Hemostatic disorders in women

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Summary. The past few decades have seen major advances in multidisciplinary obstetric care and management of gynecological conditions in women with bleeding disorders. Awareness of the impact of bleeding disorders has improved among the obstetric and gynecological community. Undiagnosed bleeding disorders can be the underlying cause for a significant proportion of women with heavy menstrual bleeding. They may also be the cause or a contributory factor for other gynecological problems, such as dysmenorrhea, intermenstrual bleeding, and endometriosis. Hemostatic assessment should be considered in women referred for menstrual abnormalities if they have a positive bleeding history as quantified by bleeding assessment tools. The reproductive choices and options for prenatal diagnosis are also expanding for families with hemophilia with a drive toward achieving a non-invasive approach. Current non-invasive prenatal diagnostic techniques are limited to identification of fetal gender. Research is ongoing to overcome the specific diagnostic challenges of identifying hemophilia mutations, utilizing free fetal DNA circulating in maternal plasma. The management of obstetric hemorrhage has recently evolved to include a greater focus on the identification of and early treatment for coagulation disorders. Deficiencies in certain hemostatic variables are associated with progression to more severe bleeding; therefore, specific interventions have been proposed to target this. Evidence is still lacking to support such strategy, and future research is required to assess the efficacy and the safety of these hemostatic interventions in women with persistent PPH.

Keywords: hemostatic disorders, menorrhagia, menstruation, postpartum hemorrhage, prenatal diagnosis.

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Introduction

Over the past two decades, there has been a concerted effort internationally to recognize the challenges facing women with inherited bleeding disorders. Recognition that conditions such as von Willebrand disease (VWD) and hemophilia can impact on reproductive health of women has been an emerging issue. VWD, the commonest bleeding disorder, was first described by Eric von Willebrand in 1926 as a bleeding condition in a family living on the Åland Islands in the Gulf of Bothnia that primarily affected women [1]. The index case was a young girl, who subsequently bled to death during her fourth menstrual period at the age of 13. Her maternal grandmother died from postpartum hemorrhage during her first delivery. Despite this, women's issues with bleeding disorders and their morbidity remained unrecognized and underestimated for decades [2,3]. From the 1990s onward, research began in earnest to identify obstetric and gynecological morbidity among women with bleeding disorders and to establish the true prevalence of bleeding disorders in women with heavy menstrual bleeding (HMB). These findings led to a drive toward increasing awareness among clinicians of women's reproductive health issues and disorders of hemostasis. In a recent survey of 503 obstetricians and gynaecologists in the United States, VWD and other bleeding disorders were considered in the differential diagnosis of HMB in 39% of reproductive aged women and 77% of adolescents [4]. This has promisingly increased in comparison with findings from a survey 10 years earlier with corresponding figures of 4% and 16% of clinicians considering bleeding disorders in the management of HMB, respectively [5].

Women with bleeding disorders can now embark on pregnancy with the multidisciplinary support of combined speciality clinics. Prenatal diagnosis (PND) is an important aspect of pregnancy care that has undergone rapid technological development over the past few years. There has been increasing choice for families with severe inherited bleeding disorders, including non-invasive options.

Postpartum hemorrhage (PPH) remains a leading cause of maternal mortality and morbidity worldwide. A critical feature of PPH is the development of acquired coagulopathy. It is often unrecognized and undertreated, causing progression to more severe bleeding. In recent years,

several hemostatic advances specifically targeted to diagnose and treat coagulopathy have provided a research focus leading to a new approach in management of PPH.

This article provides a review of advances in diagnosis and management of women with inherited bleeding disorders and acquired coagulopathy in PPH. It also addresses the areas of controversy and ongoing research in the field.

