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Point-of-care coagulation testing for postpartum haemorrhage

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The use of viscoelastic haemostatic assays (VHAs) to guide blood product replacement during postpartum haemorrhage is expanding. Rotem and TEG devices can be used to detect and treat clinically significant hypofibrinogenaemia, although evidence to support the role of VHAs for guiding fresh frozen plasma and platelet transfusion is less clear. If Rotem/TEG traces are normal, clinicians should investigate for another cause of bleeding, and haemostatic support is not required. Guidelines support the use of VHAs during postpartum haemorrhage as part of locally agreed algorithms. There is a wide consensus that fibrinogen replacement is needed if the Fibtem A5 is <12 mm and if there is ongoing bleeding. Guidelines recommend against using VHAs to guide tranexamic acid infusion, and this drug should be given as soon as bleeding is recognised, irrespective of the Rotem/TEG traces. The cost-effectiveness of VHAs during postpartum haemorrhage needs to be addressed.

Introduction

Postpartum haemorrhage (PPH) is a common complication of childbirth and the leading cause of maternal death worldwide [1]. Bleeding is usually caused by an obstetric complication such as uterine atony, trauma, abnormal placentation or retained products of conception. PPH can be exacerbated by haemostatic impairment with moderately severe bleeding, progressing to a massive haemorrhage [2]. Timely correction of abnormal blood clotting is likely to reduce bleeding and improve outcomes, although this has not been proven definitively in high-quality clinical trials.

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Professional guidelines recommend strategies to manage haemostatic impairment during PPH [3–6]. These fall into three main groups:

- Laboratory-based tests of coagulation to direct treatment.
- Empirical infusion of coagulation factors with fresh frozen plasma (FFP) and platelets in fixed ratios with red blood cell (RBC) transfusion, if laboratory tests are unavailable [4].
- Point-of-care viscoelastic haemostatic assays (VHAs) to support goal-directed replacement of coagulation factors [7–10].

There has been an increasing interest in the role of VHAs such as Rotem® (Werfen, Barcelona, Spain) or TEG® (Haemonetics, Braintree, MA, USA) to support haemostatic management during PPH, and this review will focus on these devices [7,10–12]. Although other technologies are available, for example Clotpro® and Sonoclot®, there is insufficient information about their performance in the context of PPH to be included.

Technology

VHAs monitor the developing viscosity and elasticity of a clot *in vitro* [9,10,12]. Rotem detects the developing clot using a rotating cup and pin mechanism, and earlier versions of TEG used similar technology. The most recent version of TEG (TEG6s) monitors clot evolution by inducing vibration and measuring resonance using an optical system. Both technologies display results graphically and report specific parameters numerically (Fig. 1). Rotem reports results in terms of clot firmness, whilst TEG reports amplitude. The most recent versions, Rotem Sigma and TEG6s, use cartridges with prefilled reagents, and both platforms have been largely automated, thus making their use more straightforward. These versions facilitate use outside of routine working hours by less-experienced staff. Earlier version required manual pipetting of samples and reagents, prompting personnel certification and government oversight in some countries in an attempt to minimize sources of analytical variation.

Both technologies initiate clot formation using a variety of activators. The Extem (Rotem) and rapid TEG (TEG) use tissue factor to initiate the extrinsic pathway, whilst Intem (Rotem) and Kaolin TEG

