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Review

An update on post-partum hemorrhage

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Abstract

Post-partum hemorrhage can be a devastating complication of delivery and is still responsible for substantial maternal morbidity and mortality around the world. The aim of this narrative review is to focus on its optimal management, according to the most recent literature and most recent guidelines. All aspects are considered, from anticipation of the problem during pregnancy and determination of risk factors, early diagnosis and determination of the underlying cause, resuscitation, goal-directed coagulopathy correction, as well as obstetrical, surgical, and radiological management. Post-event team debriefing, and psychological support for the patient are also addressed. We emphasize the necessity to have institutional protocols to guide practitioners in managing this life-threatening emergency and insist on the utility of multidisciplinary simulation sessions. Improving readiness and response to, as well as recognition and reporting of post-partum hemorrhage can improve efficiency in dealing with this challenging emergency through better resource management and appropriate care bundling.

Keywords: **Post-partum hemorrhage, anesthetic management, obstetrics, resuscitation.**

Introduction

Post-partum hemorrhage (PPH) can be a devastating complication of childbirth, accounting for a quarter of maternal deaths worldwide[1]. Anesthesiologists are on the frontline when it occurs, to ensure, in collaboration with obstetricians and midwives, the most favorable outcome to the patient. They may be involved not only in patient resuscitation, and control of bleeding, but also in the anesthetic management when a surgical or an interventional procedure is necessary. For this, perfect proficiency in knowledge of the pathology is essential, including most recent developments in the domain. In this narrative review, we provide the reader with complete information on the topic, including epidemiology, causes and risk factors, prevention, and treatment.

Methodology

Our methodology was first based on an exhaustive literature search, collected using the PubMed® search engine and Google Scholar®, and a combination of keywords including post-partum hemorrhage, and anesthetic management. The literature was browsed between 2000 and 2024, and only papers written in English or in French were retained. Types of papers considered for the review included original studies, systematic reviews, meta-analyses, and scientific societies' recommendations and guidelines. Relevance was decided based on the title of the publication

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and the content of its abstract, and necessitated agreement by all authors.

Definition and epidemiology

Immediate PPH is primarily defined by the World Health Organization (WHO) as a blood loss of 500 mL or higher within 24 hours of birth, regardless of the mode of delivery[2]. PPH occurs in 5 to 10% of births and severe PPH (≥ 1000 mL of blood loss within 24 hours) remains a leading cause of maternal mortality[3], with an annual fatality rate of 70,000 patients globally[2]. Death is considered avoidable in 80%[4] to 94%[5] of cases. PPH accounts for 19.7% of direct maternal deaths in low-income countries, as compared to approximately 8% in high-income countries, and 11% in the United States[2]. Secondary PPH is defined as abnormal vaginal bleeding between 24 hours and 12 weeks postnatally. Other definitions of PPH exist, with no worldwide consensus but similarities between them[154]. Most scientific societies align with the WHO definition[6,7]. In 2017, the American College of Obstetricians and Gynecologists (ACOG) changed the definition to a cumulative blood loss ≥1000 mL or blood loss associated with signs or symptoms of hypovolemia within 24 hours of delivery by any mode[155], while the Royal College of Obstetricians and Gynaecologists (RCOG) defines different degrees of severity according to the estimated blood loss (EBL)[8]. In any case, a blood loss greater than 500 mL should be considered abnormal and investigated[9]. Aiming for an early and accurate recognition of severe PPH and appropriate treatment, experts have integrated a novel approach with a more detailed clinical definition. The expert consensus suggests, in addition to the EBL, that vital signs, clinical symptoms and acidosis should be considered[10] (Table I).

Causes of post-partum hemorrhage

The major increase in uterine blood flow, up to 600 $mL.min^{-1}$, during late pregnancy explains why persistent bleeding rapidly worsens the patient's clinical status if left untreated. Consequently, it is of utmost importance to identify the source of the bleeding rapidly, and a systematic review of all possible causes should be undertaken immediately, using the mnemonic help of the 4 T's (Tone, Trauma, Tissue, Thrombin) (Figure 1), while keeping in mind that the cause can be multifactorial.

Tone

When bleeding occurs after delivery, the first reflex is to manually assess any lack of uterine tone, which should prompt the administration of uterotonic medication[11]. Uterine atony is responsible for approximatively 70% of PPHs. It represents the most common cause, and its incidence has increased other the last past years[12,13]. In a 2021 meta-analysis, key risk factors of atonic PPH were identified[14], namely iatrogenic induction of labor (odds ratio: 1.23), macrosomia (1.46), multiple gestation (1.46), hypertensive disease (1.84), diabetes (1.22), and chorioamnionitis (1.93). In some countries, ethnic origin, if representative of a local minority (e.g. Hispanic or Asian in the USA), may increase the risk, probably because of lack of access to adequate treatment. Interestingly, a prolonged second stage of labor, a planned cesarean delivery, and polyhydramnios were not identified as risk factors for atonic PPH[14]. The role of obesity remains controversial, not being associated to an increased risk in some publications[14], to a modestly increased risk in others[15], and to a significantly higher risk after cesarean deliveries when considering severe obesity (body mass index between 50 and 59.9 $Kg.m^{-2}$; odds ratio: 1.69)[15]. Of note, the need for red blood cells (RBC) transfusion may be lower in obese patients, due to their hypercoagulable state[15]. The administration of magnesium sulfate was not statistically correlated with an increase in the incidence of atonic PPH[16,17], despite the fact that magnesium decreases uterine tone through a calcium channel blocking effect, an attenuation of the effect of acetylcholine at the

Table I. — Criteria to define a severe ongoing post-partum hemorrhage. Adapted from Hofer et al.[10]

Tachycardia >100 bpm, despite balanced intravascular volume status and adequate pain control
Pallor/Drop in Hb >2g.dL^{-1} before crystalloid administration
Low blood pressure (blood pressure ≤85/45 mmHg or 20% drop as compared to baseline value)
Critical values in blood gas analysis (base excess <-4, pH <7.2)
Shock index >0.9
Lactate >4.0 mmol L^{-1}
Oliguria (diuresis <500 mL^{-1}.24h)
Excessive volume requirement
Inappropriate fear or restlessness
Coagulopathy (clinical or assessed by viscoelastic testing)
bpm = beats per minute, Hb = hemoglobin concentration.

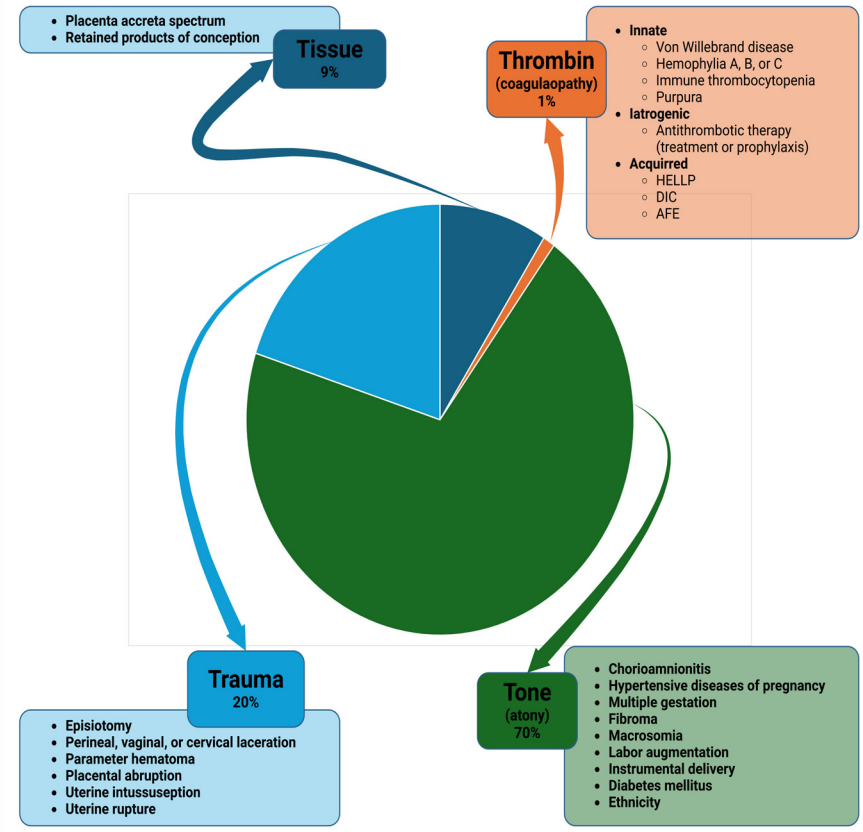

Fig. 1 — The etiologies of postpartum hemorrhage, classified according to the 4 T's mnemotechnic rule. PPH = Post-Partum Hemorrhage; HELLP = Hemolysis, Elevated Liver enzymes, and Low Platelet count syndrome; DIC = disseminated intravascular coagulation; AFE = Amniotic Fluid Embolism. Created in BioRender.com.

myometrium neuromuscular junction, and an anti-N-methyl-D-aspartate glutamate receptor effect leading to catecholamine depletion.

