Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously

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Management of postpartum haemorrhage: how to improve maternal outcomes?

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Summary

Postpartum hemorrhage is the leading cause of maternal mortality and severe morbidity. Despite efforts to improve maternal outcomes, management of postpartum hemorrhage still faces at least four challenges, discussed in this review. First, current definitions for severe postpartum hemorrhage hamper early identification of women with high risk of adverse outcome. Adaptations to the definitions and the use of clinical tools such as shock index and early warning systems may facilitate this early identification. Second, surgical and radiological interventions to prevent hysterectomy are not always successful. More knowledge on the influence of patient and bleeding characteristics on the success rates of these interventions is necessary. Scarce data suggest that early timing of intra-uterine balloon tamponade may improve maternal outcomes, whereas early timing of arterial embolization seems to be unrelated to maternal outcomes. Third, fluid resuscitation with crystalloids and colloids is unavoidable in the early phases of postpartum hemorrhage, but may result in dilutional coagulopathy. Effects of different volumes of clear fluids on the occurrence of dilutional coagulopathy and maternal outcomes is unknown. Fourth, a better understanding of diagnosis and correction of coagulopathy during postpartum hemorrhage is needed. Low plasma fibrinogen levels at the start of postpartum hemorrhage predict progression to severe hemorrhage, but standard coagulation screens are time-consuming. A solution may be point-of-care coagulation testing, however, clinical usefulness during postpartum hemorrhage has not been demonstrated. To date, early administration of tranexamic acid is the only hemostatic intervention that was proven to improve outcomes in women with postpartum hemorrhage.

Keywords: blood transfusion, hemostasis, point-of-care testing, postpartum hemorrhage, resuscitation

Introduction

In 2014, the WHO concluded from a systematic analysis that postpartum hemorrhage accounts for almost one fifth of maternal deaths worldwide, ranging from 8% of all maternal deaths in developed regions to 29% in Eastern Asia and 32% in Northern Africa [1]. Incidences of postpartum hemorrhage continue to increase, even in high-resource settings [2-7]. Depending on the definition used, the incidence of postpartum hemorrhage ranges from 3 to 8% of all deliveries [2-4,6].

Main causes of postpartum hemorrhage are uterine atony and placental problems including retained placenta and abnormally invasive placenta. Even though numerous risk factors for postpartum hemorrhage have been identified, it is still an unpredictable obstetric emergency. As a consequence, every woman is considered at risk of developing postpartum hemorrhage following delivery[8].

Quality improvement tools such as triggers, bundles, checklists and protocols in women with postpartum hemorrhage may improve maternal mortality and severe maternal morbidity [9-11]. Introduction of these tools was reported to reduce the use of blood products and improve patient safety in women with postpartum hemorrhage [11]. However, there may be room for improvement in the separate components of these tools. Consequently, optimization of the management of ongoing postpartum hemorrhage still faces numerous challenges

In this article, we review the literature on these controversial issues. We discuss 1) adaptations to postpartum hemorrhage definitions and clinical tools for early identification of women at high risk of adverse outcome, 2) timing of obstetric interventions to stop bleeding, 3) timing of switch from volume resuscitation with clear fluids to transfusion of packed red blood cells and 4) timing of hemostatic interventions to correct coagulopathy in women with severe postpartum hemorrhage.

Improving maternal outcomes: timely recognition of patients with severe postpartum hemorrhage

Definition of severe postpartum hemorrhage

Currently, postpartum hemorrhage and its severity are defined by estimated blood loss within 24 hours following delivery [12]. Cut-off values of 500 and 1000 mL are used for defining postpartum hemorrhage, with the latter mostly used in high-resource settings [13]. However, these cut-off values are relatively poor in identifying women with high risk of severe maternal morbidity and mortality, as only a small proportion of women that reach these cut-off values of blood loss progress to hemorrhage leading to hysterectomy or maternal death.

In a recent Delphi study performed by the International Network of Obstetric Surveillance Systems (INOSS), consensus definitions of several conditions of severe maternal morbidities were developed. The proposed definition for severe primary postpartum hemorrhage was blood loss exceeding 2000 mL and/or the need of transfusion of at least four units of packed red blood cells [14]. This definition enables selection of women with a higher risk of adverse maternal outcome than women with blood loss exceeding 500 or 1000 mL, while facilitating international comparisons of incidences of severe maternal morbidity and mortality as a result of postpartum hemorrhage. In practice, however, this definition excludes the possibility of early identification of women at high risk of adverse maternal outcome, as this definition reflects an intermediary or even end stage of hemorrhage.

