications were not comparable to each other as they differed relevantly in their definitions, various application details as well as other essential issues. Therefore, and despite the fact that one of the first articles on this topic was published as early as 1901 [7], strong evidence-based recommendations are currently impossible for almost all steps of PPH management. Additionally, treatment options might differ in respect of local resources and settings. The aim of this update was to create a structured, consensus-based guideline for the German-speaking countries and to generate recommendations according to the AWMF's classification of the strength of consensus [8]. Besides the recommendations, we made statements (S).

The purpose of this article is to describe the most important recommendations and statements for the haemostatic management of PPH; these will be highlighted in italic letters followed by the respective number and the consensus in square brackets. Specific obstetrical examinations and treatment measures like sonographic risk stratification, compression sutures, vessel ligatures, arterial catheter embolisation, and others are essential parts for effective management of PPH and are listed and discussed in detail in the guideline but exceed the scope of this article.

Definition, Risk Factors, and Preparation

Still, there is no internationally accepted definition of PPH. Physiologically, the differentiation between vaginal delivery and caesarean section is not helpful but part of some definitions.

The German definition of PPH differentiates threshold BLs according to the mode of delivery, although most international recommendations do not use this distinction, with the exception of the California Maternal Quality Care Collaborative [9]: BL ≥500 mL following vaginal and ≥1,000 mL following caesarean delivery but adds the clinical signs of a haemorrhagic shock (shock index > 0.9) [2.E1; strong consensus]. The use of the shock index in the setting of PPH was encouraged by recent publications [10–12]. Clinical signs are also used by other organisations' recommendations (ACOG [13], CMQCC [9], SOCG [14]).

The aetiologies for PPH can be memorised using the 4 T's: tone, tissue, trauma, and thrombin (Table 1). Of note, a large proportion of women developing PPH do not have identifiable risk factors, suggesting that essentially every woman might be at risk [15]. While only about 1/3 of pregnancies have risk factors, those women will be responsible for almost 2/3 of massive transfusions [16].

Being Prepared

We recommend a standard operating procedure (SOP) for PPH for every hospital with an obstetric ward adapted

Table 1. Aetiologies for PPH: the "four T" [1]

Tone (focal or diffuse uterine atony; responsible for at least 80% of PPH)	Uterine distension (multiple gestation, polyhydramnios, foetal macrosomia) Uterotonics Quick or prolonged labour (long) oxytocin exposure chorioamnionitis Uterus myomatosus	
Tissue (placenta)	Retained placenta Placenta accreta spectrum (placenta adhaerens, accreta/increta/percreta)	
Trauma	Vulvovaginal injury Episiotomy/perineal suture Uterine rupture Inversion of the uterus	
Thrombin (coagulopathy)	Gestational: DIC (i.e., with preeclampsia, HELLP syndrome, intrauterine foetal death, placental abruption, amniotic fluid embolism)	
	As part of PPH: depletion of coagulation factors (loss, consumption, dilution)	Pre-existing: VWD, plasmatic coagulopathies, platelet function disorders, coagulopathies

DIC, disseminated intravascular coagulation.

to the hospital's infrastructure and logistics. This SOP defines therapeutic procedures and considers all available pharmacological, haemostatic, interventional, or surgical treatment options [10.E1; strong consensus]. For women at risk, we recommend the following actions to be performed before induction of labour:

- Obstetrician and anaesthesiologist are on site and informed, experienced obstetrician and experienced anaesthesiologist on call.
- Appropriate vascular access for every woman giving birth, large bore access in case of complications.
- Providing uterotonics.

Check logistics:

- Provide tranexamic acid (TxA).
- Availability of laboratory measurements (blood count, blood gas analysis, aPTT, INR, and – if available – fibrinogen, FXIII, viscoelastic haemostatic assays [VHAs]).
- Blood bank: AB0/rhesus typing and red cell antibody screening/crossmatching.

Check availability of coagulation factors, i.e., fibrinogen, FXIII, recombinant factor VIIa (rFVIIa) [4.E8; strong consensus]. Visual estimation of BL is inaccurate. Validated measurement methods are preferred once a PPH is suspected [5.S1; consensus]. For assessment of BL, we recommend considering the woman's clinical status: shock index [heart rate/systolic blood pressure] >0.9 [10, 11] [5.E2; strong consensus].

Uterotonics

Prophylactic use of uterotonics is standard of care for the active management of the third stage of labour. For pharmaceutical prophylaxis of PPH, oxytocin 3–5 IU i.v. or carbetocin 100 µg i.v. (both as a short infusion) or – for vaginal delivery – i.m. shall be considered. Of note, carbetocin has a longer duration of action with the same side effects [17] [4.E3 (vaginal delivery)/4.E7 (caesarean); strong consensus].