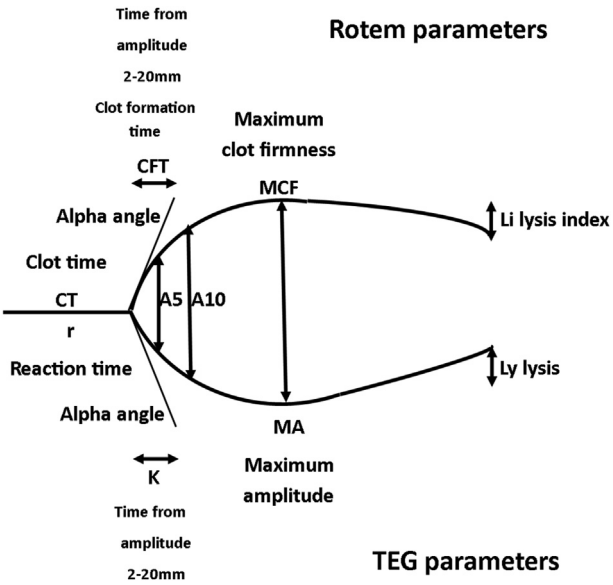

Fig. 1. Standard Rotem and TEG traces and main parameters Legend: Schematic representation of Rotem and TEG traces.

activate the intrinsic pathway [9]. The time until clot formation starts is detected by the clot time (CT Rotem) or reaction (r) time (TEG) (Fig. 1) [12]. These parameters are interpreted as a measure of the combined ability of coagulation factors to generate thrombin and initiate cleavage of fibrinogen to fibrin. Prolongation of CT/r suggests a deficiency of coagulation factors and is treated with FFP.

Both technologies report the point of maximum clot viscoelasticity, maximum clot firmness (MCF Rotem), and maximum amplitude (MA TEG). These parameters reflect the contribution of fibrinogen and platelets to the developing clot. Both systems report clot viscoelasticity at fixed times earlier than the maximum, for example, after 5 or 10 min. The clot strength in both Rotem and TEG after 5 min is called the A5 (amplitude at 5 min) and after 10 min as A10 (Fig. 1). These parameters correlate very strongly with MCF and MA, but they are available earlier [13,14], especially during haemostatic impairment, and therefore, can be used to guide treatment before the trace has completed.

Both systems have an assay in which platelet function is inhibited: Fibtem (Rotem) and Functional Fibrinogen (FF) (TEG). The clot strength in these assays reflects the contribution of fibrinogen to clot development. During PPH, there is a moderate correlation between Fibtem/FF and the laboratory assay (Clauss fibrinogen) [13,15–18]. It is important to recognise that Fibtem/FF measure different haemostatic properties to Clauss fibrinogen and their role in the management of PPH has been the subject of investigation over the past few years (see below). Both Fibtem and FF can be interpreted early using the A5 or A10 parameters, thereby allowing rapid intervention if required [13].

The clot strength in the standard assay minus the strength in the fibrinogen assay (Extem MCF-Fibtem MCF or Kaolin MA-FF MA) is interpreted as a measure of the contribution of platelets. These parameters have not been validated in the context of PPH although encouraging results have been published [13,17,19]. Assays that measure platelet function have not been studied in the context of PPH and will not be reviewed.

After maximum viscoelasticity (MCF/MA), the clot starts to break down through the action of plasmin in the process of fibrinolysis. This is measured by the decrease in viscoelasticity after a period of time and is reported as the lysis index (LI Rotem) or lysis (LY TEG) (Fig. 1). For example, after 30 minutes, the parameter is reported numerically as LI_{30} or LY_{30}. Higher LI or LY values indicate more fibrinolysis. Increased fibrinolysis will be detected only if it is disseminated, and hyperfibrinolysis localised to the uterus and placenta does not affect the assays. Both Rotem and TEG are relatively insensitive to fibrinolysis [20], and administration of tranexamic acid should not be withheld simply on the basis that the assays are normal [5,9].

The alpha angle in both Rotem and TEG is a marker of how rapidly the viscoelasticity of the clot increases and is influenced by platelet count and fibrinogen. This parameter is not commonly used in the context of treating PPH although some data have been published [13,17].

It is important that the manufacturers' recommendations for quality assurance are followed, and both internal and external quality control is required [9].