Qualitative studies among experienced birth attendants show that severity of hemorrhage not only depends on volume of blood loss, but also on rate of bleeding and physiological response to bleeding [15]. In recognition of these determinants, several guidelines incorporated clinical signs of shock to express physiological response to bleeding in the definition of severe postpartum hemorrhage [16,17]. In addition, an international expert panel proposed to add *response to treatment* as a determinant of severity to the definition of postpartum hemorrhage, and suggested defining severe postpartum hemorrhage as persistent (ongoing) hemorrhage >1000 mL within 24 hours following birth that continues despite the use of initial measures to stop bleeding [8]. Adding *refractoriness to initial measures* to the definition of postpartum hemorrhage has the potential advantage of early identification of women at high risk of adverse maternal outcome by considering women as having a severe hemorrhage

as soon as initial uterotonic treatment fails to stop hemorrhage. Whether or not this adaptation will improve maternal outcomes might become clear in the near future, as this extension has already been implemented in a national guideline (figure 1)[18].

Clinical tools for early recognition of women with severe postpartum hemorrhage

Cardiac output increases during pregnancy due to a physiologic increase in heart rate and blood volume and blood pressure decreases due to lower systemic vascular resistance [19,20]. Cardiac output further increases during labor and delivery, because of a higher preload caused by uterine contractions. After delivery, preload further increases as a result of relief of inferior vena cava compression by the gravid uterus and the return of uterine blood to maternal circulation. As a result, early recognition of a deterioration in clinical condition in women with postpartum hemorrhage is difficult [21].

This early detection of deterioration in clinical condition has gained a lot of interest over the past decades, both in the pregnant and non-pregnant patients. Recent studies examined whether the *shock index* and *early warning systems* can be used to monitor women with postpartum hemorrhage. The *shock index* is the ratio of heart rate to systolic blood pressure. In the non-pregnant population a shock index >1.0, thus a higher heart rate than systolic blood pressure measured at least once in the observation period, has been associated with morbidity and mortality in critically ill patients suffering trauma, sepsis and after surgery [22-25]. A study among 8874 women without postpartum hemorrhage reported a range of 0.5 to 1.1 for the shock index immediately following delivery [26]. Another study among 233 women with postpartum hemorrhage with blood loss exceeding 1500 mL concluded that a shock index ≥1.7 was a predictor of intensive care unit admission, invasive surgical procedures and transfusion of ≥4 units of packed red blood cells, with respective area under the curves 0.75 (95% confidence interval 0.63-0.87), 0.62 (0.45-0.79) and 0.67 (0.58-0.76) [27]. Correspondingly, a secondary analysis of 958 women with hypovolemic shock due to postpartum hemorrhage in low-resource settings showed similar results for a composite maternal outcome for this cut-off value of ≥1.7 for the shock index, area under the curve of 0.76 (0.71-0.81). The composite outcome in this study consisted of maternal death, severe end-organ failure, intensive care unit admission, emergency hysterectomy and transfusion of ≥5 units of packed red blood cells [28].

Early warning scoring systems were also introduced to improve early recognition

of life threatening conditions. These scores are repeatedly calculated based on physiological parameters: heart rate, systolic blood pressure, respiratory rate, temperature and mental state [29]. The principle is that acute deterioration is preceded by subtle changes in these physiological parameters, and that these would be noticed earlier using *early warning scoring systems* than waiting for obvious changes in individual parameters [29,30]. In a systematic review, *early warning systems* were shown to successfully predict mortality in non-pregnant patients in different clinical settings [31]. Another systematic review focused on critically ill patients and concluded that the use of many different *early warning score systems* with different trigger thresholds hampered meta-analysis of conflicting findings [30].

Studies on the use of early warning systems in obstetric populations generally focus on several severe conditions in pregnancy and puerperium simultaneously, including preeclampsia, postpartum hemorrhage and sepsis. A retrospective study among 702 obstetric patients, in a low-resource setting, admitted to the intensive care unit showed an area under the curve for maternal death for high early warning scores of 0.84 (0.75-0.92) [32] . Similarly, several other obstetric early warning systems also showed to be able to differentiate well between women with and without an adverse outcome [33-36]. Maternal outcomes were also reported to improve after introduction of a Maternal Early Warning Trigger tool, as compared to before introduction of the tool. In this study, hysterectomy rates decreased from 0.94/1000 to 0.63/1000 deliveries [37].

To conclude, adding *refractoriness to initial measures* to definitions of severe postpartum hemorrhage may warrant early identification of women at high risk of adverse outcome. Clinical tools as *shock index* and *early warning scores* seem to have a good ability to predict adverse outcomes in women with postpartum hemorrhage. Further studies to quantify the added clinical value with respect to preventing adverse outcomes are to be awaited.