Disorders of hemostasis and gynecological conditions

Menstruation and ovulation are unique hemostatic challenges that occur monthly in women of reproductive age. Integral hemostatic systems are required to control excessive bleeding during these events. While men with mild inherited bleeding disorders are often asymptomatic, women suffer a significant morbidity and impaired quality of life mainly with menstrual-related bleedings [3,6,7]. HMB is often the presenting symptom of an underlying bleeding disorder and can be the only bleeding symptom in women [8]. HMB was recognized as a valuable predictor for diagnosis of bleeding disorders in the mid-1990 [9]. A prospective study of 150 women presenting with HMB found the frequency of undiagnosed bleeding disorders of 17%, and VWD was the most common with a incidence of 13% [8]. Subsequently, a systematic review of the literature confirmed an overall incidence of 13% (95% CI 11%, 15.6%) of VWD among 988 women in 11 studies [10]. Mild platelet function defects are also a frequently found inherited bleeding disorder in women with HMB. However, disorders of platelet function are more likely to remain undiagnosed due to the complex and specialized testing that requires fresh specimens. There are only a few studies in the literature that assess the incidence of platelet function disorders in women with HMB [11–13]. These studies reported platelet function defects to be more common than VWD and were found in approximately 50% of women presenting with HMB [11–13]. Racial differences have been observed with platelet function defects being significantly more prevalent in black women compared with white women in US studies [11,13].

Thus, the association of HMB in women and inherited bleeding disorders is well established. This is reflected in the national and international guidelines that recommend consideration of testing for disorders of hemostasis in women presenting with HMB [14,15]. Comprehensive testing for underlying bleeding disorders in all women with HMB is neither practical nor necessary. There is so far no consensus on how to screen and identify women who are likely to have an underlying bleeding disorder, thus require hemostatic assessment. The use of quantitative bleeding assessment tools (BAT) have been proposed and recommended for screening patients with bleeding symptoms [16,17]. The clinical diagnostic utility of BAT was recently evaluated in 215 patients (including 126 women) referred for hemostatic assessment [18]. A bleeding score ≤ 3 was reported to have a very high (99%) negative predictive value in patients referred with bleeding symptoms. Thus, it was concluded that a bleeding score of ≤ 3 could be used to exclude mild bleeding disorders without the need for detailed hemostatic assessment in patients referred with bleeding symptoms. The Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis (ISTH) developed a new bleeding assessment tool (ISTH/SSC-BAT) in 2010. The aim was to establish a standardized BAT that could be applied to both adult and pediatric populations to improve the diagnosis of mild bleeding disorders and describe severity of symptoms in patients with known bleeding disorders. Bleeding symptoms that apply only to females (HMB and postpartum hemorrhage) were detailed more extensively. The validity, reliability, and predictive power of the ISTH/SCC-BAT, specifically when applied to women, require prospective testing [17].

In addition to HMB, other gynecological conditions have also been reported in association with bleeding disorders including dysmenorrhea, hemorrhagic ovarian cysts, and endometriosis [6,19]. Further research is required to prove whether bleeding diathesis underlies the pathogenesis of these gynecological conditions. Local factors play a key role in the maintenance of hemostasis within the endometrium. Recent research has highlighted the importance of procoagulants such as tissue factor (TF), and plasminogen activator inhibitor 1 (PAI-1) in maintaining hemostasis within endometrial stromal cells [20]. A fall in the endometrial VWF expression has been reported with menstruation, and low endometrial VWF has been suggested in the pathogenesis of HMB [21]. Targeted interventions such as antifibrinolytic agents and desmopressin for the management of HMB have been developed from enhanced knowledge of such hemostatic mechanisms within the endometrium. A full discussion on management of HMB in women with inherited bleeding disorders is outside the scope of this review article. References [22,23] provide a full discussion for the interested reader. Optimizing treatment strategies according to the underlying disorder of hemostasis may result in better response to medical treatment, improved quality of life, and less surgical intervention, such as hysterectomy [24].

Prenatal diagnosis

Prenatal diagnosis is an important aspect of pregnancy care for women in families with severe bleeding disorders. Current methods of PND are invasive and pose a risk to the fetus. It is offered to women with severe inherited bleeding disorders, mainly hemophilia, if they wish to opt for selected termination of an affected pregnancy. More often it is undertaken to determine whether the fetus is affected, to help guide appropriate management during delivery [25]. The uptake for PND varies worldwide but

is generally low in high resource countries that can provide effective lifelong care [26]. Many carriers of hemophilia do not consider hemophilia to be a severe enough condition to justify the termination of pregnancy [25]. In addition, hemophilia carriers state fear of fetal loss, associated with invasive tests, as reasons against opting for PND [25]. Currently, definitive PND of hemophilia can only be achieved by invasive testing. Chorionic villus sampling (CVS) at 11-14 weeks of gestation is the preferred and most commonly used method. Amniocentesis is also used for PND in some centres after 15 weeks of gestation. Third trimester amniocentesis is now offered for couples who do not wish to have early PND to help management of labor and delivery. Cordocentesis from 20 weeks of gestation for the evaluation of coagulation factors in cord blood sample is used for PND when genetic testing is not possible. For full details of these techniques and other reproductive choices for carriers and families with hemophilia, please refer to reference [27].