Oxytocin's dose range of 3–5 IU refers to the different contents in one vial of oxytocin in Germany, Switzerland, and Austria but is also recommended by other authors [18, 19]. Prolonged application of oxytocin receptor agonists for labour induction/augmentation might cause a receptor desensitisation [4, 20, 21], possibly requiring a switch to prostaglandins.

Carbetocin is a synthetic, long-acting agonist at oxytocin receptors, given only once because of its half-life of approximately 40 min, inducing sustained uterine contractions [22]. A 2018 Cochrane analysis concluded that carbetocin may be more effective than oxytocin without an increase in side effects [23]; this was confirmed by a meta-analysis in 2020 [22]. However, it should be noted that carbetocin is licensed for prophylactic, but not for therapeutic use.

Oxytocin receptor agonists given as an infusion, instead of a bolus, cause less cardiovascular instability; therefore, this update expressively recommends application as a short infusion [24]. We suggest not to use methylergometrine (stronger side effects; 4.E4; strong consensus) and misoprostol (less efficacy and off-label; 4.E5; strong consensus) as first-line drugs for the prevention of PPH.

Current guidelines of the International Federation of Gynaecology and Obstetrics (FIGO) for low- and middle-income countries recommend methylergometrine and misoprostol for prevention of PPH only in settings where oxytocin is unavailable, or its quality cannot be guaranteed [2].

The recommendations for the therapeutic use of uterotonics are the following: we recommend using oxytocin as first-line therapy for primary PPH. Compared to misoprostol, it has, especially following vaginal delivery, a higher efficacy with less side effects. It shall be used with 3–5 IU as short infusion, followed by 10–40 IU in 500–1,000 mL as continuous infusion [6.E1; strong consensus].

If first-line uterotonics fail, we recommend using prostaglandins without delay. Due to its good efficacy and relatively minor side effects, sulprostone (prostaglandin E2) is recommended [6.E4; strong consensus].

We suggest against using oxytocin receptor agonists and prostaglandins simultaneously. If a quick change from oxytocin receptor agonists to sulprostone is required, we suggest monitoring cardiovascular side effects thoughtfully [6.E5; strong consensus].

We recommend administering sulprostone solely intravenously [no intramyometrial or intracervical application; 6.E7; strong consensus]. Contrary to sulprostone's Summary of Product Characteristics, the working group recommends a de-escalating dosing: 500 µg in 500 mL solution via infusion pump; 3 min of 500 mL/h (8.3 µg/min), followed by 7 min 100 mL/h (1.7 µg/min) continued by 10–20 mL/h (0.2–0.4 µg/min) with a maximum of 1,500 µg/d.

Prostaglandin F2alpha is not discussed in the guideline, as it is not available in Germany, Austria, and Switzerland, and prostaglandin E2 is used instead. Due to available alternatives in Europe and its side effects, we suggest against using methylergometrine for PPH [6.E3; strong consensus]. Due to delayed efficacy and availability of better and licensed alternatives, misoprostol is not suited for therapy of persistent PPH [6.S1; strong consensus]. However, current FIGO guidelines for low- and middle-income countries recommend methylergometrine and misoprostol for treatment of PPH only if intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin [2].

Hysterectomy

The prevailing opinion in obstetrics regards a hysterectomy as an ultima ratio approach. To start an intervention that causes an average BL of 2–3 L and takes approximately 2 h [25] in the setting of haemodynamic instability, coagulopathy requires a very nuanced and appraising approach; however, all efforts described in this article (and essential surgical interventions like compression sutures or vessel ligatures) are intended to prevent this situation and maintain fertility of the mother [26]. An absolute indication for emergency hysterectomy is a septic uterus, in which hysterectomy is the causative measure to save the mother's life [27].

Conservative treatment to preserve the uterus is only reasonable if the patient does not bleed life-threateningly and is maintained in relatively stable haemodynamic condition. We suggest against performing a hysterectomy too late [28, 29] [8.E4; strong consensus].

To avoid unnecessary BL, a bimanual compression of the aorta up to 20 min or a Hamilton manoeuvre is recommended [30, 31]. If hysterectomy does not stop the bleeding, we suggest packing pelvis and abdomen with damped swabs. If radiological intervention is available, a temporal occlusion of the aorta might be considered [8.E1; strong consensus].