Improving maternal outcomes: obstetric interventions to stop bleeding

Initial measures to stop bleeding depend on the primary cause of hemorrhage. In case of uterine atony, the uterus is massaged as soon as uterine atony is diagnosed, and uterotonic agents are administered. The first-choice uterotonic agent is oxytocin, but if unavailable, misoprostol or ergot alkaloids are recommended [12,38]. If postpartum hemorrhage occurs with the placenta still in utero, manual removal of the placenta is performed. If the placenta has already been delivered, examination of the uterine

cavity under anesthesia to exclude placental remnants should be considered. However, when postpartum hemorrhage proves to be refractory to these initial measures to stop bleeding, guidelines prostaglandins as second-line uterotonic agents for treatment of uterine atony [16,18,39]. Bimanual uterine compression is recommended as a temporizing measure awaiting definitive uterotonic, surgical or radiological interventions to stop bleeding [12]. Surgical and radiological interventions to stop bleeding include intrauterine balloon tamponade, arterial embolization, arterial ligation and uterine compression sutures (brace sutures). If bleeding persists despite these interventions, hysterectomy should be performed.

Hysterectomy to avoid maternal death should be performed "sooner rather than later", according to the Royal College of Obstetricians & Gynaecologists (RCOG)[16]. Intrauterine balloon tamponade, arterial embolization, arterial ligation and uterine compression sutures have all been reported to be effective in stopping hemorrhage and preventing hysterectomy [40-51]. Yet, if unsuccessful, these interventions may also delay hysterectomy, especially because they are performed with low frequency, and thus, experience with these techniques may be insufficient.

When it comes to these interventions to avoid hysterectomy in women with severe postpartum hemorrhage two important issues on the appropriate timing of hysterectomy need to be resolved. First, we need to be able to recognize situations in which hysterectomy will be needed anyway. If surgical and radiological interventions fail most of the time in women with already high volumes of blood loss, high bleeding rates or who are hemodynamically unstable at moment of employment of these interventions, perhaps treating physicians should immediately perform the hysterectomy [52-54].

Second, we would argue for more insight into the interaction between the timing of the surgical and radiological and interventions and their success rates. Early employment of these interventions could minimize delay in hysterectomy in women in whom the bleeding proves refractory to these interventions. A study among 420 women with estimated blood loss >500 mL after vaginal delivery and >1000 mL after cesarean delivery assessed the effect of timing of uterine balloon tamponade and uterine artery embolization on maternal morbidity including hysterectomy and intensive care unit admission [55]. Timing of intervention was expressed as a function of estimated blood loss at the moment of employment of the intervention, and early timing of balloon tamponade (n=48) was associated with improved maternal

outcomes. For early timing of arterial embolization (n=20), this association was not shown. Larger studies are needed to know whether these findings are robust, and whether earlier surgical and radiological interventions to stop bleeding result in a reduction in adverse maternal outcomes.

In conclusion, a better understanding of the influence of patient and bleeding characteristics and timing of interventions on the success rates of surgical and radiological interventions to stop bleeding is necessary to improve outcomes of women with postpartum hemorrhage.

Improving maternal outcomes: timing of switch from resuscitation with clear fluids to transfusion of blood products

Fluid resuscitation should start as soon as the severity of postpartum hemorrhage becomes evident, to maintain circulating blood volume and preserve tissue oxygenation [8]. The first stage of fluid resuscitation consists of administration of crystalloids and colloids, and in case of ongoing hemorrhage, this stage is followed by the second stage consisting of transfusion of blood products.

In addition to abovementioned goals of resuscitation, blood products are also administered to support hemostasis and correct coagulopathy. Transfusion of plasma provides deficient coagulation factors, and packed red blood cells may also support primary hemostasis through different mechanisms. Red blood cells in the center of the vessel lumen may increase platelet concentrations near the endothelium [56]. Theoretically this so-called margination of platelets might support primary hemostasis, but this has not been supported by quantitative evidence. In addition, red blood cells may enhance platelet reactivity [57,58], support shear-induced platelet aggregation [59] and support thrombin generation by exposing procoagulant phospholipids [60-62].

Fluid resuscitation with high volumes of crystalloids and colloids, induces dilution of clotting factors and platelets, causing dilutional coagulopathy and thus aggravating hemorrhage [63]. In women with severe postpartum hemorrhage it has never been assessed, nonetheless, which volumes of clear fluids cause dilutional coagulopathy, nor whether dilutional coagulopathy contributes to adverse maternal outcome. A study examining varying degrees of hemodilution in healthy volunteers showed both in vitro and in vivo that hemodilution with normal saline decreased concentrations of coagulation and antifibrinolytic factors (α2-antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI)), and decreased thrombin generation [64,65]. Impaired

thrombin generation was also confirmed in bleeding patients with dilutional coagulopathy during major surgery, concomitant with impaired fibrin clot formation [66]. In these patients, volume of crystalloids, colloids, but also red blood cells, exceeded 5L.