Trauma

Obstetric trauma accounts for up to 20% of PPH. Lacerations of the genital tract (perineum, vagina, cervix) are the most common traumatic complications and can be the result of instrumental delivery, precipitous delivery, or episiotomy. Broad ligaments hematomas are occult sources of bleeding. They can be spontaneous or secondary to instrumental vaginal delivery. Uterine rupture occurs in 3 over 1000 deliveries during spontaneous labor. It is characterized by sudden abdominal or scapular pain, abnormal fetal heart rate (FHR) and vaginal bleeding. Its incidence is higher during a trial of labor in women with a past history of cesarean section[18]. The administration of prostaglandins for labor augmentation also increases the risk in patients with a scared uterus, and the risk is higher with those medications than with oxytocin[18]. In case of uterine rupture, an immediate surgical repair is necessary, as tamponade is ineffective. Uterine inversion is a rare lesion occurring in the third stage of labor. In that case, the atonic fundus protrudes into the uterine cavity, being retained by the tonic cervix or extending through the vagina. This condition may result from connective tissue disorders, prolonged labor, abnormal placentation, uncontrolled cord traction, manual placental removal, and preeclampsia[19]. Inversion stimulates pelvic parasympathetic pathways and induces a deep vagal shock, which worsens the hemodynamic status in addition to the hemorrhagic hypovolemia. Management includes shock resuscitation, general anesthesia, and administration of tocolytics prior to a manual repositioning or surgical correction of the inversion[20]. Tocolysis should be reversed after successful correction, and control of the hemorrhage[19].

Tissue

Retained placental tissue is responsible for 10% of excessive bleeding after childbirth[21]. This situation is encountered in case of incomplete delivery of the placenta or membranes, the presence of an abnormally invasive placenta, or placenta implantation anomalies (placenta accreta spectrum; PAS). Manual revision is part of the stepwise etiological assessment and treatment of retained placental tissue. It also serves for the detection and removal of intrauterine clots that hinder proper uterine contractility. The management of PAS requires specific obstetrical and anesthetic skills, as related mortality rises from 7% to 30% when

undiagnosed prenatally[22]. This type of pathology is involved in 34.8% of peripartum hysterectomies[23].

Thrombin

Hemostasis disorders account for less than 2% of PPH. They can be constitutional and inherited (von Willebrand disease, hemophilia A, B, or C, …) or acquired (anticoagulation therapy, complications of pregnancy like severe pre-eclampsia, amniotic fluid embolism (AFE), intrauterine fetal demise, placental abruption, …). Placenta abruption is a particular antenatal bleeding emergency, often associated with fetal demise,
provoking concealed bleeding, consumption of clotting factor and platelets through systemic release of tissue factor[156].

Risk factors

Risk factors of PPH should be screened throughout pregnancy, upon admission to the obstetrical ward, and during and after labor, as patients can often worsen their risk status. The RCOG recommends that women with known risk factors should only be delivered in a hospital with a blood bank on site[8]. The major risk factors for PPH (with odds ratio when known), can be summarized as follows: multiple pregnancy (4.7), previous PPH (3.6), preeclampsia (5.0), fetal macrosomia (2.4), failure to progress during the second stage of labor (3.4), prolonged third stage of labor (7.6), retained placenta, placenta accreta (7.8), episiotomy (3.3), perineal laceration (4.7), or general anesthesia (>2.0).

Risk assessment tools, such as the California Maternal Quality Care Collaborative (CMQCC) (Table II), allow classifying the risk of severe PPH upon arrival at the labor ward, and during labor and after birth[24]. These criteria may serve to design specific management algorithms within institutions. Of note, 40% of patients experience PPH in the absence of recognized risk factors[10], and an often neglected risk factor is gestational age >41 weeks at delivery, with an odds ratio >1.5[25].

Early recognition

Early recognition of PPH and accurate blood loss estimation are crucial for prompt and adequate treatment. During pregnancy, plasma volume increases by almost 150% at the end of the third trimester[26], to a total of 100 mL.Kg^{-1} of circulating blood volume. Consequently, a loss of 25% of the total blood volume or up to 1500 mL often occurs before clinical signs of hypovolemia appear. A detection of PPH before the deterioration of vital signs is thus necessary to initiate early treatment. A visual estimation of blood loss is not precise enough, insofar as practitioners tend to overestimate small blood losses and underestimate the severe ones by 33-50%[27,28]. Visual aids improve the clinicians' visual estimation skills, but training must be repeated since this improvement drops within 9 months after training[27]. A quantitative assessment (quantitative blood loss estimation, QBLE) using calibrated drapes rather than gravimetric methods provides a better estimation of blood losses of more than 500 mL[29]. Neither the experience of healthcare providers[30], nor the use of visual aids or simulation provide additional accuracy as compared to QBLE[31]. Hence, it is suggested that QBLE should be favored over a simple visual estimation when bleeding exceeds 300 mL[32]. QBLE has been shown to reduce PPH-related morbidity only when integrated into an adequate bundle of care[33–35]. Quantitative measurements through combined gravimetric and volumetric methods are even more accurate (calibrated under-buttocks drapes or calibrated canisters and weighing of blood-soaked items and clots), but this can be uneasy to perform in real time in case of rapid blood loss. In any case, the volume of urine and amniotic fluid should be subtracted, and blood on the surgical drapes should be considered. The Triton colorimetric system (Gauss Surgical, Inc., Los Altos, CA) is a promising quantitative tool involving a mobile application on a tablet computer that uses image capture from the tablet's camera to derive the mass of hemoglobin on the surgical sponges. The use of this device seems to improve the detection of severe blood loss[36], but further validation is still needed. When the hemorrhage is concealed (placenta abruption, parametrial laceration, retroperitoneal bleeding), PPH can only be suspected and recognized when the clinical signs of hypovolemia are evident. The heart rate (HR) and blood pressure are usually maintained in the normal range until blood loss exceeds 1000 mL, tachycardia and a slight fall in systolic blood pressure (SBP) appear when blood loss ranges between 1000 and 1500 mL, and a drop in SBP below 80 mmHg associated with a worsening of tachycardia is seen when blood loss is >1500 mL[157].

A Modified Early Obstetric Warning Score (MEOWS)[37] has been developed to facilitate a fast and unbiased detection of a compromised maternal condition. It includes the respiratory rate, oxygen saturation, temperature, HR, consciousness level, SBP and diastolic blood pressure (DBP). The Obstetric Shock Index (SI), corresponding to the ratio between HR and SBP, is also a marker of hemodynamic compromise. It is particularly helpful in case of concealed bleeding (Table I). A normal SI ranges between 0.7–0.9 in laboring

Table II. — Risk of severe post-partum hemorrhage as defined by the California Maternal Quality Care Collaborative (CMQCC). Adapted from[24]. PPH = post-partum hemorrhage; EBL = estimated blood loss; PAS = placenta accreta spectrum; HELLP = hemolysis, elevated liver enzymes, low platelet syndrome.

Risk of severe PPH		
Upon arrival at the labor ward		During labor and after birth
Low		
No previous uterine incision Singleton pregnancy Less than 4 vaginal deliveries No known bleeding disorders No history of PPH		
Medium		Medium
Prior cesarean delivery or myomectomy Multiple gestation More than 4 vaginal deliveries Chorioamnionitis One previous PPH Large uterine fibromas	Platelets count 50,000-100,000 Hematocrit <30% Polyhydramnios Gestational age <37 or >41 Preeclampsia Prolonged labor (>24 h)	Second stage or urgent cesarean delivery Instrumental vaginal birth 3rd or 4th degree laceration EBL 500-1,000 mL
High		High
Placenta previa or low lying Suspected/known PAS Active bleeding Abruption Known coagulopathy Repeated history of PPH	HELLP syndrome Platelet count <50,000 mm^{-3} Hematocrit <24% Fetal demise ≥2 medium risk factors	Ongoing bleeding (>1 pad h^{-1}, clot >6 cm) Retained placenta Vertical or fundal hysterotomy EBL >1,000 mL Patient treated for hemorrhage General anesthesia Uterine rupture

patients. A value >0.9 should trigger low resources facilities to transfer the patient to a tertiary care hospital[38]. When >1, it signs massive PPH and helps predicting the need for blood and blood products[39]. However, when used in high income countries, the predictive performance of SI can be inconsistent[40]. Therefore, quantitative measurements, clinical alarm signs, and biological signs of metabolic acidosis should all be integrated to improve the early recognition of abnormal bleeding.