Haemostasis and Coagulation Management

The pathophysiological correlate of a parturient with a severe PPH is a haemorrhagic shock with cellular hypoxia. PPH differs from the traumatic-haemorrhagic shock of trauma patients. In PPH, the level of tissue destruction is mostly less severe, and pregnancy-related changes in the blood's composition and maternal haemodynamics in a "healthy" parturient permit a haemostatic and cardiovascular adaptation for expected moderate BL. Coagulopathy is not observed a priori in all women suffering from obstetric haemorrhage and cannot be predicted solely by BL [32]. Therefore, the transfer of knowledge and management options of coagulopathy of the trauma setting (e.g., trauma-induced coagulopathy) to that of PPH needs to be done carefully. On the other hand, quantitative BL is regularly underestimated if not measured [6, 33] and, regardless of the primary cause of PPH, ongoing BL will result in coagulopathy at some point if early intervention is not successfully applied [34, 35]. For a therapeutical approach, the following settings need to be considered:

- Primary bleeding by atony as well as vascular or tissue disruption: initially, the coagulation is intact, and bleeding should be treated with uterotonics and primary bleeding control combined with avoidance of a secondary coagulopathy by consumption and dilution.
- Coagulopathy by prolonged shock or wash-in of mediators (e.g., disseminated intravascular coagulation, hyperfibrinolysis): besides surgical bleeding control, supportive options (volume, TxA, substitution of coagulation factors) are required.
- Pre-existing coagulopathy by underlying disease or drugs: surgical control and supportive options, too.
- Peripartal thrombocytopenia increases the risk of PPH [36].

The leading causes for PPH are atony, trauma, and retained parts of the placenta. A primary coagulopathy is rare. Coagulopathy is most often an acquired one [10.S1; strong consensus].

Cellular hypoxia might cause release of endothelial t-PA (tissue plasminogen activator) [37]. Prevention of cellular

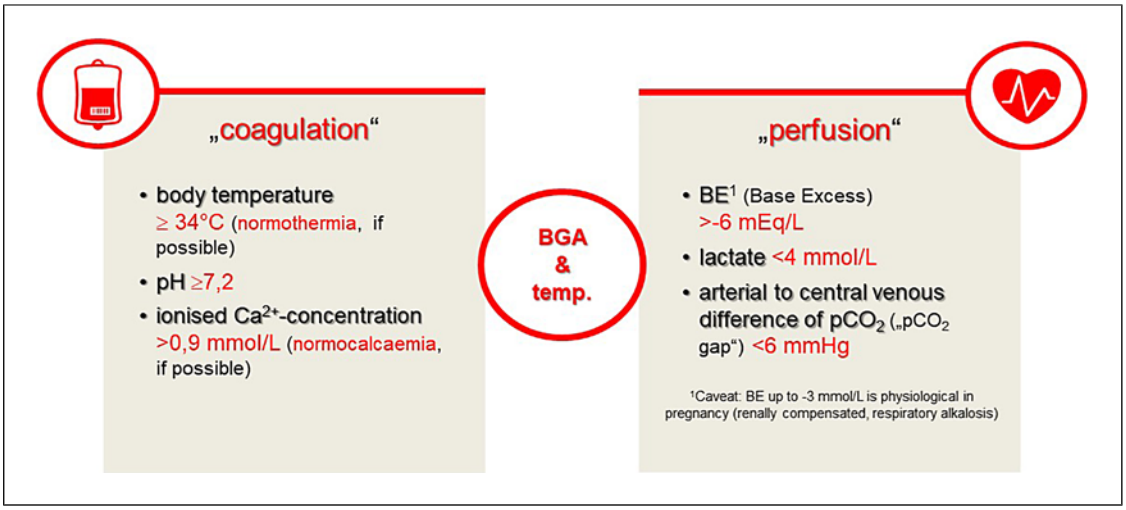

Fig. 1. Blood gas analysis (BGA) and temperature as the "simplest" coagulation monitoring. Treatment targets are given for resuscitation of coagulation and perfusion.

hypoxia requires immediate treatment of shock by tailored volume substitution [10.E9; strong consensus] avoiding iatrogenic dilution ("damage control resuscitation") [31] together with temporal permissive hypotension (mean arterial pressure ~65 mm Hg) [38, 39]. Administration of larger volumes of crystalloids or even worse artificial colloids is associated with more severe deterioration of coagulation parameters corresponding to dilution [40]. Possible perioperative aims for haemodynamic therapy are shown in Figure 1. As the timely course of these parameters is essential, early and repeated measurements are required [41]. The target range for packed red blood cell (pRBC) substitution in ongoing massive bleeding shall be a haemoglobin of 7–9 g/dL (4.3–5.5 mmol/L) [13, 42, 43].

Early plasma transfusion within the first 60 min of persistent PPH is not associated with better outcome than no or later plasma transfusion [44]. The German Medical Association indicates plasma primarily in massive transfusion as a substitute for loss of plasma volume (i.e., loss of ~50–60 mL/kgBW at term) and recommends initially ≥30 mL/kgBW [42].