Moreover, colloid fluids have been associated with impairment of different aspects of coagulation. Colloid fluids like hydroxyethyl starches, dextrans and gelatins have been associated with impaired platelet function, inhibition of fibrin polymerization and increase of fibrinolysis, and may lead to decreased levels of von Willebrand factor [65,67]. Clinically relevant effects of colloid fluids on coagulation in non-pregnant patients seem to arise when larger volumes are administered [67]. Effects of administration of colloid fluids on adverse maternal outcome in women with postpartum hemorrhage are unknown.

The RCOG guideline on prevention and management of postpartum hemorrhage recommends a maximum volume of clear fluids of 3.5L before start of blood transfusion, comprising up to 2L crystalloids and 1.5L colloids [16]. This advice was based on consensus from a Working Party of Haemostasis and Thrombosis Task Force [68]. However, thus far there is insufficient quantitative evidence to support this hypothesis. As a consequence, it is uncertain which volumes and combination of clear fluids increase the risk of adverse maternal outcome in women with postpartum hemorrhage.

Summarizing, resuscitation with clear fluids in women with postpartum hemorrhage is generally unavoidable because of the unpredictability of postpartum hemorrhage. However, switching to transfusion of blood products when these are available would probably reinforce hemostasis and thus be beneficial for women with ongoing postpartum hemorrhage.

Improving maternal outcomes: timing of hemostatic interventions to correct coagulopathy

Diagnosis of coagulopathy in women with postpartum hemorrhage

Pregnancy is a hypercoagulable state due to changes in the coagulation system throughout the pregnancy (figure 2) [69-72]. The majority of procoagulant factors increase, while the level of protein S as endogenous anticoagulant and fibrinolytic activity decrease. The most marked increases in procoagulants seem to occur in

concentrations of factor VII, factor VIII, von Willebrand factor and fibrinogen [72]. Fibrinogen concentration increases to approximately twice the non-pregnant values at term, with levels between 4 and 6 g/L [71]. The physiologic increase in plasma volume in pregnancy may also cause a mild thrombocytopenia [73]. Altogether, haemostatic changes of pregnancy lead to a slightly shortened prothrombin time (PT) and activated partial thromboplastin time (APTT), within the range of non-pregnant reference values [69,71,73].

A woman with ongoing postpartum hemorrhage may develop coagulopathy due to loss, dilution and consumption of platelets and clotting factors. All factors involved in coagulation may become deficient, procoagulant and anti-coagulant proteins, as well as fibrinolytic and antifibrinolytic proteins [66]. Impairment of hemostasis may also occur because of disseminated intravascular coagulation [64]. Risk factors for developing disseminated intravascular coagulation are placental abruption, preeclampsia with HELLP syndrome, and amniotic fluid embolism [64].

The monitoring of coagulation in women with severe postpartum hemorrhage is subject of debate. Conventional hemostasis assays such as the PT and APTT tests are considered unsuitable because of an inability to detect specific changes in coagulation, a disregard of large parts of coagulation (i.e. platelet function and fibrinolysis) and long turn-around times [74]. Studies that assessed the changes in PT and APTT during postpartum hemorrhage reported values within non-pregnant reference values during postpartum hemorrhage, even with high volumes of blood loss [75,76]. Among 356 women with postpartum hemorrhage PT and aPTT measured at 1-1.5L blood loss were not associated with progression to blood loss >2.5L [77].

Data on changes in platelet counts and function during postpartum hemorrhage are scarce. Available studies report minimal decreases of platelet counts during postpartum hemorrhage, and platelet counts measured in women with blood loss between 1 and 1.5L seem not to be associated with progression to higher volumes of blood loss [78,79].

Several observational studies reported a plasma fibrinogen level measured early during postpartum hemorrhage to be predictive of progression to more severe bleeding and invasive procedures in women with postpartum hemorrhage [75,77,79-81]. Positive predictive value of a fibrinogen level ≤2g/L for progression to severe bleeding was reported to be 100%, whilst negative predictive value of fibrinogen >4 g/L was 79%

[79]. Reported odds ratios for fibrinogen <2 g/L for progression to severe hemorrhage were 12.0 (95% confidence interval 2.6-56.1) and for fibrinogen between 2 and 3 g/L 1.9 (1.2-3.1) [80]. A point-of-care test to measure fibrinogen within a few minutes or seconds might be a promising monitoring tool for women with severe postpartum hemorrhage.