Readiness and patient preparation

Preparedness to adequate PPH management starts during the prenatal period, with an accurate identification of anemia, an active treatment of pathologies favoring uterus atonia such as gestational diabetes and pre-eclampsia, a multidisciplinary approach to congenital or acquired coagulopathies, the avoidance of unnecessary cesarean or instrumental deliveries, and the early identification and referral of PAS cases.

Anemia

The WHO defines gestational anemia as a decrease in hemoglobin (Hb) concentration to <11 $g.dL^{-1}$ at any gestational age, although this is debated. Some experts state that Hb levels should be the same as in non-pregnant women, and hence higher, at the condition that iron stores are optimal. The main cause of anemia during pregnancy is iron deficiency (50 to 75% of cases), since daily iron requirements in childbearing patients are higher than in non-pregnant patients, ranging between 30 and 60 ferrous elements per day. Supplementation, offered early during pregnancy, reduces maternal anemia at term by 70%[41]. The presence of low ferritin (<30 $g.L^{-1}$) during the first trimester, in addition to the initial Hb level, should be checked, as it accurately predicts anemia in pregnancy, and guides iron therapy[42]. Anemia per se does not increase the incidence of PPH[43], but moderate anemia (Hb ≤10 $g.dL^{-1}$) increases the probability of its clinical manifestations (odds ratio: 1.2), while severe prepartum anemia (Hb <7 $g.dL^{-1}$) is associated with an increased risk of death or near miss in case of PPH[44]. This is due to the low initial reserve and might be worsened by the alteration of the rheological properties of blood in severe anemia, potentially impeding hemostasis. Intravenous (IV) iron is currently reimbursed in Belgium when pregnant patients have iron deficiency and Hb ≤9 $g.dL^{-1}$, or proven malabsorptive iron deficiencies. In case of programmed cesarean delivery, thresholds are majored to <13 $g.dL^{-1}$, with ferritin <100 $mcg.L^{-1}$ and transferrin saturation index <20% or C-reactive protein >5$mg.L^{-1}$ [42]. Other vitamin deficiencies (such as deficiencies in folic acid or

vitamin B12) should be ruled out, especially in patients suffering from an inflammatory bowel disease or having undergone bariatric surgery.

Hemoglobin optimization is particularly important for patients with rare blood types, hemoglobinopathies, solid or hematologic cancers, and chronic renal failure. Such situations should be managed by a multidisciplinary senior team early in pregnancy, with delivery planned in a facility equipped with a blood bank, intrauterine tamponade devices, ability to perform embolization through interventional radiology, and availability of cell salvage devices. Pregnant patients who decline blood transfusion should also be managed by a senior team and informed that thresholds for a decision of hemostasis hysterectomy will be lowered, as their obstetric mortality risk is increased by 44 to 160 fold[45]. Likewise, recombinant human erythropoietin should be limited to its well-established indications, namely hypo-proliferative anemia or chronic renal failure after proper iron supplementation. Its safety during pregnancy has been shown in small clinical trials[42,46], but the level of evidence is not strong enough to approve it for refractory anemia, all the more since it has prothrombotic side effects.

Hemostasis disorders

A prenatal identification of hemostasis disorders in a pregnant woman can be done using scores such as the HEMSTOP (Table III)[47], which usually prompts routine coagulation testing if ≥2. This questionnaire has recently been tested amongst obstetrical patients, showing a 100% negative predictive value, a 96% specificity and a 39% sensitivity[48]. When anomalies are evidenced by routine testing, secondary hemostasis assessment may occur to adequately identify the underlying minor or major constitutional bleeding disorder. In turn, a multidisciplinary consensus between anesthesiologists, transfusion practitioners, hemostasis specialists, obstetricians and pediatricians should be reached regarding the adequate preparation to labor, delivery and neonatal care. Patients requiring antithrombotic treatment during pregnancy should be followed by a multidisciplinary team. They should benefit from a planned delivery with transitory interruption of their treatment, taking account of the bleeding/thrombotic risk balance.

Others

PAS should be excluded in each pregnancy by antenatal ultrasound during the first and second trimester. Ultrasound is the gold standard for the diagnosis of PAS, with an estimated 91% specificity and 97% sensitivity[49]. However, there can be inter-operator variability or visualization difficulties. Magnetic resonance imaging can be a complementary diagnostic tool in case of complex situations, such as posterior placentation, multiple pregnancy, and maternal obesity. Deliveries of patients with PAS should be handled in a tertiary center by an expert multidisciplinary team and an adequate bundle of care should be provided to patients early after diagnosis[50]. Other indirectly helpful measures for preparedness include early screening for pre-eclampsia and adequate prevention with aspirin before the 16th gestational week, control of diabetes, and protection of patients from preterm delivery and chorioamnionitis.

Prevention during the third stage of labor

The third stage of labor begins with birth and ends with the delivery of placenta and membranes. Its management can be active, by applying early cord clamping, prophylactically administering uterotonics, and applying a controlled cord traction at signs of separation, or expectant, involving cord clamping only when pulsation has ceased, and the placenta is delivered spontaneously or by maternal effort. It has been shown that an active management reduces the mean maternal blood loss at birth, the probability of blood loss >500 mL, and the need for uterotonics[51]. The most effective measure of an active management is the

Table III. — The HEMSTOP score. Two or more positive answers should lead to further hemostatic investigations. Reproduced from[47].

Hematoma	1. Do you experience bruises/hematomas larger than 2 cm without trauma or severe bruising after minor trauma?
Hemorrhage	2. Have you ever consulted a doctor or received treatment for prolonged or unusual bleeding such as nosebleeds, minor wounds?
Menorrhagia	3. Have you ever consulted a doctor or received a treatment for heavy or prolonged menstrual periods (contraceptive pill, iron, etc.)?
Tooth extraction	4. After a tooth extraction, have you ever experienced prolonged bleeding requiring medical/dental consultation?
Obstetrics	5. Did you experience prolonged or excessive bleeding after delivery? What was the origin of the bleeding?
Parents	6. Is there anyone in your family who suffers from coagulation disease (such as hemophilia, von Willebrand disease, etc.)?

administration of uterotonics, with oxytocin as the drug of choice, because it possesses the best balance between potency, cost-effectiveness, and side effects[52,53]. Omitting cord traction and uterine massage appears to have little effect on the amount of bleeding[54,55]. Early cord clamping is also no longer advised, since it results in lower mean birth weight, reflecting a lower blood volume for the baby, without a significant reduction in blood loss[11], while delayed clamping, two minutes after birth, appears to be beneficial for the newborn and its future neurodevelopment[56]. The NICE guidelines recommend cord clamping at least one minute after birth, unless there are concerns about the newborn's well-being[57]. Uterine massage, early breastfeeding or nipple stimulation do not bare any proven preventive effect on HPP[11]. Uterine massage hurts and interferes with parent/child bonding, but it is still prioritized by some midwives over oxytocin, due to preconceived notions that should be debunked.

Uterotonic medications

The administration of uterotonics (Table IV) is a major step in the prevention and treatment of PPH[53,58,59]. All existing agents are effective at preventing blood loss ≥500 mL, reducing the need for second-line medications and reducing the need for blood transfusion[60]. The agent of choice therefore depends on local resources (e.g. oxytocin needs to be stored between 2 and 8°C to remain effective).

First Line medications

Oxytocic medications

1. Oxytocin

Oxytocin (Syntocinon®) is a nonapeptide endogenously secreted by the pituitary gland. It binds to a G-protein on the cellular surface. This binding results in the generation of diacylglycerol (DAG) and inositol triphosphate (IP3) by the action of phospholipase C (PLC). DAG stimulates prostaglandin synthesis and IP3 stimulates the release of calcium by the sarcoplasmic reticulum. The action of oxytocin also results in the activation of type 2 cyclo-oxygenase with a subsequent increase in prostaglandin synthesis. Oxytocin receptors can be found at the surface of uterine myocytes, but also in the cardiovascular system and central nervous system. Throughout pregnancy, myometrial oxytocin receptors are expressed at an increasing density, up to a hundred-fold increase at the onset of labor[61]. The physiological action of oxytocin on uterine myocytes results in a rhythmic, and progressive contraction and relaxation of the uterus. It is metabolized by both the kidneys and liver, and its plasma half-life is quite short (1-6 min). A prolonged exposure to exogenous oxytocin can lead to a progressive desensitization of the myometrial receptors through epigenetic down-regulation[62]. This explains the possible exhaustion of the effect of oxytocin after prolonged exposure, and the need for a second-line uterotonic treatment to avoid PPH.