The discovery of cell-free fetal DNA (ffDNA) in maternal plasma provided a fundamental advance in non-invasive PND. Fetal gender determination using amplified Y chromosome sequences (Y-PCR) found in ffDNA is now a well-established aspect in PND of hemophilia [28]. ffDNA in maternal plasma has been detected as early as 5 weeks of gestation; however, sensitivity and specificity increases with advancing gestation. A recent meta-analysis and systematic review of the literature found a sensitivity and specificity of 94.5% and 98.9%, respectively, in tests performed from 7 to 12 weeks of gestational age [29].

Y-PCR testing with ffDNA has the advantage of negating the need for invasive testing and its associated risk of fetal loss for female fetuses as they are either unaffected or carriers of hemophilia. However, invasive testing is still required for pregnancies with male fetuses that have a 50% chance of being affected with hemophilia. Despite advances in the field of ffDNA in the maternal circulation, PND of hemophilia in a male fetus remains difficult because the mothers are carriers of the mutation and the maternally inherited fetal allele is indistinguishable from the maternal DNA [30]. The contribution of ffDNA to the pool of DNA in the maternal plasma leads to an overrepresentation of the DNA concentration with the allele inherited by the male fetus (Fig. 1A). In a recent study, digital quantitative PCR technology was used to detect this allelic imbalance, thus diagnosing fetal genotype. The method is referred to as a relative mutation dosage (RMD) approach (Fig. 1). The authors reported accurate identification of the mutant or wild-type alleles inherited by the fetus in 12 maternal samples from seven pregnant carriers of hemophilia with male fetuses, including a sample obtained at 11 weeks of gestation [31]. These promising results indicate the potential for the use of this method for specific PND of hemophilia in the first trimester. The concentration of ffDNA in the maternal circulation increases with advancing gestation [32]. Thus, the
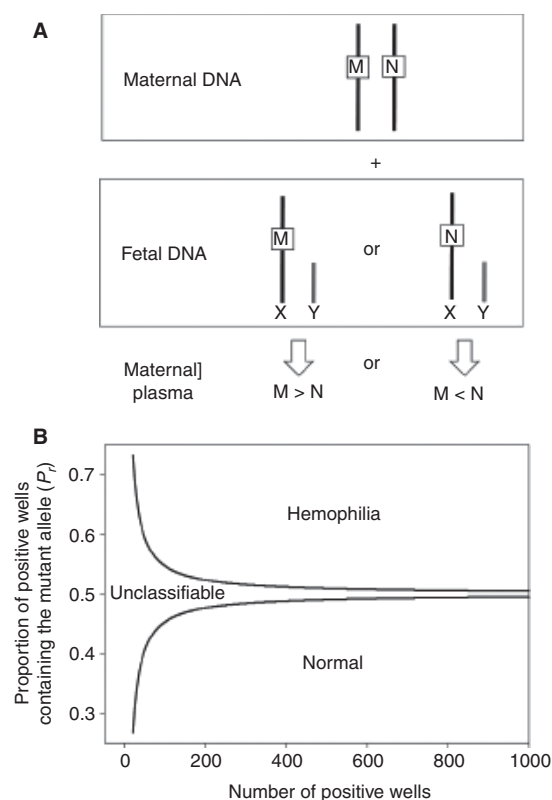

Fig. 1. Digital relative mutation dosage (RMD) for non-invasive detection of hemophilia in maternal plasma. (A) The male fetus inherits either the mutant allele (M) or the wild-type allele (N) from the mother, leading to an overrepresentation of the M or the N allele, respectively, in maternal plasma. (B) Sequential probability ratio test (SPRT) for hemophilia detection. Samples with mutant allele proportion (Pr) above the upper boundary and below the lower boundary are classified as mutant and wild-type, respectively. Samples with Pr between 2 curves are unclassifiable and require additional digital PCR analysis. Tsui *et al.* [31].

detection of the allelic imbalance is more easily achieved in late pregnancy. For couples who would not consider the option of termination of affected fetuses, third trimester digital RMD testing can offer an accurate non-invasive method of PND to aid obstetric management [31].