Since obtaining results of standard coagulation screens are time-consuming, coagulation monitoring with point-of-care tests is increasingly used in women with severe postpartum hemorrhage to detect coagulopathy and guide hemostatic interventions. However, the clinical usefulness of thromboelastography and thromboelastometry in women with postpartum hemorrhage has not been established [74]. As with the standard coagulation screens, thromboelastography and thromboelastometry values are different from the non-pregnant population due to the prohemostatic changes of pregnancy [63,74]. Several observational studies reported reference values for these point-of-care tests in pregnancy and the peripartum period, confirming the increased coagulability with faster initiation of coagulation and decreased fibrinolysis [82-84]. The next steps to be undertaken to eventually determine the clinical usefulness of these point-of-care tests in women with postpartum hemorrhage are 1) investigation of the changes in the measured values during postpartum hemorrhage and whether these measured values reflect impaired coagulation, as compared with standard coagulation assays, 2) investigation of appropriate interventions to correct these changes and 3) investigation of effects of the use of these tests in treatment algorithms for postpartum hemorrhage on clinically relevant maternal outcomes [85].

Overall, there seem to be minimal changes in PT, aPTT and platelet counts during postpartum hemorrhage, and only low plasma fibrinogen concentrations seem associated with progression to larger bleeds. Clinical usefulness of thromboelastography and thromboelastometry in women with postpartum hemorrhage is yet to be determined.

Correction of coagulopathy: early timing of fresh frozen plasma

Early timing of fresh frozen plasma, expressed as a high fresh frozen plasma to packed red blood cells ratio, seemed to reduce mortality in (non-pregnant) trauma patients in observational studies. Despite concerns about high risk of bias in these studies, massive transfusion protocols incorporating high ratio plasma and platelets to red blood cells were widely implemented in many different clinical settings with major

hemorrhage. A randomized clinical trial among 680 trauma patients with major bleeding receiving either a plasma:platelets:red blood cells ratio of 1:1:1 or ratio 1:1:2 showed no statistically significant difference in 24 hours and 30 days mortality with risk differences -4.2% (95% confidence interval -9.6 to 1.1) and -3.7% (-10.2 to 2.7) [86]. Death from exsanguination, a secondary outcome, was significantly decreased in patients that received a high ratio as compared with a low ratio, difference -5.4% (-10.4 tot -0.5).

In women with postpartum hemorrhage, studies on early timing of plasma to correct coagulopathy and improve maternal outcomes are limited. An observational before-and-after study among 142 women with severe postpartum hemorrhage, defined as postpartum hemorrhage requiring the second-line prostaglandin analogue sulprostone and packed red blood cells transfusion within six hours following delivery, compared fresh frozen plasma to red blood cells ratio of >0.5 with ratio ≤0.5 on advanced interventional procedures [87]. To account for confounding by indication, propensity score matching was performed for the 41 women who received plasma. In this study, a low fresh frozen plasma to red blood cells ratio was associated with more advanced interventions, odds ratio 1.3 (1.1-1.5), suggesting a beneficial effect of administering plasma early during the course of postpartum hemorrhage [87].

High ratios of plasma to red blood cells in women with postpartum hemorrhage were also studied within massive transfusion protocols. These massive transfusion packs were part of an obstetric hemorrhage protocol that included a whole series of other changes in management [11]. The combination of changes in management seemed to reduce blood product use in these women, but the ratios of blood products in the designated “obstetrics hemorrhage pack” were based on evidence from trauma-related hemorrhage. Future studies need to address the comparison of different transfusion protocols for postpartum hemorrhage.

Interestingly, in a recent observational study among 605 women with postpartum hemorrhage exceeding 1L of blood loss fresh frozen plasma was administered when thromboelastometry showed signs of fibrinogen deficiency (Fibtem A5 ≤15 mm)[88]. The women who did not reach Fibtem A5 below 15 mm did not develop clinically significant hemostatic impairment, defined as continued bleeding and laboratory hemostatic failure (PT or aPTT >1.5 times the midpoint of the normal range or fibrinogen <2 g/L).

Concluding, whether early administration of plasma during the course of

postpartum hemorrhage improves maternal outcomes is still unclear.

Correction of coagulopathy: early timing of tranexamic acid

The effect of early administration of the antifibrinolytic agent tranexamic acid on maternal mortality and hysterectomy, as compared with placebo, has recently been assessed in the WOMAN trial, an international randomized controlled trial among 20060 women with postpartum hemorrhage [89]. Postpartum hemorrhage was defined as 500 or 1000 mL depending on the mode of delivery, or blood loss causing hemodynamic instability. In this study all-cause mortality and composite outcome consisting of all-cause mortality and hysterectomy did not differ between women treated with tranexamic acid or placebo, corresponding risk ratios 1.02 (0.88-1.07) and 0.97 (0.87-1.09). Compared with placebo, death due to bleeding was significantly reduced in women treated with tranexamic acid, risk ratio 0.81 (0.65-1.00), and when administered within three hours following birth 0.69 (0.52-0.91). Importantly, administration of tranexamic acid was not associated with an increased risk of venous thromboembolism.