The therapeutic goal for platelet concentrates (PC) in severe bleeding is 70,000–100,000/µL [42, 43, 45]. In ongoing bleeding, the proof of a haemostatic deficiency enables a targeted therapy. We suggest guidance by laboratory values and – if available – VHA [10.E3; strong consensus] (see below).

The European guideline on perioperative bleeding recommends the consideration of a ratio-driven protocol (pRBC:plasma:PC) early in uncontrolled massive bleeding outside the trauma setting followed by a goal-directed approach, guided by VHA, as soon as possible ("hybrid approach") [41]. As Austria and Germany only offer pooled or apheresis PC with 2–4 × 10^{11} platelets [42] (instead of US single-donor PC with 5.5 × 10^{10} platelets [46]), a ratio-driven therapy will consist of 4 pRBC:4 fresh frozen plasma (FFP):1 PC [42].

Tranexamic Acid

We recommend against using TxA for routine prophylaxis, but rather therapeutically at the time of the diagnosis of PPH [4.E6; strong consensus]. In the multicentre, double-blind, randomised controlled TRAAP 1 trial, TxA for prevention of BL after vaginal delivery did not result in a significantly lower rate of PPH of at least 500 mL compared to placebo [47]. The multicentre, double-blind, randomised controlled TRAAP2 trial, investigating the impact of prophylactic TxA on BL and transfusion requirements after caesarean section, showed a significantly lower incidence of calculated estimated BL greater than 1,000 mL (26.4 vs. 31.5%, adjusted risk ratio [aRR] 0.84 [0.75–0.94]), but it did not result in a lower incidence of haemorrhage-related secondary clinical outcomes. The statistically significant difference in BL was 107 mL (63–152 mL). This clinically irrelevant reduction was accompanied by an aRR of 1.84 (0.73–4.62) for arterial embolisation, emergency surgery, or hysterectomy; an aRR of 4.01 (0.85–18.92) for deep-vein thrombosis or pulmonary embolism; and an aRR of 1.19 (1.08–1.30) for nausea or vomiting [48]. A recent analysis of 14 systematic reviews of randomised controlled trials (RCTs) with 32 independent RCTs on the effect of TxA for the prevention of BL after caesarean section concluded that a reduction in BL of 33–185 mL is not a patient-oriented outcome and is of questionable clinical significance; clinicians should be cautious when considering prophylactic TxA until more rigorous studies are available [49].

We recommend therapeutical application of TxA 1 g i.v. with the diagnosis of PPH at the time of the application of

(therapeutic) oxytocin, without prior coagulation test. The earlier, the better [6.E2; strong consensus].

The recommended standard treatment of general fibrinolysis with 1 g TxA is equivalent to 15 mg/kg body weight. Less might not be effective [50].

We suggest treating a possible increased fibrinolytic activity with TxA prior to the application of procoagulant drugs (e.g., fibrinogen, platelets, factor [F] XIII, 4-factor prothrombin complex concentrate [PCC]) [10.E4; strong consensus].

PPH-related early increase in D-dimers is reduced by TxA [51]. In the WOMAN trial, 20,060 women (90% in developing countries) were enrolled and randomly assigned to receive TxA (n = 10,036) or placebo (n = 9,985). Death due to bleeding was significantly reduced in women given TxA (155 [1.5%] patients vs. 191 [1.9%] patients in the placebo group, RR 0.81, 95% confidence interval [CI] 0.65–1.00; p = 0.045), especially in women given treatment within 3 h of giving birth (89 [1.2%] vs. 127 [1.7%] in the placebo group, RR 0.69, 95% CI 0.52–0.91; p = 0.008). 1.9% of the included women died without and 1.4% with TxA. The absolute reduction of death due to bleeding by 0.4% resulted in a number-needed-to-treat of 250. The absolute reduction of death by 0.5% if TxA is given within 3 h resulted in a number-needed-to-treat of 200 [52]. It is of note that Ian Roberts, the main author of the WOMAN trial, wrote in a response to Letters to the Lancet's Editor: "We agree that tranexamic acid should not replace another effective intervention and that our results do not support the prophylactic use of tranexamic acid in all women who deliver" [53]. The WHO "strongly recommends early use of intravenous TxA (within 3 h of birth) ... for women with clinically diagnosed post-partum haemorrhage" [54]. Current FIGO guidelines for low- and middle-income countries recommend TxA "as soon as PPH is diagnosed but within 3 h of birth . . . for women with clinically diagnosed PPH" [2].