Oxytocin is recommended as a first-line for atony prevention, because it has been shown to be effective at reducing overall blood loss with fewer side effects than the other uterotonic agents[53,58]. The recommended preventive dosage ranges between 3 and 10 IU, slowly administered intravenously, or 10 IU administered intramuscularly. Higher dosages are unlikely to be more effective[59]. The onset time after an intravenous administration is very short, and the peak concentration occurs at 30 minutes[53]. Intramuscular administration leads to a longer onset time (3 to 7 minutes) and longer effect duration (up to one hour). For elective cesarean deliveries, the effective intravenous dose for an adequate uterine tone achieved in 90% of patients is as low as 0.35 IU in non-obese patients[63] and 0.75 IU in obese patients[64]. According to an international group of experts, the recommended oxytocin dose during elective cesarean deliveries is an initial intravenous bolus of 1 IU followed by an infusion at 2.5-7.5 $IU.h^{-1}$, and an additional dose of 3 UI slowly titrated after 2 minutes if the initial dose is not sufficient[65]. Indeed, a slow intravenous bolus of 3 to 5 IU appears as efficient as a dose of 10 IU with fewer adverse effects[65,66]. Oxytocin can also be used to prevent secondary atony, but its total dose should not exceed 40 IU[6].

The side effects of oxytocin depend on the total dose and rate of administration. For this reason, the total dose of oxytocin should be reduced to the necessary minimum and titrated slowly. Side effects mainly consist in cardiovascular manifestations, such as hypotension, tachycardia, arrythmias, ST depression, myocardial ischemia, vasospasm, and fetal bradycardia (when administered antenatally). Other side effects include nausea, vomiting, flushing, headache and hyponatremia (due to mimetic activation of vasopressin V2 receptors by oxytocin, and water retention). Recently, concerns have been raised regarding a possible interference of exogenous oxytocin with the endogenous pulsatile oxytocin secretion, with possible consequences on breastfeeding, postpartum depression and anxiety, but this has been refuted[67,68]. Contraindications to the use of oxytocin are coronary artery diseases, hypotension, and suspected allergy to the medication. Cross-allergy has been reported

Table IV. — Summary of the principal characteristics of uterotonic medications that are available in Belgium. IU = international unit; IV = intravenous; IM = intramuscular; PPH = post-partum hemorrhage; IR = intrarectal; SL = sublingual; IVG = intravaginal - 1/2.

Oxytocin	
Presentation	10 IU.mL^{-1} vials
Place in uterotonic therapy	First line
Special precautions and properties	Store between 2 and 6°C Tachyphylaxis in case of prolonged exposure
Kinetics	IV onset: 1 min IV half-life: 1 to 6 min IM onset: 3 to 7 min
Side effects	Hypotension, tachycardia, arrythmia, prolonged QT, ST depression, myocardial ischemia Nausea and vomiting Headache, skin flush, shivering Crossed allergy with latex Water retention and hyponatremia
Dosing	Vaginal delivery, prevention: 3 to 10 IU slow IV PPH treatment: 10 IU slow IV Intrapartum cesarean delivery: 3 IU slow IV followed by 7.5 to 15 IU.h-1 (max 10 IU) Maximum dose: 40 IU in 500 mL saline over 4 h Secondary atony, prevention: 10 IU in 1000 mL saline over 24 h
Carbetocin	
Presentation	100 mcg.mL^{-1} vials
Place in uterotonic therapy	First line
Special precautions and properties	Should be administered only after fetal delivery More effective than oxytocin in cesarean delivery Use in vaginal delivery only if 2 or more risk factors of atony
Kinetics	IV onset: 2 min IV half-life: 40 min
Side effects	Hypotension, tachycardia, arrythmia, prolonged QT, ST depression, myocardial ischemia Headache, skin flush, shivering
Dosing	Planed cesarean delivery, prevention: 20 to 100 mcg slow IV
Carboprost	
Presentation	0.25 mg.mL^{-1} vials
Place in uterotonic therapy	Second line
Special precautions and properties	Store between 2 and 6°C Contraindicated in pulmonary, renal and hepatic disease No other route than IM
Kinetics	IM plasma peak: 20 to 30 min IM half-life: 2 h
Side effects	Diarrhea, nausea, vomiting, abdominal pain, bronchospasm
Dosing	0.25 mg IM every 15 min Max 2 mg IM
Misoprostol	
Presentation	200 mcg tablets
Place in uterotonic therapy	Second line
Special precautions and properties	Contraindicated in sepsis and cardiovascular disease Vaginal route contraindicated if PPH
Kinetics	IR plasma peak: 30 min IR half-life: 20 to 40 min SL onset: 4 to 10 min SL time-to-peak: 15 to 30 min
Side effects	Nausea, pyrexia, abdominal pain, diarrhea
Dosing	IR: 600 to 1000 mcg SL and oral: 400 to 600 mcg, max 800 mcg

Table IV. — Summary of the principal characteristics of uterotonic medications that are available in Belgium. IU = international unit; IV = intravenous; IM = intramuscular; PPH = post-partum hemorrhage; IR = intrarectal; SL = sublingual; IVG = intravaginal 2/2.

Methylergometrin	
Presentation	0.2 $mg.mL^{-1}$ vials
Place in uterotonic therapy	Second line
Special precautions and properties	Contraindicated if hypertension, myocardial disease, stroke history, Raynaud syndrome, pre-eclampsia Store between 2 and 6°C
Kinetics	IVG time-to-peak: 35 to 100 min IM onset: 5 to 10 min IM duration: 3.9 h IV onset: 2 to 5 min IV half-life: 30 to 120 min IV duration: 45 min
Side effects	Acute hypertension, coronary vasospasm, myocardial infarction Headache, seizure, stroke Nausea, vomiting
Dosing	IM: 0.2 mg IV dose: 0.2 mg, slowly over 1 minute Can eventually be repeated at two to four hours intervals

between latex and oxytocin[69]. Oxytocin is heat-sensitive and should be stored between 2 and 8°C.

2. Carbetocin

Carbetocin (Pabal®) is a long-lasting, heat-stable synthetic octapeptide oxytocin analog, with a longer half-life due to its degradation-resistant chemical structure. Carbetocin is more lipophilic than oxytocin and subsists longer in the biophase. It acts like an oxytocin receptor agonist and induces rhythmic uterine contractions. Its potency on myometrial receptors can be hindered by prior oxytocin exposition[70]. Its onset time is 2 minutes after an intravenous administration and its half-life is 40 minutes. It first induces 6 minutes of sustained contractions followed by rhythmic contractions for 60 minutes. The intramuscular route has a slower onset time and longer effect (up to 120 minutes)[53].

Carbetocin use was initially restricted to cesarean deliveries only, because of financial concerns. The dose ranges between 20 and 100 mcg, both intravenously and intramuscularly. In elective and non-elective cesarean deliveries, the use of carbetocin is associated with a higher postoperative Hb level, shorter length of stay, and lower cost of stay than other uterotonics[71]. It reduces the need for second-line uterotonic medications and uterine massage following delivery, at an intravenous dose as low as 20 mcg in an elective setting and in non-obese patients[65,72]. The dose efficient in 90% of patients rises to 80 mcg in the obese undergoing elective cesarean delivery[73] and can rise to 120 mcg in cesarean deliveries for labor arrest[74]. Due to a higher incidence of cardiovascular side effects at higher doses, the maximum recommended dose is 100 mcg, administered slowly intravenously[65]. In vaginal deliveries, carbetocin is non-inferior to oxytocin and has an equivalent safety profile[53] but is less cost-effective. The heat resistance of carbetocin confers a potential advantage to oxytocin in case of difficult storage conditions and during heat waves[75].

The side effects of carbetocin can be cardiovascular, including hypotension, tachycardia, and alterations of the ST segment. Flushing, nausea and abdominal pain and fever can occur. Carbetocin does not activate the V2 receptors and therefore does not induce water retention and hyponatremia[76].