Generalizability of the results of the WOMAN trial has been questioned, as almost all study participants (97%) were recruited in low-resource settings with high maternal mortality ratios [90-92]. Effect of adding tranexamic acid to treatment algorithms in high-resource settings, with advanced uterotonic, surgical and radiological interventions and transfusion of blood products available, on severe maternal morbidity and mortality remains unclear. A randomized controlled trial in a high-resource setting among 144 women with postpartum hemorrhage >800 mL following delivery compared the effect of high-dose tranexamic acid versus no tranexamic acid at moment of diagnosis of postpartum hemorrhage on total blood loss and invasive interventions to stop bleeding [93]. Tranexamic acid reduced median additional blood loss from moment of diagnosis of postpartum hemorrhage till end of bleeding slightly from 221 (interquartile range 105 to 564) to 173 mL (59 to 377) (p-value 0.04), and there was no difference in advanced interventions to stop bleeding. Similarly, a before-and-after observational study in a high-resource setting including 289 women with hemorrhage ≥500 mL following delivery, did not show a decrease in mean estimated blood loss after incorporating tranexamic acid in the treatment algorithm [94]. Additionally, early administration of tranexamic acid did not reduce adverse maternal outcome in a cohort study among 1260 women in the Netherlands with postpartum hemorrhage >1L and refractory to first-line obstetric interventions, odds ratio 0.9 (95% confidence interval 0.7-1.3) [95].

In women with postpartum hemorrhage, early tranexamic acid seems to reduce the risk of maternal death due to exsanguination, with a favorable safety profile. However, the effect on maternal outcome in women with postpartum hemorrhage in high-resource settings may be limited. Future studies need to establish whether and when tranexamic acid improves clinical outcomes of women with postpartum hemorrhage.

Correction of coagulopathy: early timing of fibrinogen concentrate

Two randomized controlled trials investigated the effect of fibrinogen concentrate on maternal outcome. In the first trial, including 249 women with severe postpartum hemorrhage (after vaginal delivery >0.5L blood loss with retained placenta or >1L blood loss and intended manual exploration of the uterus, or >1L blood loss after caesarean delivery), pre-emptive treatment with 2g fibrinogen concentrate did not reduce the need for packed red blood cell transfusion or secondary outcomes, as compared with placebo [96]. At inclusion mean blood loss was 1459 mL (standard deviation 476 mL) and mean plasma fibrinogen level was 4.5 g/L (standard deviation 1.2). In the second trial, that randomized 55 women to fibrinogen concentrate or placebo, fibrinogen concentrate was administered in case the Fibtem A5-value, the thromboelastometry surrogate measure of plasma fibrinogen level, was below 15 mm [97]. This cut-off value for Fibtem was chosen after a preceding observational study among 365 women with postpartum hemorrhage (1-1.5L) indicating a predictive role of low Fibtem values for development of severe hemorrhage [77]. Median blood loss at time of study medication infusion was 1950 mL (interquartile range 1500-2285) and median fibrinogen level 2.5 g/L. In this trial administration of fibrinogen concentrate did not reduce the number of transfused blood components.

There are some published data on the use of algorithms to guide treatment of postpartum hemorrhage using thromboelastography and thromboelastometry. A before-and-after observational study with Rotem-guided fibrinogen concentrate administration reported a lower blood components use as compared with administration of fresh frozen plasma in major hemorrhage transfusion packs [98]. The study included 93 women with ongoing postpartum hemorrhage (>1500 ml) and coagulopathy defined as Fibtem A5 <12mm.

Thus, administration of fibrinogen concentrate to women with ongoing postpartum hemorrhage and fibrinogen level above 2g/L does not seem associated with better

maternal outcomes. Trials with fibrinogen administration in women with postpartum hemorrhage and plasma fibrinogen levels below 2g/L might demonstrate an effect on maternal outcomes. Before performing these trials, we need a test that provides fast and accurate estimates of a woman's fibrinogen concentration.