Currently, this technology has several limitations and remains as a research tool. It requires a sophisticated digital PCR technology. Because of the low fractional fetal DNA concentration, typically 10–20% of total maternal pool, the small degree of allelic overrepresentation cannot be differentiated by conventional PCR technology. In addition, hemophilia A and B are highly heterogenous at the mutational level with over 1000 different mutations recorded on international databases [33]. Therefore, a specific real-time PCR assay is required for each mutation [31]. About half of severe hemophilia A is caused by intron 22 inversion. Research is in progress to achieve PND in such cases. This will provide a universal test that can be used worldwide for a significant number of severe cases that are more likely to opt for and benefit from PND.

Preimplantation genetic diagnosis (PGD) is a potential reproductive option for families with hemophilia who do not wish to undergo invasive testing early in pregnancy or termination of an affected pregnancy. Initially, this technique involved the identification of male embryos using single-cell biopsy at the 6- to 10-cell cleavage stage of preimplanted embryo produced by *in vitro* fertilization. Diagnosis of fetal sex is performed by DNA amplification to isolate the Y chromosome, and only female fetuses are returned to the uterus [34]. Although this prevents the birth of an affected child, it results in all male embryos being discarded, including the 50% that are unaffected. More recently, improved technologies in molecular genetics have allowed mutation-specific PGD of hemophilia and identification of affected male embryos [35]. This has the advantage of increasing the total number of embryos available for reimplantation and the potential for healthy male offspring. However, PGD is an expensive technique that has limited pregnancy rates (24%) and carries the intrinsic risks associated with *in vitro* fertilization, including multiple pregnancy and potential for misdiagnosis. It also requires specialized services with considerable financial implications that are not available for the majority of families with hemophilia worldwide [27].

Postpartum hemorrhage and disorders of hemostasis

Pre-existing coagulation disorders are known risk factors for PPH but are often under diagnosed in this population group. A recent population-based study conducted in Norway determined that VWD was second only to emergency cesarean section as a risk factor for severe obstetric hemorrhage (PPH > 1500 mL) [36]. Several case studies have demonstrated that women with inherited bleeding disorders are more likely to experience prolonged and heavy bleeding in the puerperium [37,38]. A recent case–control study in women with known inherited bleeding disorders demonstrated that primary PPH was significantly greater among these women ($P < 0.001$). Forty-eight percent of hemophilia carriers, 32% of patients with VWD and 44% of women with rare bleeding disorders experienced primary PPH vs. only 7.5% of controls [39]. A recent case–control study reported that women with hemostatic variables at the low or high end of the population distribution were more at risk of severe PPH. The low (but not deficient) variables significantly associated with PPH included fibrinogen, VWF antigen, factor XI, and platelet CD42b. Increased closure aperture times using collagen-ADP cartridge on the PFA-100 system were also associated with severe PPH [40]. Widespread screening of antenatal populations for coagulation disorders would not be cost-effective or informative due to the low incidence and insufficient data on reference ranges in pregnancy. The causes of PPH are multifactorial; therefore, diagnosing an underlying bleeding disorder is more likely if there is a pre-existing history that correlates with a bleeding tendency. The management of labor and delivery in women with known inherited bleeding disorders requires a specialized and individualized multidisciplinary approach. Awareness of the hemostatic changes in pregnancy and specific maternal and neonatal bleeding complications that may arise is essential. For full details regarding the obstetric management of women with inherited bleeding disorders, please refer to Huq & Kadir 2011 [41]. Table 1 provides detailed information on suggested hemostatic levels required during labor and delivery and the therapeutic options for women with various inherited bleeding disorders.

A critical feature of obstetric hemorrhage is the development of acquired coagulopathy [42]. In contrast to major hemorrhage resulting from trauma or surgery, coagulopathy occurs early during obstetric hemorrhage. It is often unrecognized and therefore remains untreated, causing progression to more severe bleeding. The high mortality rates associated with severe obstetric hemorrhage are related to the well-described 'lethal triad' characterized by coagulopathy, acidosis, and hypothermia [43]. During obstetric hemorrhage, there is depletion of coagulation factors due to blood loss itself and the consumption of factors due to coagulation activation. Attempts to maintain the circulating volume and tissue perfusion often involve the infusion of large volumes of crystalloid and colloid fluid that results in dilution of the remaining coagulation factors [44]. During the postpartum period, there is evidence of increased fibrinolysis of up to 30% [45]. This further compounds coagulopathy during PPH.