Second line medications

Prostaglandins

Prostaglandins act by stimulating prostaglandin receptors (PGE1, PGE2, PGF2α subtypes), which in turn activate a G-protein coupled receptor, leading to an increase in intracellular calcium concentrations. This improves uterine contractility. Prostaglandin receptors are present throughout pregnancy and prostaglandins effects are not affected by prior exposure to oxytocin. Prostaglandins are not currently used as a first line therapy in high income countries but should be considered promptly after the recognition of a failure of the first line agents.

1. Carboprost

Carboprost (Prostin®) is a long-lasting analogue of prostaglandin F2α. F2α receptors are found in the myometrium and the placenta, and their expression is majored during physiologic labor, peaking five minutes after delivery. Carboprost

binding to the receptor is 20 to 100 times stronger than endogenous prostaglandin F2α binding[77]. After an intramuscular administration, the peak plasma concentration occurs at 20 minutes, and the elimination half-life is 2 hours. Metabolization occurs in the liver and the lungs, excretion of the metabolites is urinary, with an 80% elimination within the first 10 hours.

The recommended intramuscular dose is 250 µg to obtain an adequate tone in 80% of patients and 500 µg in 90% of patients[70]. The administration can be repeated every 15 minutes up to a maximum of 2 mg. Intravenous or intramyometrial administration is contraindicated, as side effects are exacerbated through an accelerated systemic resorption.

The side effects of carboprost include asthma deterioration, possible live-threatening bronchospasm in non-asthmatic patients, pulmonary vasoconstriction, and intrapulmonary shunt with hypoxemia. Abdominal pain, nausea, vomiting and aqueous diarrhea are frequent. Pyrexia may occur, resulting from the blood-brain barrier penetration of carboprost and activation of thalamic prostaglandin receptors. Other side effects include myalgia and flushing.

Given the above-mentioned elements, patients with known pulmonary, hepatic, or renal disease should not be offered carboprost.

2. Misoprostol

Misoprostol (Angusta®, Cytotec®) is a heat stable long-lasting cheap prostaglandin E1 analogue.

The oral or sublingual administration provides the shortest onset time (4 to 10 minutes) and time to peak effect (5 to 35 minutes) among prostaglandin derivatives. A vaginal administration has a 35 to 100 minutes time to peak, with longer duration of action and best bioavailability in non-bleeding patients. In PPH, the intrarectal route should be favored. Misoprostol has mainly a renal clearance and metabolites are found in breast milk for several hours after an oral intake[78].

The WHO recommends oral and sublingual doses between 400 and 600 µg, the intrarectal dose being between 800 and 1000 µg[70]. The intravaginal dose is not recommended in case of PPH.

The side effects of misoprostol are less frequent than with other prostaglandins. They include abdominal pain, diarrhea, nausea, and headache. Fever and shivering are more frequent than with other prostaglandin derivatives. It can be stored at room temperature.

3. Sulprostone

Sulprostone is a synthetic prostaglandin E2 derivative and is currently recommended in Dutch[79], German[80] and French guidelines[6]. The recommended route of administration is intravenous, and in that case, the onset time is shorter than the one of intramuscular methylergometrin and oxytocin[81]. However, intravenous sulprostone has not been thoroughly compared regarding its potency, onset time, and duration of effect to other uterotonic agents. It achieves adequate uterine contractility in 87 to 92% of cases[77]. The usual dose is 500 mcg in 500 mL saline, infused intravenously over one hour, followed by a continuous infusion of 60 to 120 $mcg.h^{-1}$ [79]. The maximum dose is 1500 mcg over 24 hours. Other administration routes than the intravenous one are contraindicated[82].

Severe side effects may occur in 0.1 to 1% of cases[83] such as myocardial infarction secondary to coronary spasm, heart block with ventricular fibrillation, cardiac arrest, limb ischemia in a case of accidental subcutaneous injection[84], and pulmonary oedema in cases of intramyometral injection[83]. Milder side effects are mainly digestive (e.g. nausea, abdominal cramps, diarrhea) and pyrexia[77]. It should not be used in heavy smoking patients, patients with cardiovascular risks, and patients aged above 35 years old[6]. Other contra-indications include prostaglandin allergy, hypertension, asthma, epilepsy, deep venous thromboembolism, uncontrolled diabetes, and hepatic and renal disease[85].

Methylergometrin

Methylergometrin (Methergin®) is a semisynthetic ergot alkaloid with serotonergic properties. It has affinities for the 5-HT2 myometrial receptors. It also acts as a weak dopaminergic antagonist and α-adrenergic partial agonist with known activation of α-adrenergic receptors in the myometrium. Low doses cause rhythmic myometrium contractions, while high doses cause sustained tetanic contractions.

The intramuscular route is recommended with an onset time of 2 to 8 minutes and a time to peak plasma level of 15 minutes. Mean elimination half-life is 3.39 hours. Alternatively, careful intravenous administration has an immediate onset, a time-to-peak of 2 to 3 minutes, and an elimination half-life of 2.3 hours. The intramuscular route has the best bioavailability as compared to the oral route, due to the avoidance of the liver first-pass effect. Methylergometrin is mainly eliminated by the liver through the cytochrome 3A4, with possible interactions with other medications. Indeed, its elimination is slower in case of concomitant treatment with transcriptase inhibitors, macrolides, and azole antifungals[86]. Methylergometrine is recommended as a second line treatment by the

ACOG[158] and RCOG[159]. It is more effective than placebo at reducing the incidence of PPH and the need for additional uterotonics[87].

The intramuscular dose is 0.2 mg. The same dose can also be administered intravenously, but slowly over 1 minute. Eventually, this dose can be repeated at 2-to-4-hour intervals.

As an alkaloid agent, methylergometrine causes vasoconstriction and can lead to acute high blood pressure peaks and coronary vasospasm. Headaches, seizures, cerebral strokes, nausea, and vomiting can occur. It is contraindicated in patients suffering from hypertension, myocardial disease, stroke history, Raynaud syndrome and pre-eclampsia.

It is vulnerable to heat, light and humidity, and should be stored in a 2 to 6°C refrigerated environment.

Blood sparing techniques

Blood-sparing techniques in the context of PPH are mainly based on the early administration of tranexamic acid, use of the cell salvage techniques, early fibrinogen administration (when fibrinogen concentration drops <2 $g.dL^{-1}$), maintenance of normocalcemia and normothermia, and prophylactic intrauterine tamponade. Other blood-saving techniques have been studied but are not currently recommended, such as normovolemic acute hemodilution and autologous prenatal storage for later transfusion[88].

Antifibrinolytic therapy

Tranexamic acid (trans-4-aminomethylcyclohe xanecarboxylic acid, TA) is an antifibrinolytic agent preventing the conversion of plasminogen to plasmin, thereby inhibiting the breakdown of fibrin bonds and fibrin degradation. When clinical PPH is diagnosed, the recommended initial dose is 1 g, slowly administered intravenously over 10 minutes. The dose can be repeated once after 30 minutes if bleeding is still ongoing, or within 3 hours in the case of iterative bleeding. It is heat stable and should be stored separately from any local anesthetic agent for safety purposes, insofar as its inadvertent neuraxial administration is highly toxic and can lead to death. Although the early administration of TA increases its effectiveness, it should not be routinely offered as part of PPH prevention as it does not significantly reduce the incidence of >500 mL bleeding during vaginal deliveries[89]. The systematic prophylactic use of TA in elective and urgent cesarean deliveries has not been supported[90]. Nevertheless, TA reduces the risk of >1000 mL bleeding in cesarean deliveries and the need for blood transfusion[90]. It should therefore be administered prior to skin incision in high-risk settings such as PAS[90], or during the delivery of patients with mild platelet deficiency, hemophilia types A, B and C and von Willebrand disease[91,92]. TA administration in PPH significantly reduces the risk of bleeding-related death, of laparotomy to control bleeding, but not the risk of hemostasis hysterectomy[93]. Thus, the administration of TA should not be delayed in ongoing PPH, regardless of the bleeding etiology or of the onset time of co-administered uterotonics. No study has shown any increased risk of seizures, or venous or arterial thromboembolism in patients or their lactated infants after the use of TA in the obstetric setting[89,90,93]. Nausea, vomiting, transient increase in liver aminotransferases and dizziness are quite common after TA administration.