Correction of coagulopathy: recombinant activated factor VII

Following an abundance of case series, only one randomized controlled trial has been published on administration of recombinant activated factor VII in women with postpartum hemorrhage for correction of coagulopathy [99]. In this open-label trial 84 women with severe postpartum hemorrhage (>1.5L) refractory to the uterotonic agent sulprostone were randomized to a single dose of recombinant activated factor VII (60 ug/kg) or standard care. Randomization occurred one hour after onset of sulprostone, and outcomes were the need of advanced surgical or radiological intervention after randomization. Early administration of recombinant factor VII was associated with a reduction in advanced interventions to stop bleeding, relative risk 0.56 (0.42-0.76). However, information bias could have influenced the study results, as there was no allocation concealment in the study. Venous thromboembolism occurred in 5% of women who received recombinant activated factor VII, and did not occur in the women who underwent standard care. In a meta-analysis including only randomized controlled trials among non-obstetric bleeding patients this hemostatic agent was associated with arterial thromboembolism with odds ratio 1.7 (1.2-2.4), but not with venous thromboembolism (odds ratio 0.9 (0.7-1.2)) [100].

Correction of coagulopathy: prothrombin complex concentrate

To date, comparative studies on administration of prothrombin complex concentrate in women with postpartum hemorrhage have not been published. A randomized controlled trial comparing prothrombin complex concentrate and fibrinogen concentrate with fresh frozen plasma (NCT01910675) did not get permission from the appropriate Medical Ethical Committee, because it was not feasible to get proper informed consent from these acute, severely ill patients (personal communication).

Conclusion

In the optimization of management of postpartum hemorrhage we are still facing several challenges. Early recognition of women at high risk of adverse outcomes because of postpartum hemorrhage may be achieved by adaptations to the definition of severe postpartum hemorrhage and the use of clinical tools such as *shock index* and

early warning scores.

Optimization of timing of surgical, radiological and hemostatic interventions in these women to stop bleeding and timing of switch from resuscitation with clear fluids to transfusion of blood products is of utmost importance to reach the goal of improving maternal outcomes. However, well-designed studies on obstetric interventions to stop bleeding are scarce and results from studies on hemostatic interventions to stop hemorrhage in these women show conflicting results. Broadening our understanding of the interaction of individual patient characteristics with these interventions will enable us to improve management and outcomes of women with severe postpartum hemorrhage.

Addendum

D.D.C.A. Henriquez collected literature and wrote the first draft of the manuscript. All authors were involved in interpretation of data and revision of the manuscript.

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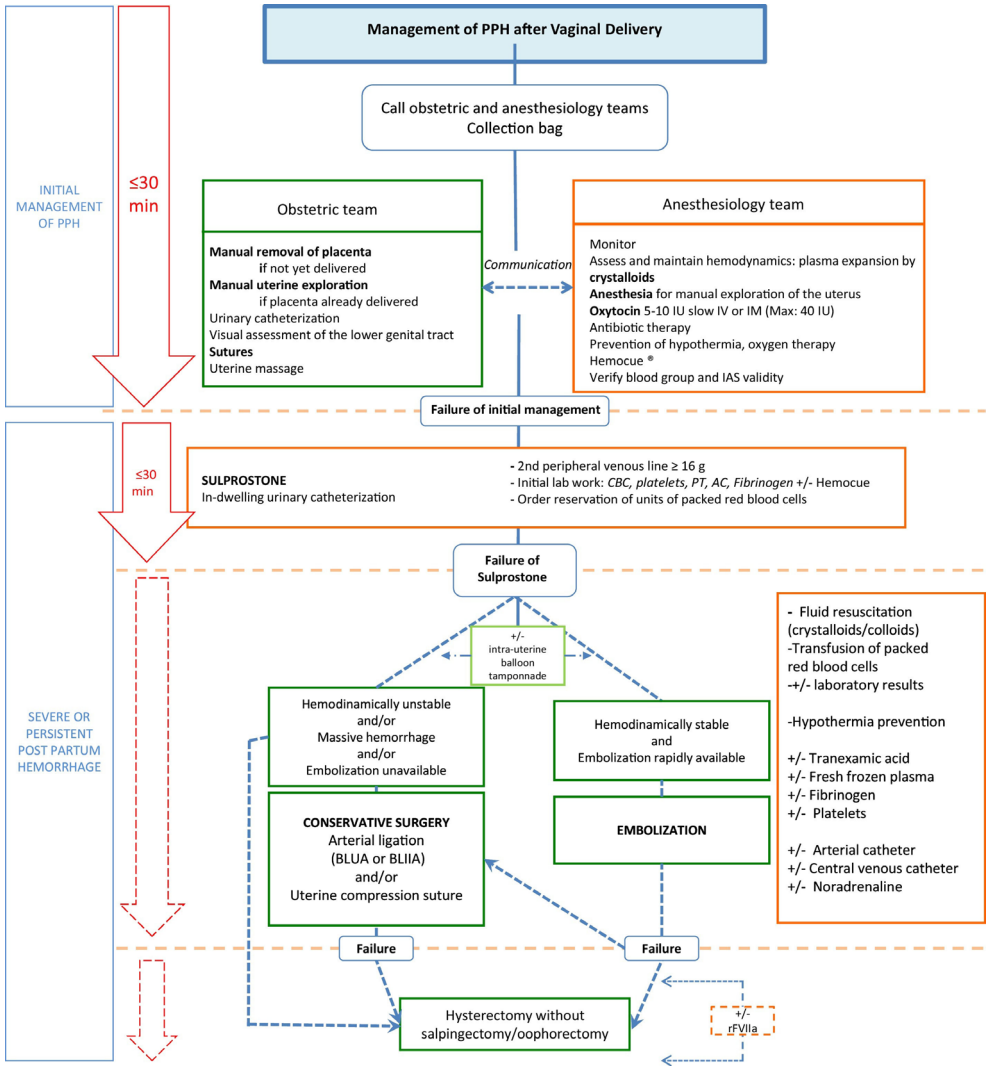