In a secondary analysis of the WOMAN trial with 167 patients from Nigeria, 23% had evidence of hyperfibrinolysis and 34% of coagulopathy [55]. A secondary analysis of the multicentre prospective "Towards better prognostic and diagnostic strategies for haemostatic changes during Major Obstetric Haemorrhage (TeMpOH-2)" study with 17,203 patients in the Netherlands and BL between 800 and 1,500 mL identified 1% as having hyperfibrinolysis [56]. In a 2022 update on the current applications and limitations of TxA use in the perioperative period, the authors stated for PPH: "Less clear is the extent to which hyperfibrinolysis contributes toward the magnitude of blood loss in women with severe PPH. . . . these meta-analyses report relatively modest mean reductions in blood loss with TxA versus placebo ranging from 65 to 160 mL, which may be of limited clinical significance" [57].

Component Therapy

A BL of 1,500 mL corresponds to about a quarter of the circulating blood volume at term [58], and the incidence is ~3% of all births [32, 59]. While some women may compensate this BL, for others, the haemodynamic impairment and the risk of coagulopathy will worsen if BL is not successfully treated. At this point, the pocket card (Fig. 2) changes from yellow to (light) red.

We suggest calling for best-available expertise (consultant level) for both obstetrics and anaesthesiology for ongoing BL ≥1,000 mL and recommend it for ongoing BL ≥1,500 mL [10.E8; strong consensus]. Sufficient oxygen supply must be secured (consider intubation [10.E10; strong consensus]), and substitution of coagulation factors and platelets shall be considered [10.E5; consensus].

A BL of >2,000 mL is regarded as life-threatening, the woman will be of high risk of haemorrhagic shock, the incidence is ~ 15/1,000 maternities [59], and the pocket card changes to (dark) red. A BL ≥2,500 mL must be expected in ~6/1,000 maternities [59]. Massive transfusion is usually required. The common definition of massive transfusion, ≥10 pRBC/24 h, originates from the Vietnam war [60], while a more recent and reasonable one is ≥3 [61] or 4 [62] pRBC/1 h. Almost half of the massive transfusions will be caused by emergency hysterectomies, and 2/3 will present outside regular working hours [63].

In the context of ongoing PPH, the prophylactic application of factor concentrates without coagulation factor deficiency is neither sensible nor useful. There is no evidence for the use of 2 g fibrinogen concentrate as a preemptive treatment for severe PPH in patients with normal fibrinogenaemia [64], neither for early and systematic administration of 3 g fibrinogen concentrate, as it did not reduce BL, transfusion needs, or postpartum anaemia [65].

In ongoing bleeding, the proof of a haemostatic deficiency enables a targeted therapy. We suggest guidance by laboratory parameters (e.g., blood count, blood gas analysis, aPTT, INR, and – if available – fibrinogen, FXIII as well as VHA) [10.E3; strong consensus].

For coagulation management of ongoing therapy requiring bleeding, we recommend the following:

- A SOP adapted to the respective hospital's logistics and resources.
- Securing the preconditions of haemostasis (see Fig. 1).
- TxA immediately with the diagnosis of PPH.
- FFP (30 mL/kg) for massive transfusion.
- Targeted coagulation therapy, parallel to surgical, mechanical, or pharmaceutical options:
  - Coagulation factor concentrates, i.e., fibrinogen, FXIII (e.g., BL >50% of blood volume), PCC
  - Platelets
  - rFVIIa

[10.E5; consensus].