Haemostasis at term

The haemostatic system at term differs from the non-pregnant state (Table 1) [12,21]. Plasma fibrinogen increases from 2–4 g/L to 4–6 g/L, and this is reflected in high values of MCF and MA (Fig. 2). Increased levels of other coagulation factors, most notably factor VIII, are reflected in shorter CT/r parameters, for literature review see Amgalan et al. [7]. Studies have reported variable changes in fibrinolysis, but it is usually reported to be decreased at term [14,22,23]. Fibrinolysis increases after delivery especially locally to the uterus [22,24]. These haemostatic changes result in a prothrombotic state at term, which acts as a physiological buffer against evolving coagulopathy but also makes women more prone to venous thrombosis.

Coagulopathy of postpartum haemorrhage

Coagulopathy during PPH results from three broad mechanisms: consumptive and/or dilutional coagulation factors and platelets and increased fibrinolysis [12,21]. From a simplified, clinical perspective haemostatic failure during PPH can be thought of in terms of:

Table 1
Changes in TEG and Rotem during normal pregnancy

Parameter Rotem/TEG	Effect of pregnancy	Haemostatic mechanism
CT/r	Shorter	Increased levels of coagulation factors
CFT/K	Shorter	Increased coagulation factors and fibrinogen
MCF/MA	Increased	Increased fibrinogen with normal platelet count
A5/A10	Increased	Increased fibrinogen
Fibtem/Functional fibrinogen MCF/MA and A5, A10	Increased	Increased fibrinogen
Alpha angle	Increased	Increased fibrinogen
Li/Ly	Systemic fibrinolysis decreased at term Fibrinolysis increases after delivery especially local to the uterus, but this may not be detected	Increased PAI-2 and reduced tissue plasminogen activator

Pregnancy is associated with a prothrombotic state due to progressive changes in coagulation factors with gestation. These changes are reflected in viscoelastometric assays as indicated. Clot time (CT), reaction (r), clot formation time (CFT), kinetics (K), maximum clot firmness (MCF), maximum amplitude (MA), amplitude at 5 or 10 minutes (A5/A10), lysis index (Li)and (lysis) Ly, PAI-2 plasminogen activator inhibitor 2.