In recent years, the recognition of coagulopathy as an important aspect of PPH has gained attention. New strategies have been proposed to help early diagnosis and use of hemostatic agents specifically targeted to prevent or treat coagulopathy.

Diagnosis of coagulopathy during PPH

The correction of coagulopathy during PPH is currently without guidance of specific measurements of hemostasis. Appropriate hemostatic interventions depend on rapidly available tests to provide reliable diagnosis of coagulopathy. Conventional laboratory tests require 45–60 min for results to become available. Decisions regarding transfusion are therefore made inappropriately and are not based on the current hemostatic profile [46]. Prothrombin time (PT) and activated partial prothrombin time (APTT) are routinely measured to screen for coagulalopathy during PPH. However, the APTT is shortened in pregnancy due to elevated FVIII levels and therefore is relatively insensitive to hemostatic alterations [46]. The prolongation of APTT and PT is a late finding in the development of coagulopathy during obstetric hemorrhage and both tests can remain in the normal range during severe PPH [47].

Table 1 Suggested hemostatic levels and therapeutic options for invasive procedures during pregnancy and management of delivery

Inherited bleeding disorder	Normal range (IU dL^{-1})	Suggested hemostatic level (IU dL^{-1})	Preferred therapeutic option*	Secondary therapeutic option
von Willebrand Disease	50–175	50	DDAVP- or VWF-containing concentrates	Platelets (in type 2B VWD)
Hemophilia A carrier	50–150	50	DDAVP or rFVIII	FVIII concentrate
Hemophilia B carrier	50–150	50	rFIX	FIX concentrate
Fibrinogen deficiency/abnormality	2.0–4.0 (g L^{-1})	1–1.5 (g L^{-1})†	Fibrinogen concentrate	SD plasma
Factor II deficiency	50–150	20–30	PCC	SD plasma
Factor V deficiency	50–150	15–25	SD plasma	N/A
Factor VII deficiency	50–150	10–20	rFVIIa	FVII concentrate
Factor V and VIII deficiency	50–150	15–25 (V) 50 (VIII)	SD plasma or rFVIII	SD plasma
Factor X deficiency	50–150	10–20	PCC	SD plasma
Factor XI deficiency	70–150	20–70	FXI concentrate, rFVIIa or tranexamic acid	
Factor XIII deficiency	70–150	20–30‡	FXIII concentrate	SD plasma

*All factor concentrates should be virally inactivated and recombinant where possible. †Aim to maintain > 1.0 g L-1 throughout pregnancy. ‡Aim to maintain > 3 IU dL-1 throughout pregnancy. VWF, von Willebrand factor; VWD, von Willebrand disease; DDAVP, desmopressin; F, factor; r, recombinant; PCC, prothrombin complex concentrates; SD plasma; fresh frozen plasma virally inactivated using a solvent detergent technique.

Fibrinogen is a plasma protein that is critical to hemostasis and effective clot formation. The blood plasma concentration ranges from 1.5 to 4 g dL^{-1}, but due to the physiological hypercoagulation that occurs during pregnancy, the levels reach 4–6 g dL^{-1} by term [48]. Fibrinogen consumption occurs rapidly during obstetric hemorrhage, and decreased fibrinogen level has been shown to be associated with an increased risk of bleeding [49]. Charbit et al. performed serial coagulation tests in 128 women during PPH and demonstrated that fibrinogen concentration at the point of enrollment was the only parameter independently associated with progression toward severe bleeding. The risk for severe PPH was 2.6-fold higher for every 1 g dL^{-1} decrease in fibrinogen concentration. Fibrinogen levels of $\geq$ 4 g dL^{-1} had a negative predictive value of 79% for severe hemorrhage, whereas fibrinogen concentration of $\leq$ 2 g dL^{-1} had a positive predictive value of 100% [49]. These findings indicate that the assessment of fibrinogen level should be an integral part of hemostatic evaluation of PPH. The study findings also cast doubt on current UK national guidelines that recommend fibrinogen supplementation in PPH when plasma levels are below 1 g dL^{-1} [50].