The cell-salver techniques

The use of cell-saver technology has been proven to reduce blood transfusion needs and is currently recommended in elective and urgent cesarean deliveries with >500 mL of anticipated blood loss. When used, a systematic administration of 1500 IU of anti-Rhesus antibodies should be performed in Rhesus-negative patients, due to a significant risk of alloimmunization[94]. No cases of iatrogenic AFE during the use of the cell-saver have been published yet using separate suction systems for amniotic fluid and blood, and blood collection starting after removing the placenta are advisable. In addition, fetal debris can be eliminated by double washing or the use of Leukogard filters. These filters are costly, they slow down the infusion rate and can lower blood pressure due to the release of vasoactive components[95]. The cell-saver technique requires a mindful cost-effective approach, and adequate training for urgent settings[96]. It should not be offered to patients with sepsis, active malignancy, and sickle cell disease. Its use for vaginal deliveries is difficult and has not been validated so far.

Early fibrinogen administration

The fibrinogen concentration physiologically increases throughout pregnancy, reaching median values at the third trimester between 3.3 and 6.0 $g.L^{-1}$, and even higher during the immediate postpartum period, up to 8 $g.L^{-1}$ [97]. Most cases of PPH are minor to moderate and do not lead to an acquired coagulopathy. An early systemic fibrinogen administration is not effective at lowering total blood loss, blood transfusion and anemia, especially when fibrinogen is >2$g.L^{-1}$ [98]. In massive PPH, fibrinogen seems to be pivotal for timely management. The decrease in fibrinogen concentration starts earlier than other clotting

factors, and is highly correlated with the total blood loss[99]. A fibrinogen concentration <2 $g.L^{-1}$ is an early predictor of massive hemorrhage[100], with a 100% positive predictive value[101]. It is also predictive of transfusion, hysterectomy and intensive care unit (ICU) requirements[102]. Maintaining levels >2 $g.L^{-1}$ is currently recommended[103], ideally through a goal-directed guidance[104,105]. Fibrinogen has a better safety profile than cryoprecipitate, due to its pasteurization and mode of storage. Reconstitution requires preparation with aqueous distillate rather than a saline solution.

Avoidance of hypothermia

Hypothermia delays thrombin generation and decreases the enzymatic activity of clotting factors and the effective count of circulating platelets. Hypothermia is correlated with a higher mortality rate and should be prevented early, using forced-air warming devices, infusion warming systems, and by shortening as much as possible the length of time with an open abdomen when surgery is needed[106].

Correction of hypocalcemia

The eventual presence of hypocalcemia should regularly be assessed, and actual hypocalcemia treated to prevent further coagulopathy. Hypocalcemia can follow massive blood transfusion, due to the chelation of the ion by the important amount of citrate contained in RBC units. It can also be the consequence of magnesium sulfate infusions in the context of pre-eclampsia. The target of plasma ionized calcium should always be >1.1 $mmol.L^{-1}$.

Early hemodynamic resuscitation and balanced transfusion thresholds

Transfusion of allogenic blood products exposes to the risk of transfusion-related immunosuppression, fever, acute lung injury, cardiac overload, citrate toxicity, acute hemolysis, or transmission of infectious diseases. Blood supply can be inconstantly available due to shortage or incompatibility with a rare group. A sensible use according to the need of the patient minimizes adverse events and spares collective resources.

The hemodynamic management of PPH starts with limited crystalloid and colloid infusions, in addition to a vasoactive drug support to restore adequate perfusion. The goal is to maintain a slight hypotensive permissive state, with a systolic blood pressure between 80 and 90 mmHg in healthy patients[107], and restore the circulating volume until blood units are available. The total infusion should not exceed 2 L of crystalloids and 1.5 L of colloids[92]. Higher clear fluid infusion volumes (>3.5 L) are associated with dilutional coagulopathy[108]. Blood transfusion should start in cases of massive ongoing bleeding (>1,500 mL) or concealed/unknown bleeding with rapid clinical worsening. The objective is to prevent or mandate hypoperfusion-related acidemia, a key contributor to coagulopathy and dilutional loss of clot factors. In vaginal deliveries, a SI >0.85 is a useful trigger for starting hemodynamic resuscitation. Yet, its low sensitivity at predicting total blood loss makes it unsuitable as a sole transfusion trigger in both vaginal[109] and cesarean deliveries[109]. Compared to SI, point-of-care abdominal ultrasound with inferior vena cava (IVC) measurement is a more accurate tool to guide blood and clear fluid therapy in severe PPH, in spontaneously breathing patients[110,111]. It is also particularly useful in case of hypertensive disorder, preeclampsia, and AFE to avoid overload. A lactate level >3.2 $mmol.L^{-1}$ is another useful therapy trigger[110].

Blood products, coagulation factors and massive transfusion protocols

Red blood cells, plasma, and platelets

The targeted hemoglobin concentration in patients with active PPH should be at least 8 $g.dL^{-1}$ [12,112]. The transfusion of RBC should be anticipated in severe PPH and given in a fixed initial shock pack in case of massive PPH. Several ratios between RBC units, fresh frozen plasma (FFP) and platelet cups to be transfused have been proposed in the literature (namely 6 RBC:4 FFP:1 platelets, 4:4:1, or 1:1:1), which were mainly derived from trauma resuscitation data[113]. Platelets transfusion should aim for minimal counts >50,000 mm^{-3}. FFP serves to treat coagulation factors depletion, when prothrombin time is prolonged (International Normalized Ratio or activated partial thromboplastin time >1.5 times the normal value). Of note, following fixed ratio protocols exposes to the risk of volume overload[113], and does not allow providing fibrinogen enough to compensate for loss in PPH[92].

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) is a synthetic serine protease indicated in the management of hemophilic patients. At a dose of 60 $\mu g.Kg^{-1}$, it can be used to control refractory coagulopathy in the context of an uncontrolled hemorrhage. In Belgium, its reimbursement is subject to strict criteria (coagulopathy, uncontrolled hemorrhage, potential hysterectomy after failure of uterotonics, fibrinogen >2$g.L^{-1}$, platelets >50, 000

mm^{-3}, a body temperature >35°C, blood pH >7.2)[114]. Arterial and venous thrombotic events, some of them being life-threatening, have been described after rFVIIa administration in the obstetric setting. Its use should be cautious and discussed with experienced practitioners[99].

Viscoelastic assays and goal-directed therapy

Viscoelastic hemostatic assays (VHAs), including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been used since the 1990's for the point-of-care assessment of coagulopathies encountered in cardiothoracic bypass surgery, in trauma patients and in obstetrics. They allow the detection of coagulopathy within 10 minutes. Their use may reduce the overall mortality in bleeding adults and children, and significantly spares transfusion of RBC, FFP, and platelets[115].

In the context of obstetrics, VHAs are thus interesting tools in cases of massive PPH (>1,500 mL). They can easily detect and regularly reassess the presence of coagulopathy throughout a massive transfusion process and allow for a goal-directed approach. Through this approach, and similarly to other bleeding circumstances, the use of VHAs for guiding the administration of transfusion products in PPH permits to lower the amount of transfused RBC, FFP, and platelets, as well as blood loss and ICU length of stay[116]. However, VHAs cannot detect inherited and drug-induced platelet dysfunction, and lack sensitivity at detecting von Willebrand factor and factor XIII deficiencies[117].

It is beyond the scope of this paper to review TEG and ROTEM interpretation in details (for a summarized description, see https://litfl.com/thromboelastogram-teg/), but one of the biggest advantages of these tests is the early detection of fibrinogen deficits. For example, the ROTEM FIBTEM A5 test studies the contribution of fibrinogen to the clot formation after platelet inactivation. During an ongoing massive bleeding, a FIBTEM A5 <12 mm indicates that the fibrinogen concentration is probably <2 gL^{-1} and should trigger fibrinogen administration (3 to 4 g IV)[118,119], although the evidence that this attitude helps controlling blood loss or reduces transfusion rates is controversial[120,121]. Of note, this cutoff value of <12 mm for FIBTEM A5 is valuable only for devices using a single platelet-inhibited assay. It drops to ≤8 mm when a dual platelet-inhibited assay is used[122]. When FIBTEM A5 does not provide any result, it is indicative of a fibrinogen concentration close to zero and of no initiation of clot formation. This finding is key for the early diagnosis of AFE[123]. The ROTEM APTEM and the FIBTEM MCF tests also allow the detection of hyperfibrinolysis, which may be encountered in AFE or placenta abruptio, and the guidance of management in that case[121,124,125]. The EXTEM CT test activates the extrinsic coagulation pathway through the addition of tissue factor, and thus assesses coagulation factors, fibrin polymerization, and platelet function. A normal EXTEM CT ranges between 43 and 82 seconds in obstetric patients. A value >80 seconds indicates a coagulation factor deficiency and a value >100 seconds or even >75 seconds with ongoing bleeding should prompt the administration of 15 to 20 $mL.Kg^{-1}$ of FFP[121,126].