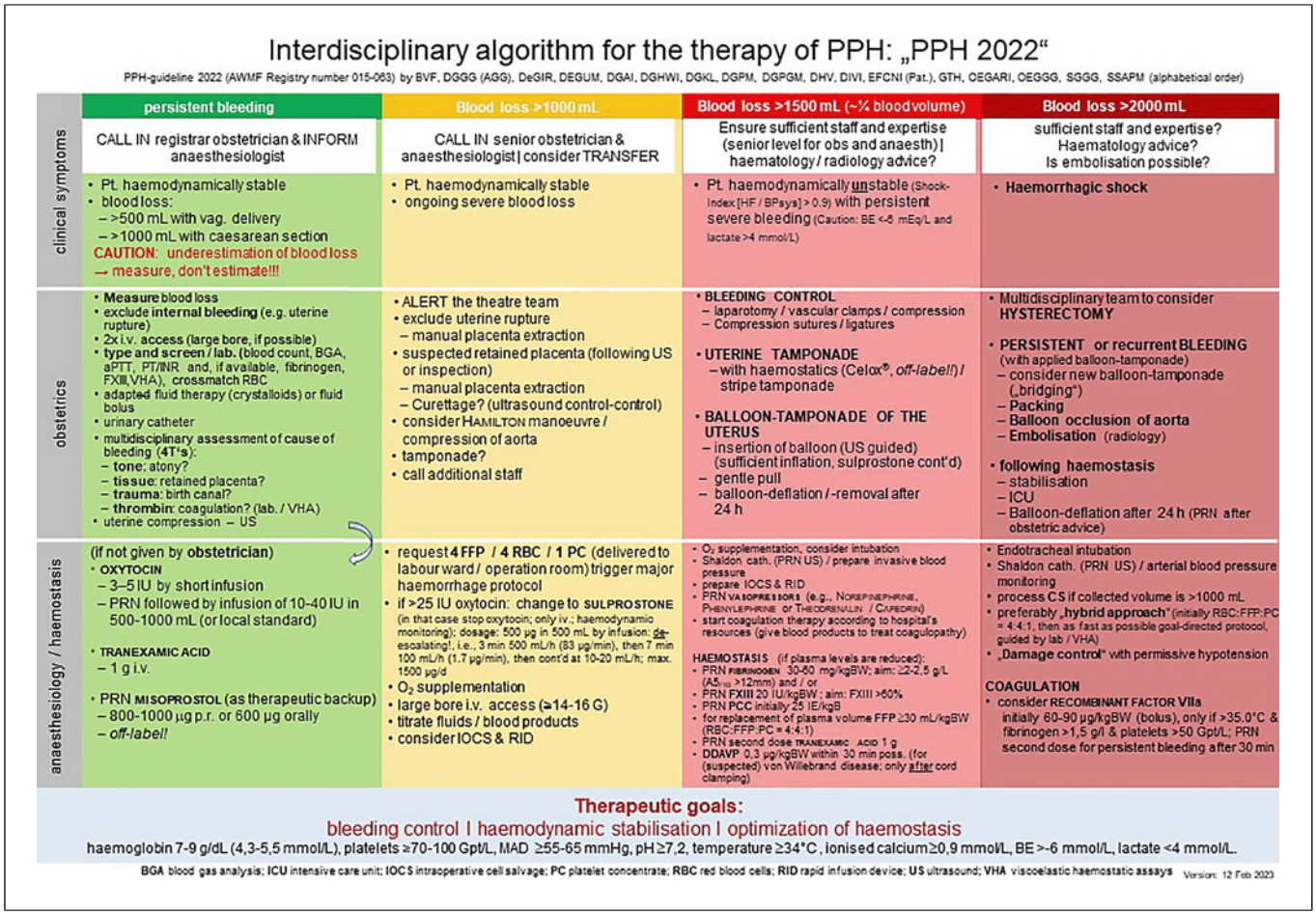

Fig. 2. Interdisciplinary algorithm for the therapy of PPH: "PPH 2022." The traffic light colouring of this pocket card matches the severity of the situation. The first line focuses on the clinical symptoms, the second line on obstetrical measures, and the third line on haemostaseological/anaesthesiological measures.

Fibrinogen is the first and most common coagulation factor to fall in PPH [66]. One of the few therapeutic options with international consensus might be the threshold for fibrinogen replacement of <2 g/L [41, 67, 68]. For a prior non-anaemic woman at term, this is rarely the case with a BL of 1,000 mL (2.4% [63]) but almost always, if bleeding volume is >4,000 mL [66, 67]. Of note, some obstetric bleeding aetiologies like placental abruption or amniotic fluid embolism may initially induce a hyperfibrinolytic state with early coagulopathy and low fibrinogen.

Maternal FXIII is the only coagulation factor that decreases during pregnancy, by 17% [69] to 30% [70], at term. Acquired deficiency is frequent and is believed to be caused by relatively reduced synthesis, consumption during regular pregnancy, and increased consumption following massive bleeding [42, 70, 71, 72]. FXIII activity is a superior predictor of intraoperative need for red cell transfusion in elective surgery with best performance (ROC curve) at roughly 65% [73]. Early replenishment of FXIII in the bleeding patient seems rational as it is the only factor that decreases during pregnancy up to term and as it is the only factor that is a significant predictor of postpartum bleeding independent of a defined cut-off [72]. The target population and the level of FXIII required to avoid or treat PPH are yet to be defined by further trials investigating larger samples of patients with higher BLs [71].

Thrombin generation is often preserved despite significant BL, but deficient thrombin contributes to the shock-induced coagulopathy [74]. Therefore, PCC might be indicated in severely bleeding women with haemorrhagic shock. Further studies in the setting of PPH are required.

There is no reliable data on the use of DDAVP (desmopressin) in obstetrics authorising an evidence-based recommendation [75], although positive effects are published (after cutting the cord) [76]. Attention shall be paid to a goal-directed substitution of proven or expected coagulation factor deficiencies. Justifiable goals are FXIII >60% [72, 73], fibrinogen >2–2.5 g/L [77–79], and platelets 70,000–100,000/µL [42].