The use of thromboelastography (TEG®; Haemonetics Corp., Braintree, MA, USA) or more recently the advanced rotational thromboelastometry (ROTEM®; Tem International GMbH, Munich, Germany) to guide transfusion during obstetric hemorrhage has been proposed. They provide rapid point-of-care (POC) assessment of coagulation. TEG®/ROTEM® tests involve the analysis of whole blood and assess the coagulation process from coagulation initiation through to clot lysis, including clot strength and stability. Therefore, it can distinguish between coagulopathy caused by fibrinogen, platelet, and clotting factor deficiencies and hyperfibrinolysis. The common variations of

ROTEM®-based tests and their specific applications within coagulation are demonstrated in Table 2 below. Importantly, several of the values generated with TEG®/ROTEM®-based monitoring are obtained within minutes, allowing for rapid assessment of the required hemostatic interventions.

TEG®/ROTEM®-based monitoring of hemostasis has been used to guide transfusion during hepatic, cardiothoracic and trauma surgery [51–53]. Use of TEG®/ROTEM® tests in obstetrics has been limited by the availability of appropriate reference ranges for pregnancy [54]. FIBTEM® is a modified version of thromboelastography with a reagent that inactivates platelets and therefore is specific for fibrin polymerization. A case–control study demonstrated that the median clot amplitude of the FIBTEM® test was significantly lower in women with PPH than in controls [54] with a strong correlation between the TEG®/ROTEM® parameters and fibrinogen plasma concentration (Fig. 2). This supports the use of this rapidly available POC tests to guide fibrinogen supplementation during obstetric hemorrhage. Prospective studies are required to demonstrate the effectiveness of TEG®/ROTEM®-based monitoring or protocols to guide transfusion management in obstetric hemorrhage.

Specific interventions for management of coagulopathy during PPH

Ratio of transfusion products

Reversal or prevention of coagulopathy traditionally involves the use of plasma-derived products such as platelets, fresh frozen plasma (FFP), and cryoprecipitate. The optimum timing and ratio of red blood cells and plasma product transfusion during PPH is currently unknown,

Table 2 Commercially available ROTEM®-based coagulation tests and their diagnostic uses within various coagulation pathways

| Test (reagent)	Activator	Additional modifications	Diagnostic use
NATEM (star-tem®)	None added	–	Sensitive test measuring coagulation without added activator, although not applicable in emergencies due to slow clotting times
INTEM (in-tem®)	Ellagic acid	–	Defects in the intrinsic pathway of coagulation activation; heparin anticoagulation
EXTEM (ex-tem®)	Recombinant tissue factor	–	Defects in the extrinsic pathway of coagulation activation; prothrombin complex deficiency; platelet deficiency (in parallel with FIBTEM)
FIBTEM (fib-tem®)	Recombinant tissue factor	Cytochalasin D	Fibrin-based clot defects, fibrin/fibrinogen deficiency
APTEM (ap-tem®)	Recombinant tissue factor	Aprotinin	Hyperfibrinolysis (in comparison with EXTEM)
HEPTEM (hep-tem®)	Ellagic acid	Heparinase	Heparin/protamine imbalance (in conjunction with INTEM or kaolin-activated TEG)
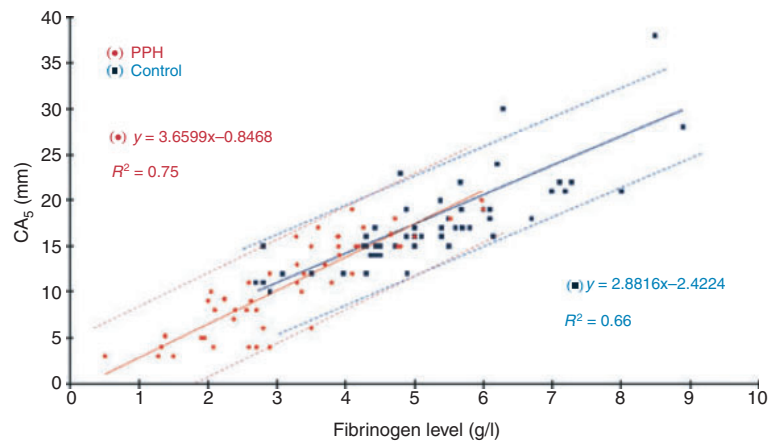
Fig. 2. Linear regression depicting the relationship between CA_5-FIBTEM and fibrinogen in controls and postpartum hemorrhage (PPH) [54].

and there is a lack of randomized controlled trials to guide transfusion protocols.