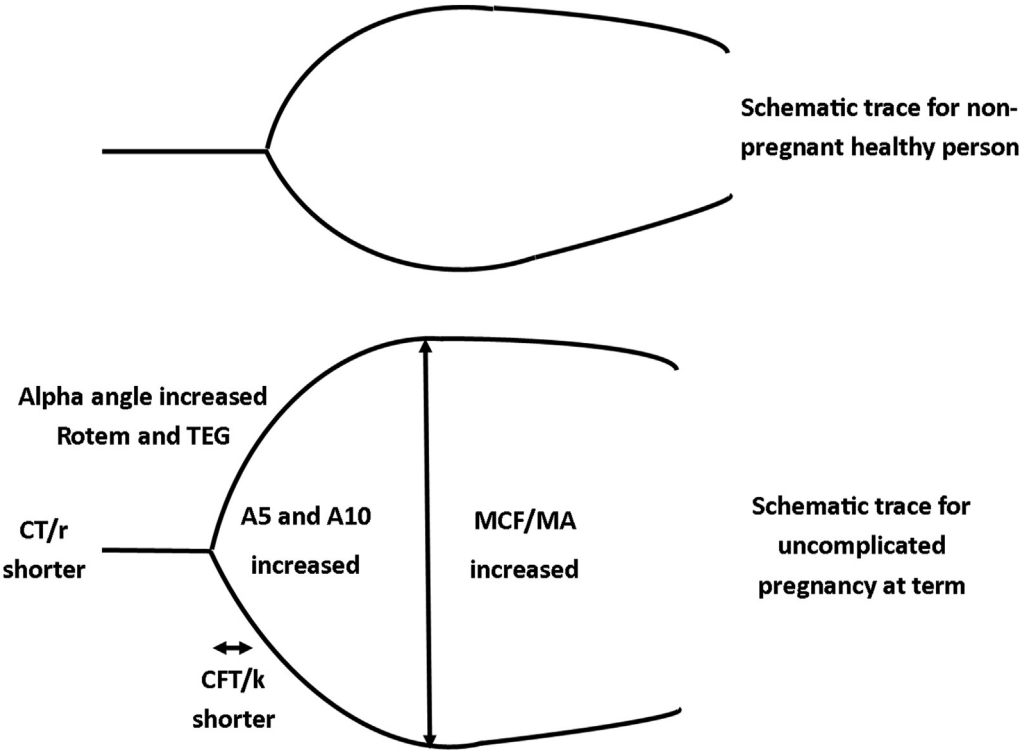

Fig. 2. Rotem and TEG traces at term.
Legend: Typical schematic Rotem and TEG traces at term compared to the non-pregnant state, see also Table 1.

1. Deficiency of fibrinogen.
2. Increased fibrinolysis.
3. Reduction in coagulation factors that generate thrombin.
4. Thrombocytopenia.

Consumptive coagulopathy predominantly leads to reduced fibrinogen and platelets with other clotting factors initially remaining adequate for haemostasis [25]. Consumption may occur early after placental abruption (often before delivery) [26] and is very common after amniotic fluid embolus [27,28]. Early coagulopathy may also be seen in situations such as sepsis, leading to disseminated intravascular coagulation or in complications of pregnancy such as pre-eclampsia or fatty liver of pregnancy and can be detected by VHAs [7].

Dilutional coagulopathy worsens consumptive coagulopathy if haemorrhage cannot be controlled. In the absence of significant consumption, for example, in most cases of PPH caused by atony or trauma, coagulopathy evolves only during larger bleeds as coagulation factors are diluted during resuscitation and clinically significant haemostatic impairment becomes progressively more common with blood loss larger than 3 L [17,25,29,30].

During PPH of any cause, fibrinogen falls to critically low levels earlier than other coagulation factors, and this can be detected using either Fibtem or FF assays (Fig. 3). Despite this, Clauss fibrinogen >2 g/L, which is the lower end of the non-pregnant normal range, is adequate for haemostasis during PPH [31]. The incidence of fibrinogen <2 g/L is about 5% in bleeds of 1.5 L and about 17% in bleeds >2.5 L [32].

Deficiencies of coagulation factors other than fibrinogen are usually treated with FFP, but the efficacy of this treatment is unproven [33]. There are no data to establish an adequate level of coagulation factors during PPH, but it is usually assumed that if PT/aPTT are, normal coagulation factors are adequate and if PT/aPTT are >1.5 times the normal level, there is significant haemostatic impairment [34]. Most guidelines recommend maintaining a platelet count $>75 \times 10^9$/L during active PPH [3–5].

Fibrinolysis is common during PPH, and early administration of tranexamic acid reduces mortality [35]. It is recommended to administer tranexamic acid as soon as a PPH is diagnosed and at the latest within 3 h [5]. VHAs may detect increased fibrinolysis during PPH [36], but a lack of evidence of fibrinolysis on VHAs should not be used to withhold tranexamic acid administration [9].

Once bleeding is controlled, women are at an increased risk of venous thrombosis and should receive standard venous thromboprophylaxis.

Fibrinogen to predict the progression of postpartum haemorrhage

Multiple studies, using a variety of designs and endpoints, have shown that a low Clauss fibrinogen measured early during PPH predicts progression to more severe bleeds [37–41]. Charbit reported that a fibrinogen <2 g/L was 100% predictive for the need for 4 units RBC or an invasive procedure to control bleeding [37], although other studies have not been as clear cut. Clauss fibrinogen often takes too long to be clinically useful during a rapidly progressing bleed, and therefore, its utility as a predictive biomarker is unclear.