Anesthetic considerations

Neuraxial anesthesia should be performed with caution in case of ongoing PPH and should be avoided if the EBL is >1,500 mL, and in case of preeclampsia or chorioamnionitis, due to the inherently associated coagulopathy and neuraxial septic contamination risk. When urgent anesthesia is necessary, hemodynamic instability, massive hemorrhage, uterine inversion, clinical coagulopathy, or need for laparotomy should prompt general anesthesia with rapid sequence intubation.

Obstetrical and interventional management

Initial measures

Obstetrical management of PPH requires an early and careful clinical examination. This starts with bladder emptying before a thorough examination of the perineum, vagina and cervix to detect eventual laceration needing a suture. Under adequate neuraxial or general analgesia, a manual ultrasound-controlled removal of membranes or persistent placenta residues inside the uterus may be necessary, with antibiotic prophylaxis covering anaerobes. Bimanual uterine compression by applying direct pressure on the anterior vaginal fornix and pressure on the abdomen may offer immediate control of bleeding, until other measures are undertaken[112].

Persistent uterine atony

When uterine atony persists, a primal technique consisted in dabbing the uterus cavity with surgical gauze. This technique has been disregarded because of the risk of infection and lower efficacy as compared to other mechanical tamponade techniques. There has been a recent resurgence in the use of gauze coated with hemostatic agents such as chitosan (a derivative of chitin). This technique has only been studied in retrospective settings or in small trials for atony and PAS, and does not seem to be superior to a tamponade by a Bakri balloon[127]. The modified chitosan-coated gauze

(Celox®) allows forming a pseudoclot. It strongly absorbs water, forms a cationic gel, which in turn attracts and retains RBC and transforms into a soft adhesive amalgam independent of coagulation factors[128]. It can be safely used in patients with shellfish allergies and can dwell within the uterus for 36 hours, if anti-anaerobic antimicrobial prophylaxis is provided. However, further studies are still needed to confirm the efficacy and safety of this system in an obstetric setting.

The Bakri balloon is the gold standard for adequate uterine tamponade, with an estimated success rate around 90% in case of uterine atony, and lower success in PAS[129]. Its placement requires holding the balloon in place under ultrasound guidance, while up to 500 mL of saline is infused to fill it in. Vaginal packing can further secure the placement in the uterus, as displacement occurs in 10% of cases[130]. Intra-cavity quantitative drainage is possible through a lumen inside the catheter. An anti-anaerobic antimicrobial prophylaxis should be started at placement and continued until catheter removal. Complications include failure to control bleeding, endometritis, lower vaginal segment laceration, uterine incision rupture or perforation, and colic subobstruction[129]. Other mechanical uterine tamponade devices exist, including uterine vacuum devices (e.g. Jada®) that apply negative pressure inside the uterine cavity to allow its contraction and reduction of blood flow. The use of Jada®° is limited to uterine atony with >3 cm cervical dilatation, normal uterine anatomy, and no preexisting chorioamnionitis. Studies are currently too limited to recommend its use[130].

If tamponade is ineffective, several other techniques should be considered.

Surgical control of bleeding

If ongoing bleeding compromises hemodynamic stability, surgical options should be considered, namely compression sutures, vascular ligation or hemostatic subtotal to total hysterectomy.

There are several techniques of compression sutures, the most common being the modified B-Lynch technique or "brace sutures", which consists in performing a lower segment hysterotomy and suture longitudinally from the anterior to the posterior wall through the uterine cavity, passing over the fundus with tight tying of both ends at the upper anterior segment. This technique can be done within ten minutes and can have a success rate as high as 90%[131–133]. Potential complications are uterine necrosis, synechiae, and highly variable outcomes for future successful pregnancies. B-Lynch is not indicated for PAS nor placenta previa, where Cho's square sutures and Quahba's sutures are more suitable. Recently, the Nausicaa technique has been described, consisting in a simple stepwise anterior wall plication and allowing placental debris drainage from the uterine cavity[134], but it requires further studies to be validated.

As an adjunct or alternative to compression sutures, a bilateral uterine artery ligation can be performed. The technique is complex, requiring multiple steps with dissection of the broad ligament, correct identification of the ureters, and careful bladder dissection, and takes time. It should be attempted by experienced surgeons[131]. Similarly, the ligation of the internal iliac artery requires the opening of the retroperitoneal space, identification of the ureters at 2 cm from their origin, and specific surgical skills.

Damage control surgery, namely hemostatic hysterectomy, either subtotal or total, is the ultimate treatment of refractory PPH. As it can be lifesaving in case of uncontrollable bleeding, it should be considered early and discussed between the anesthesiologists and obstetricians.

Interventional Radiology

Computed tomography with intravenous contrast is a useful diagnostic tool in case of unrecognized bleeding source, as a complement to bedside ultrasound imaging. It is also required prior to any interventional radiology procedure or in cases of recurrent bleeding after embolization[135].

Bilateral uterine artery embolization should be reserved for hemodynamically stable patients suffering from uterine atony. In that case, it has a success rate of more than 90%[112,133]. Complications occur in 3 to 4.5% of patients, including asymptomatic vascular injury, hematoma at the puncture site, endometritis, and pancreatitis. Subsequent infertility is reported in 43% of cases, and pregnancies after embolization tend to end with recurrent PPH[136]. Rarely, interventional radiology may be useful to treat postpartum vascular injury or to complete an unplanned cesarean delivery for PAS.

Recently, a new blood sparing technique, the Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has been proposed for patients with PAS undergoing cesarean delivery[137]. This endovascular balloon is inserted through the femoral artery and inflated in the descending aorta. The balloon should be inserted and stabilized between the renal arteries and the aortic bifurcation under fluoroscopic and/or ultrasound guidance. Partial to complete occlusion is achieved with a gentle saline inflation (up to 30 mL), and the balloon should ideally be deflated every 15 to

30 minutes. Subsequent ischemia-reperfusion of splanchnic and lower limbs territories release vasoactive mediators that interfere cyclically with the hemodynamic stability[137]. REBOA carries the risk of thrombotic artery complications. Intermittent balloon occlusion of the iliac arteries has been studied but is a more complex procedure and mandates a hybrid (surgical and radiological) suite.

Importance of bundle of care and post event debriefing

Severe PPH is the leading cause of maternal near misses with an estimated 80% avoidability[4]. It has significant associated morbidity, which can be the consequence of advanced resuscitation, transfusion, and thrombo-embolic events. It can be followed by treatment-related infertility, persistent anemia, fatigue or even post-traumatic stress disorder (PTSD), which in turn affects adequate infant care.

Nowadays, there is an increase in the occurrence of complex pregnancies, due to the success of in vitro fertilization[138], advanced maternal age[139], increase in the incidence of PAS[140,141], and improved management of maternal comorbidities and congenital conditions allowing for a subsequent pregnancy. Meanwhile, these recent years have been challenged by the covid pandemic with its subsequent impact on our supply chains systems, adding further burden on health workers and infrastructure in dealing with obstetric emergencies. This recent destabilization in adequate care highlights already existing social and ethnic disparities, which can have an impact on the risk of atonic PPH[16,142,143]. In a broader perspective, global climate disruption increases complexity, directly and indirectly, through sudden migrations with feared increases in vector-borne diseases and a rise in adverse pregnancy outcomes such as fire and air pollution-related hypertensive disorders, and placental abruption[144]. This potential social and structural instability falls disproportionately on pregnant migrants. They face delayed antenatal care due to anxiety towards dealing with authorities, language barriers, and lack of recorded medical history with morbid and fatal consequences as shown in the 2022 MBRRACE-UK report[145].

Pragmatically, Belgium faces territorial disparities in obstetric care quality with heterogeneity in obstetrical volume units and a lack of mandatory report of PPH incidence, with low transfer rates to interventional radiology-equipped units and a higher hysterectomy rate in small volume maternities[146]. Well adhered care bundles have been associated with improved outcomes[58]. The early use of uterine tamponade devices allows reducing the risk of massive PPH and stable transfer to units equipped with interventional radiology, transfusion center and ICU. Every maternity ward should implement an adequate bundle of care with hemorrhage algorithm charts, including prompt external resources identification, readily available kits for minor to massive hemorrhage easily located in the ward, which should be routinely checked, and an established blood bank protocol[147]. Planned PAS deliveries should be handled in a tertiary center by an expert multidisciplinary team[148] and adequate bundle of care should be provided to patients early after diagnosis. Accessible and complete electronic medical records are a critical part of internal management and appropriate partnership between centers.