Several observational studies suggest that there is reduction in overall mortality in trauma patients transfused with higher plasma concentrations. Borgman *et al.* demonstrated improved mortality rates (65% vs. 19%) in military combat patients receiving a higher ratio of FFP to RBC transfusion [55]. The United States Army's Institute of Surgical Research conference in 2005 elected to implement 'damage control resuscitation', which supports a transfusion ratio of 1:1:1 of PRC, FFP, and platelets in trauma patients with massive blood loss. The rationale to support this proposal is that this ratio is more physiological and representative of whole-blood composition. However, meta-analysis of data from 26 studies in trauma patients concluded that there was insufficient statistical evidence to demonstrate a survival benefit in 1:1:1 transfusion strategies [56]. In addition, blood loss in the trauma setting is not comparable to obstetric hemorrhage due to the physiological changes associated with pregnancy. Prospective trials are required to establish the optimal transfusion ratios in PPH.

Thrombocytopenia or reduced platelet reactivity in pregnancy may be an independent risk factor for PPH. Women with severe PPH and low platelet count were more likely to require more than four units of RBC transfusion [47]. Current transfusion protocols recommend platelet transfusion when platelet count falls below $50 \times 10^9 \, \text{L}^{-1}$. However, a platelet count of $< 100 \times 10^9 \, \text{L}^{-1}$ on admission to labor ward has been found to be associated with PPH [57]. Studies are required to assess the optimum threshold for maintaining platelet count during PPH.

Fibrinogen supplementation in PPH

Early fibrinogen supplementation during major bleeding in various clinical settings has demonstrated improved outcome and a reduction in total use of blood products [58–60]. A retrospective analysis of trauma patients demonstrated improved survival rates in patients receiving fibrinogen concentration (14% mortality vs. 27.8%) compared with the non-treatment group [60]. Lower total transfusion requirements have been reported with perioperative fibrinogen administration in patients undergoing cardiothoracic surgery [59] and radical cystectomy [58]. The data supporting fibrinogen replacement in these trials and the findings that low fibrinogen concentration predicts progression to severe PPH [49] support early fibrinogen replacement in PPH management. Randomized

controlled trials to assess the use of fibrinogen concentration during PPH are imperative.

The options available for fibrinogen supplementation during PPH include FFP, cryoprecipitate, or fibrinogen concentration. Large volume of FFP is required to restore plasma fibrinogen to normal levels. In addition, FFP preparations are associated with potential risk of pathogen transmission, allergic reactions and transfusion-related acute lung injury [48]. Cryoprecipitate provides a more concentrated alternative to FFP, but each unit exposes the recipient to approximately four to six donors. Both products require thawing and cross-match prior to infusion. Fibrinogen concentrate is pasteurized and lyophilized and stored at room temperature in powder form. Thus, it is more rapidly available and can be administered without the need for cross-matching or thawing. The production of fibrinogen concentration involves the removal of antigens and antibodies rendering it less allergenic and immunogenic [61]. Although derived from a large pool of donors, the risk of viral transmission is significantly reduced because of viral inactivation and removal processes [62]. Thus, fibrinogen concentration is suggested as the hemostatic product of choice in ongoing bleeding in PPH [61]. However, it is an expensive agent and may not be available for use in every obstetric unit.

Antifibrinolytic agents in PPH

The evidence for the effectiveness of antifibrinolytic agents in improving outcome during PPH is emerging, and this is rapidly incorporated into PPH protocols worldwide. There is a theoretical benefit to using antifibrinolytic agents such as tranexamic acid during PPH. Fibrin is an essential structural component of the uteroplacental blood vessels, and fibrinolytic activity is inhibited by adjacent trophoblast cells in the terminal sections of the spiral arteries. Bleeding may result from a structural weakness caused by vascular defects in the placental bed [63]. Placental abruption and obstetric hemorrhage is characterized by the activation of the fibrinolytic system, resulting in an enhanced clot breakdown [64]. The use of tranexamic acid has been shown to significantly reduce blood loss in women undergoing vaginal or cesarean delivery in randomized controlled trials [65]. A study of 144 women with PPH demonstrated that early administration of high-dose tranexamic acid resulted in significantly reduced blood loss, shorter bleeding duration, and less progression to severe PPH and less requirement for blood transfusion (Fig. 3) [66]. Disseminated intravascular coagulation (DIC) is associated with a partial suppression of the fibrinolytic system due to an increase in serum plasminogen activator inhibitor type 1 (PAI-1) [67]. Thus, further inhibition of the fibrinolytic system could theoretically compound the situation. The use of tranexamic acid during PPH is currently being evaluated in a large randomized controlled trial (the WOMAN trial) [68].