A prospective observational study reported that the A5 parameter of the Fibtem assay, taken after about 1 L blood loss, had similar utility to Clauss fibrinogen to predict the progression to RBC transfusion and 2.5 L bleeds [38]. However, this could not be replicated in a similar study that found no relationship between Fibtem A5 and only borderline with Clauss fibrinogen and progression to 2 L bleeds, need for at least 4 units of RBCs or an invasive procedure. The study found a positive predictive value (PPV) of 50% for a Clauss fibrinogen <2 g/L and progression of PPH [42] in contrast to the 100% PPV reported by Charbit [37]. A retrospective study using TEG found that the Kaolin-MA, FF-MA and alpha angle were useful for predicting progression to >2.5 L blood loss or >4 units RBC transfusion with results similar to those found in an earlier Fibtem study [19].

Overall, these studies support the importance of fibrinogen during PPH and show that if Clauss fibrinogen, Fibtem or FF are reduced during PPH, then clinicians should be aware that bleeding may progress and should consider triggering and initiating institutional protocols for massive transfusion.

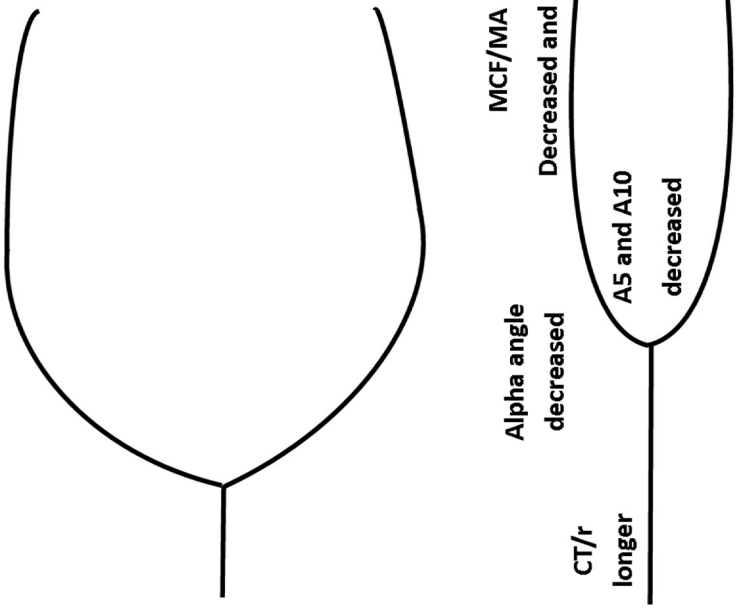

Fig. 3. Rotem and TEG traces during severe hypofibrinogenaemia.
Legend: Typical schematic Fibtem (Rotem) or Functional fibrinogen (FF, TEG) traces at the time of severe hypofibrinogenaemia during postpartum haemorrhage (PPH) compared to a non-bleeding trace at term.

Target fibrinogen level during postpartum haemorrhage

The target fibrinogen level required for haemostasis during PPH has not been established definitively, although most guidelines recommend maintaining a level >2 g/L [3–5]. The Fib-PPH trial was a double blind randomised controlled study that investigated empirical, early transfusion of fibrinogen concentrate but did not find any reduction in bleeding or need for blood transfusion [43]. The mean Clauss fibrinogen level at the time of intervention was 4.5 g/L, demonstrating that this is adequate for haemostasis. The study only included 5 women with a fibrinogen <2 g/L at the time of randomisation suggesting that targeted, goal-directed fibrinogen replacement might have a role.

OBS2 was a double-blind randomised controlled trial which allocated women experiencing PPH with Fibtem A5 <15 mm (Clauss fibrinogen of about 3 g/L) to fibrinogen concentrate or placebo treatment. There was no statistically significant decrease in blood transfusion or bleeding after the intervention [31]. Pre-specified subgroup analyses showed that a fibrinogen >2 g/L or Fibtem >12 mm were adequate for haemostasis during PPH, but there was a trend for improved outcomes if fibrinogen was infused at levels lower than 2 g/L. The study showed that if Fibtem A5 was >15 mm, FFP could be withheld safely [44].