Figure 1. Algorithm from French guideline for management of postpartum hemorrhage after vaginal delivery, with definition of severe postpartum hemorrhage as postpartum hemorrhage refractory to initial measures to stop bleeding. PPH, postpartum hemorrhage; IV, intravenous; IM, intramuscular; IU, international unit; IAS, irregular antibody screening; CBC, complete blood count; PT, prothrombin time; ACT, activated clotting time; BLUA, bilateral ligation of uterine arteries; BLIIA, bilateral ligation of internal iliac arteries; rFVIIa, recombinant activated Factor VII. Adapted from Sentilhes et al. [18]

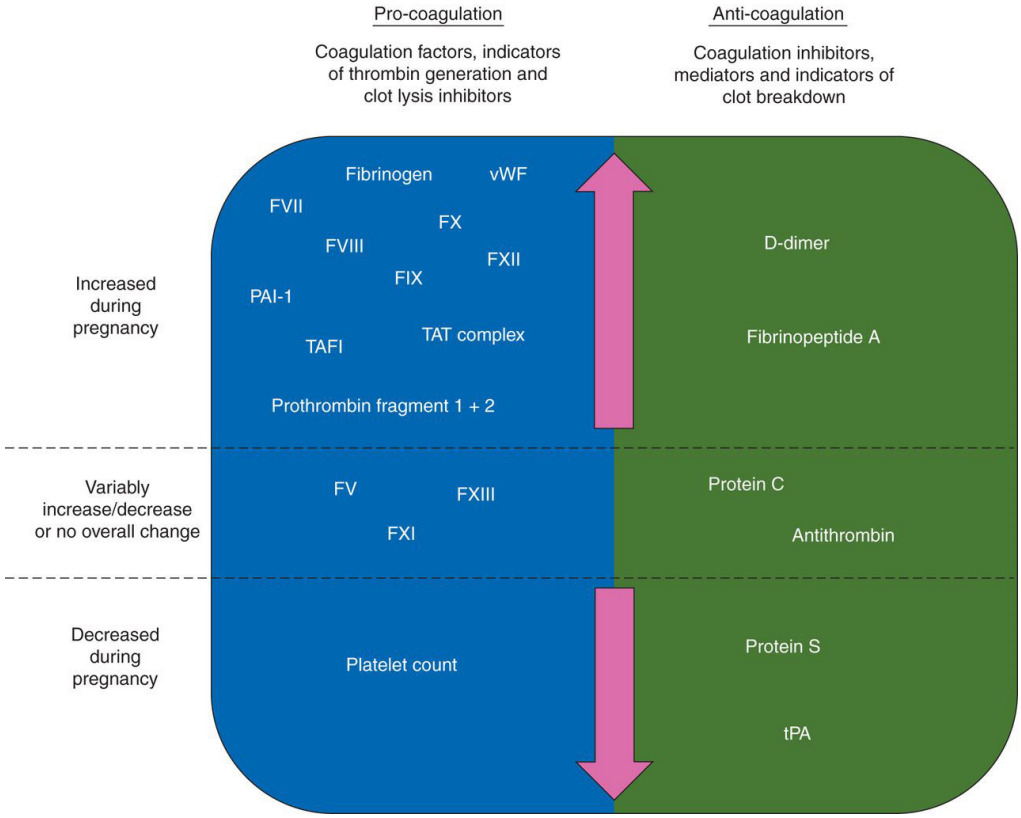

Figure 2. Hemostatic changes during normal pregnancy. The overall increase in procoagulant factors results in a hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative of the precise level of increase or decrease. FV, Factor V; FVII, Factor VII; FVIII, Factor VIII; FIX, Factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; FXIII, Factor XIII; PAI-1, plasminogen activator inhibitor 1; TAFI, thrombin activatible fibrinolysis inhibitor; TAT complex, thrombin-antithrombin complex; tPA, tissue plasminogen activator; vWF, von Willebrand factor. Solomon et al. [70]