Recombinant activated factor VII in PPH

Recombinant activated factor VII (rFVIIa) has been used over the past decade in the treatment for intractable PPH unresponsive to standard hemostatic measures. As rFVIIa is not licensed for use in obstetric hemorrhage, the responsibility and decision for 'off-label' use resides with the prescribing physician. A small number of case reports have been published to support the use of rFVIIa in obstetric hemorrhage. The majority of cases reported using rFVIIa as a last resort during massive postpartum bleeding complicated by DIC, multi-organ failure and HELLP syndrome [69]. The authors have collectively observed that rFVIIa may improve outcome, but there has been no consensus on optimal dosage, timing of
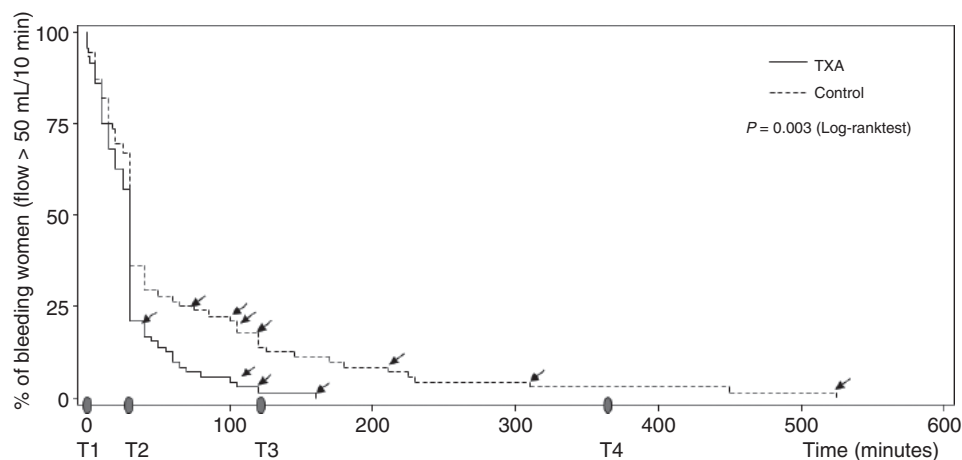
Fig. 3. Graph showing time from enrollment and cessation of bleeding in women treated with high-dose tranexamic acid and controls [66]. Solid line = tranexamic acid group (TXA), dashed line = control group. *P* = 0.003 using the Kaplan–Meier log-rank test. Time points of the study (T2 = T1 + 30 min, T3 = T1 + 2 h, T4 = T1 + 6 h) are indicated on the *X*-axis. The time of each invasive procedure is indicated by an arrow.

administration, cost-effectiveness, and potential side effects. Experience of 'off-label' use of rFVIIa has been recorded in the Australian and New Zealand hemostasis registry from July 2002 until July 2008 [70]. Among 105 women with PPH, the volume of blood and blood product transfusion required was reported to be reduced in 76% of cases, with a reduced emergency hysterectomy rate following rFVIIa administration [71]. A 1.9% venous thromboembolic complication rate was also reported. The Northern European registry collected data from 2000 to 2004 on the use of rFVIIa in 113 women with PPH. A subjective improvement in bleeding was reported in 80% of cases [72]. There were four cases of thromboembolism and one case of myocardial infarction noted. Although registries are useful to evaluate the efficacy and safety profile of such agents, high-level evidence from a randomized controlled trial is lacking. Current opinion on the use of rFVIIa in PPH is considered as a last resort if other transfusion methods have failed, and prior to performing peripartum hysterectomy [73]. Replacement of fibrinogen and platelets is essential prior to the administration of rFVIIa. Fibrinogen level > 2 g dL^{-1} and platelet count > 70 × 10^9 L^{-1} are recommended to optimize the effect of rFVIIa [74].

Conclusion

Inherited and acquired bleeding disorders in women continue to present challenges in the obstetric and gynecological setting. Although awareness about the challenges facing these women is improving, ongoing clinical efforts and research are required internationally to meet the specific needs of women with bleeding disorders. Early recognition and diagnosis of bleeding disorders help to improve care of women with these disorders and improve quality of life. This can be achieved by close collaboration between obstetrician and gynecologist, and hematology teams with multidisciplinary approach to management.

Disclosure of Conflict of Interest

The authors state that they have no conflict of interest.

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