After the final consensus meeting of this guideline, on April 22, 2022, the European Medicines Agency (EMA)

issued a "positive opinion" and on May 24, 2022, introduced a new indication for activated recombinant factor VII: "NovoSeven™ is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis." After submission of the finalised guideline to the AWMF, the EMA published their reasons for this approval that is based on the analysis of one prospective RCT, 4 retrospective cohort studies, and one meta-analysis on July 26, 2022 [80]. Since the guideline committee could not assess all published data on the use of rFVIIa in patients with severe PPH refractory to uterotonics without postponing the publication date of the guideline, it was decided to not modify the current recommendation for the use of rFVIIa as a last resort treatment after all other treatments have been shown refractory in patients with severe PPH. The next update of the guideline will assess the available literature and modify the recommendations accordingly if indicated. The extended approval indicates rFVIIa (60–90 μg/kg) after failure of sulprostone; the effect should appear within 10 min; a possible second dose might be given after 30 min.

PPH and VHAs

Of note, VHAs are tool indicating diagnostic and therapeutic options in a bleeding patient. However, VHA's parameters outside the reference range without ongoing bleeding do not need a treatment. Since 2016, more than 60 studies on the use of VHA in obstetrics were published. These devices indicate the hypercoagulable state of physiological pregnancy and may allow diagnostic and therapeutic decisions caused by impaired haemostasis [45] considerably faster than standard laboratory results [81]. An observational study of 20,349 deliveries found substantial benefits over a standardised massive transfusion protocol in terms of both patient outcomes and cost of care and concluded that VHA algorithms facilitate rapid (within minutes) and precise diagnosis of coagulopathy, thereby allowing for prompt correction of deficiencies of specific components of the coagulation cascade among patients experiencing severe obstetric haemorrhage [82].

However, a study analysing 32,647 deliveries in the Liverpool Women's NHS Foundation Trust showed that coagulopathy is not observed in all women suffering from PPH and the risk of coagulopathy cannot be predicted solely by BL. Since the switch from "shock packages" to a VHA-guided algorithm (ROTEM™; Werfen, Munich, Germany) proved substantial benefit in terms of lung injury, ICU admission, hysterectomy, and massive transfusion [32], a diagnosis of the underlying coagulopathy is needed [41]. The most essential finding, however, was that, for BL >1,500 mL, different aetiologies of PPH (abruption, adherent placenta, atony, retained placenta, rupture, trauma, others) resulted in different ROTEM results. Therefore, the use of a ratio-based transfusion algorithm may result in transfusion of blood products to women that do not need them.

The prospective obstetric bleeding study (OBS) 1 observed patients with a BL >1,500 mL, the positive predictive value of a fibrinogen <2 g/L for any transfusion was 100 (63–100), and a FIBTEM A5 <10 mm was an independent predictor of >2,500 mL BL (OR 0.85, 95% CI 0.77–0.95) [78]. The multicentre, randomised, double-blind, placebo controlled OBS2 trial showed a FIBTEM A5 >12 mm or fibrinogen >2–2.5 g/L is adequate for haemostasis. Fibrinogen replacement is not associated with a significant reduction in BL and transfusion requirements as compared to placebo in patients with a 1,000–1,500 mL BL [77]. As a FIBTEM A5 of 12 mm approximately correlates with a plasma fibrinogen level of 2.2 g/L, selective indication of fibrinogen concentrate to treat coagulopathy may be identified using ROTEM [32]. This is of special note as 2.5 g/L is the middle of the reference range for non-pregnant patients; obviously, the reference range for fibrinogen in pregnancy (4.5–6 g/L) is not required for bleeding control in PPH. The prospective observational OBSplus study including 521 parturients with a peripartum BL >1,000 mL found that the incidence of coagulation factor deficiency (measured by aPTT and/or PT) requiring treatment was rare despite >100 women having BL >2,000 mL (hypofibrinogenemia ≤2 g/L: 5.0%; prolongation of PT a./o. APTT >1.5x: 4.1%; platelet count <75,000/μL: 2.3%) [83]. The authors concluded "The use of formulaic infusion of FFP based on fixed ratios with red blood cells would have resulted in many women being exposed to blood products despite normal coagulation" [83]. This study [83] used a ROTEM sigma, and comparable results were shown with a TEG6s (Haemonetics Corp., Braintree, MA, USA) [84] (caveat: different thresholds). Multiple VHA algorithms are published, some validated [82, 85, 86]. Contrary to the trauma setting, none of the PPH studies on VHA could show a mortality benefit; therefore, definite and decisive recommendations on VHA in PPH cannot be made.