The Acrobat study investigated the feasibility of using cryoprecipitate during PPH for women who required at least one unit of RBC. The study found that only 32% of women in the intervention group received cryoprecipitate within the target of 90 min. Secondary analyses showed that there was a reduction in bleeding and RBC transfusion in the intervention group. The mean Clauss fibrinogen when first tested was 3 g/L; however, the number of women with a fibrinogen <2 g/L and the fibrinogen level and volume of blood loss at the time of the intervention were not reported [45].

Overall, the conclusions that can be drawn from these studies are that; fibrinogen replacement is likely to be required if bleeding is ongoing and fibrinogen is <2 g/L, hypofibrinogenaemia is unpredictable, empirical fibrinogen replacement will lead to many women being treated despite having an adequate level, and fibrinogen concentrate can be infused much earlier than cryoprecipitate. Clauss fibrinogen is often too slow to guide treatment, and therefore, the role of VHAs has been investigated.

Utility of TEG and Rotem for detecting clinically significant haemostatic impairment

Fibrinogen deficiency

If point-of-care goal-directed fibrinogen replacement is the chosen strategy for PPH, the key question is whether VHAs can detect a Clauss fibrinogen <2 g/L and hence guide treatment. Using Rotem Delta, Huissoud et al. showed that Fibtem correlated moderately well with Clauss fibrinogen during PPH and had good utility for detecting fibrinogen <2 g/L [16]. This work has been replicated by other groups [13,38]. Studies with Rotem Sigma, TEG 5000 and TEG6s have shown that Kaolin MA, Fibtem and FF correlate moderately well with Clauss fibrinogen and have good positive and negative predictive utility for detecting a Clauss fibrinogen <2 g/L [15,17–19].

These studies support using 12 mm for Fibtem A5 (Rotem Sigma) or 16 mm for FF at 10 min (TEG6s) to detect a Clauss fibrinogen <2 g/L, and these levels have been incorporated into treatment algorithms (Table 2) that have been associated with improved outcomes [46–49].

Deficiencies of other coagulation factors

Clinically significant depletion of coagulation factors other than fibrinogen is uncommon during PPH unless a very large bleed has occurred [17,25,29] and the indications to transfuse FFP are not well defined. Routine laboratory tests such as the PT/aPTT may be used as markers of coagulation factor deficiency, however, triggers to indicate FFP infusion have not been investigated. At term, PT/aPTT are shorter than in the non-pregnant population due to the high levels of coagulation factors. At present, guidelines based on expert consensus recommend transfusing FFP to maintain PT/aPTT < 1.5 times normal, and to achieve this, the guidelines suggest infusing FFP if the PT or aPTT are above the normal