Practically, readiness inside the facility is optimized by preparing a hemorrhage cart with basic to advanced resuscitation and uterotonic medications, catheters and IV lines for the anesthesiologist, valves, intrauterine tamponade devices, sutures for conservative techniques performed by the obstetrician, basic disinfecting kit with gazes for midwives with a checklist or management algorithm. The cart can be organized from basic to advanced management[149]. For further optimization, it is recommended to establish a response team, consisting of, among others, the local blood bank coordinator, an advanced surgical team, the responsible anesthesiologist, and the ICU coordinator on site or at the preferential tertiary hospital with preexisting transfer procedures. It is also recommended to establish a clear emergency transfusion protocol designed for obstetric patients[149]. After any PPH requiring the transfusion of more than 4 RBC units, a team debriefing is recommended at an appropriate time to allow for system learning, optimization of team management, and identification of any need for psychological support among health care providers[150]. Meanwhile, debriefing should be offered to the patient and their birthing partner, as an opportunity to discuss the events surrounding the obstetric hemorrhage at a mutually convenient time[103], as it provides useful information for a future pregnancy, as well as understanding and relief towards the steps taken to manage PPH.

The place of simulation

Massive PPH is a rare event. Hands-on clinical experience in this urgent setting is hindered by the necessity of prompt intervention by the most experienced practitioners. Simulation is effective in providing repeated practice for average and worst-case scenarios, helps in the acquisition of

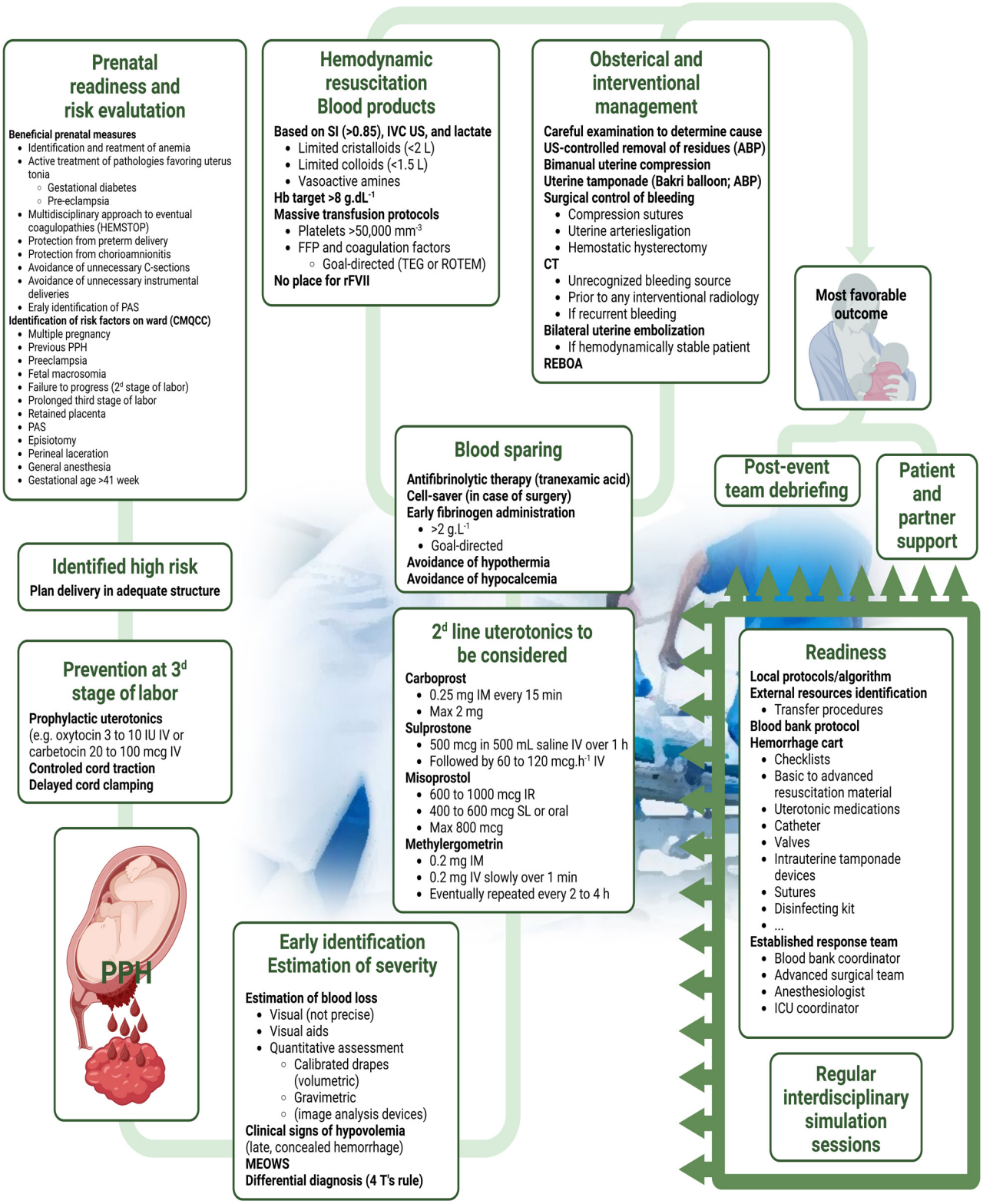

Fig. 2 — The ideal bundle of care for post-partum hemorrhage. HEMSTOP = score for the prenatal identification of hemostasis disorders; CMQCC = California Maternal Quality Care Collaborative; PPH = post-partum hemorrhage; PAS = placenta accreta spectrum; MEOWS = Modified Early Obstetric Warning Score; SI = shock index; IVC = inferior vena cava; US = ultrasound; Hb = hemoglobin; FFP = fresh frozen plasma; TEG = thromboelastography; ROTEM = rotational thromboelastometry; ABP = antibio-prophylaxis; CT = computerized tomography; REBOA = Resuscitative Endovascular Balloon Occlusion of the Aorta; IM = intramuscular; IV = intravenous; SL = sublingual; IR = intrarectal. Created in BioRender.com.

recognition and technical skills, provides objective feedback, and builds a safety culture through non-technical skills learning, such as efficient closed-loop communication, team awareness and conflict resolution[147]. It is more and more recommended as readiness enhancement through yearly drills[151]. Drills are particularly interesting if multidisciplinary and performed in situ, to allow for the participation of more caregivers, to assess on-site vulnerabilities, and identify opportunities of improvement[152]. Debriefing after simulation should be offered by qualified evaluators through a non-judgement three phases method: reaction, analysis and summary.

Psychological follow-up

Hysterectomy is associated with long-term psychological distress and the grievance of an ulterior pregnancy. It interferes with self-image and has cultural and intimacy burdens. PPH, as a life-threatening and morbid event affecting patients and their infant in a vulnerable moment, may trigger PTSD, depression, and transgenerational trauma. Adequate anesthesia management and timely information for patients and their family is key in preventing these issues. Multidisciplinary management should therefore include psychological support to prevent or manage symptoms, and patients should have access to timely empathic medical debriefing. PAS support groups have recently emerged to bridge some of the encountered shortages in the follow-up, with recognized benefits for patients[153].

Conclusion

PPH is a frequent yet complex delivery complication that can quickly worsen. It requires a multidisciplinary approach in its prevention and treatment. Its etiologies are mainly atony, genital or concealed trauma, placental retention including PAS and acquired or inherited coagulopathies. Efforts in accurate detection and an appropriate bundle of care should be made for each laboring patient since 40% of them do not belong to any risk group. Delivering patients should benefit from active third-stage management and adequate triggers should prompt treatment to reduce total blood transfusion and the risk of hysterectomy. Intra-uterine tamponade devices offer a 90% success rate in the control of bleeding in case of uterine atony. Interventional radiology is less morbid than surgery but requires hemodynamic stability. Medical therapy includes uterotonics, tranexamic acid, adequate anesthesia management, and hemodynamic gestion with balanced transfusion therapy and early fibrinogen supply. The use of the cell-saver is recommended in case of surgery but requires preparation and training. Controlling PPH requires immediate and global quality of care, readiness, recognition, response, and re-evaluation through debriefing and patient follow-up including psychological assistance (Figure 2).

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