Cell Salvage

We suggest using cell salvage (CS) for women with increased bleeding risk [10.E13; strong consensus]. Multiple international societies recommend the use of CS in PPH (e.g., American Society of Anaesthesiologists [ASA], Centre for Maternal and Child Enquiries [CMACE], European Society of Anaesthesiology [ESA], National Institute for Health and Care Excellence [NICE], Obstetric Anaesthetists' Association/Association of Anaesthetists of Great Britain and Ireland [OAA/AAGBI]). CS is an essential part of patient blood management. One litre of suctioned wound blood will result in ~200 mL RBC, depleted of plasma, coagulation factors, and platelets,

Table 2. Escalating scheme of haemostatic therapeutic options for PPH without VHA [10.E6; consensus]

1. Stabilisation of concomitant factors (prophylaxis and therapy)	Core temperature ≥34°C (preferably normothermia) pH ≥7.2 Ionised Ca^{2+} >0.9 mmol/L (preferably normocalaemia)
2. Inhibition of possible (hyper-) fibrinolysis (recommended always before fibrinogen!)	TxA initially 1 g (15 mg/kgBW), repeat once if required
3. Substitution of oxygen carriers	pRBC (in massive bleeding aiming at Hb 7–9 g/dL [4.3–5.5 mmol/L])
4. Substitution of coagulation factors (for ongoing, severe bleeding) Patients requiring massive transfusion or suffering from haemorrhagic shock may benefit from a ratio of FFP:RBC:plts of 4:4:1 or combined application of FFP and factor plus platelet concentrates	Fibrinogen 30–60 mg/kgBW; aim: ≥2–2.5 g/L and FXIII 20 IU/kgBW; aim: activity >60% or FFP ≥30 mL/kgBW if needed (4-factor) PCC initially 25 IU/kgBW
5. Replacement of plasma volume	FFP ≥30 mL/kgBW
6. Substitution of platelets for primary haemostasis	Plts (aim for bleeding requiring transfusion: ≥ 70,000–100,000/µL)
7. If necessary, thrombin burst	On a case-by-case basis, if other therapeutic options fail, and after consideration and correction of concomitant factors if needed rFVIIa Initial dose: 60 (- 90) µg/kgBW
For ongoing, severe bleeding	During ongoing bleeding: no antithrombin (may consider after bleeding stopped and PCC was given) During ongoing bleeding: no heparin

Caveat
- During ongoing bleeding: no antithrombin or heparin (may consider after bleeding stopped and PCC was given)
- Within 24 h after stopping the haemorrhage, a pharmacological thrombosis prophylaxis is obligatory
- If needed (for expected acquired thrombocytopathy and after clamping of the cord) DDAVP (desmopressin) 0.3 µg/kgBW in 30 min

which need to be given separately [87]. Studies have shown that the standardised use of CS in obstetrics will result in a re-transfusion volume of approximately 250 mL RBC [88, 89]. The cost-effectiveness is ensured by a standardised "collect only" (i.e., only the reservoir is inserted) approach, when the machine is only set up for processing (i.e., bell and tubes) in patients needing re-transfusion of salvaged blood [88]. A separate special suction tube of an isolation suction system at a vacuum pressure of 20 kPa into a sterile reservoir after delivery and placental separation might be used [90]; but it is not mandatory [88, 89]. One study used a leukocyte depletion filter (LDF) [90] to reduce the risk of a feto-maternal transfusion syndrome, one did not [89], and in one the use was optional [88]. It is notable that all adverse events probably related to CS, consisting of acute haemodynamic and respiratory reactions to the return of salvaged blood, occurred when a LDF was in use [88]. There was no case of amnion fluid embolism, neither with nor without an LDF. All rhesus D-negative unsensitised women delivering a rhesus D-positive baby should be routinely offered a standard dose of anti-D immunoglobulin as prophylaxis to minimise this risk of sensitisation [88].

Thromboprophylaxis

In high-resource countries, venous thromboembolism is the second most frequent cause of maternal mortality after haemorrhage accounting for 13.8% of all maternal deaths; venous thromboembolism remains the leading cause of direct maternal deaths occurring within 42 days of the end of pregnancy and up to a year after the end of pregnancy [91]. Due to a decreased antithrombin activity (some women with an absolute activity below 0.5 kIU/L) following the end of bleeding, an increased risk of thromboembolism must be considered; therefore, within 24 h a prophylaxis is required that, if risk factors exist, needs to be continued for up to 6 weeks postpartum [10.S23; strong consensus].

Following administration of coagulation factors, especially PCC [66], to a parturient [67], the intensive care unit might consider measurement and substitution of antithrombin [10.E7; strong consensus]. Substitution with antithrombin might aim at activities ≥80% [92] or ≥0.8 kIU/L [93], respectively. Further studies are needed.

Table 2 lists an escalating scheme of haemostatic therapeutic options for PPH without VHA. VHA-guided algorithms need to be individualised depending on the respective device [45, 94].

The Pocket Card "PPH 2022"

As PPH is a rapidly evolving obstetric emergency and to provide a clear, easily accessible, and practical tool including all the guideline's recommendations, an interdisciplinary algorithm for the therapy of PPH was developed (Fig. 2).

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