Table 2
Comparison of published algorithms

	Fibrinogen replacement with concentrate or cryoprecipitate		Coagulation factor replacement with fresh frozen plasma		Platelet infusion	
	Clauss Fibrinogen	VHA	PT/aPTT	VHA	FBC platelet	VHA
Mallaiah [47,48]	Not addressed	Fibetm A5 <7 mm or 7-12 mm with active bleeding give 3 g fibrinogen concentrate	Not addressed	Extem CT >100 s give FFP	Not addressed	Not addressed
Bell [55]	Transfuse fibrinogen concentrate if <2 g/L	Transfuse fibrinogen concentrate if <12 mm	Give 4U FFP If above normal range	Give 4 U FFP if Extem CT $\geq$75 s after fibrinogen replacement	Infuse if <75 $\times$ 10^9/L	Do not use VHAs
Snegovskikh [49]	Not addressed	Give 5–15 u cryoprecipitate if Fibtem A5 <5 mm to increase to 10 mm	Not addressed	Give 2U FFP Extem CT >80 s	Not addressed	Extem MCF <45 mm with normal Fibtem give 1 pool of platelets
Diaz [10]	Give 2–4 g fibrinogen or 5–10 ml/kg cryoprecipitate if <2 g/L	Give 2–4 g fibrinogen or 5–10 ml/kg cryoprecipitate if Fibtem A5 <7–12 mm or CFF A10 $\leq$17 mm	Give FFP if above the normal range	Give FFP if Extem CT > 75–100 s Or Kaolin TEG r > 9-12 min	Infuse if <75 $\times$ 10^9/L	Give 1–2 unit platelets If Fibtem A5 > 12 mm and Extem A10 < 47 mm Or CFF > 1 7 mm and TEG MA < 48 mm
Frigo [50]	Give 2 g fibrinogen if Clauss fibrinogen <2 g/L	Give 4 g fibrinogen if Fibem <7 mm	Give 4 U FFP whilst PT/aPTT are awaited	Give 2 U FFP Fibtem <7 mm	Infuse if <75 $\times$ 10^9/L	Give one pool of platelets if Fibtem >11 mm and Extem MCF <47
	Give 4 g fibrinogen and 2 units FFP If Clauss fibrinogen <1 g/L	Give 2 g fibrinogen if Fibtem 7–11 mm	Give 20–30 ml/kg FFP if PT/aPTT >1.5	Order FFP if Fibtem 7–11 mm		Or If FF MA >9 mm and TEG MA<54
		Or Give Fibrinogen If FF MA <6 mm		Or Give FFP If r time >1 (units not stated)		

Table 3
Comparison of published guidelines

	Fibrinogen replacement with concentrate or cryoprecipitate		Coagulation factor replacement with fresh frozen plasma		Platelet infusion	
	Clauss Fibrinogen	VHA	PT/aPTT	VHA	FBC platelet	VHA
Network for Advanced Transfusion alternatives [5]	Maintain >2 g/L	Treat if Fibtem A5 <12 mm or FF MA <14 mm	Treat if >1.5 times normal	Treat if CT or r above the normal range	Infuse if $<75 \times 10^9$/L	VHA-based care supported, but no triggers given
British Society of Haematology [9]	Not addressed	Treat if Fibtem A5 <12 mm	Not addressed	Not addressed	Not addressed	Not addressed
Royal College of Obstetrics and Gynaecology [4]	Maintain >2 g/L	Agree local algorithm	Give 15 ml/kg FFP if above normal range	Agree local algorithm	Infuse if $<75 \times 10^9$/L	Not addressed
International Society of Thrombosis and Haemostasis [3]	Maintain >2 g/L	Treat if Fibtem A5 <12 mm	Give 15 ml/kg FFP if above normal range	Not addressed	Infuse if $<75 \times 10^9$/L	Not addressed

range (Table 3). The alternative strategy is to transfuse FFP empirically in fixed ratios with RBCs based on data derived from studies in major trauma [50,51].

PT/aPTT usually stay within the normal range until bleeds reach >3 L [17,25,29]. This is due to high levels of coagulation factors at term protecting against clinically significant dilution until large volumes of bleeding and resuscitation have occurred. This differs from major trauma where coagulation factors are within the normal range at the time of injury, and hence, smaller bleeds result in clinically significant dilution in addition to the well-characterised trauma-induced coagulopathy [52]. Empirical infusion of FFP during PPH, as used in trauma, is likely to expose many women to blood products when they have adequate haemostasis.

Studies have not found VHA parameters such as the Extem CT (Rotem) [15] or Kaolin r time (TEG6s) [18,19] to be useful for detecting abnormalities in PT/aPTT or to trigger FFP infusion. This is likely to be due to the limited number of abnormal PT/aPTT results available for analysis and the reduced CT/r time values present at term. One study found that the Kaolin-TEG K parameter was useful for detecting PT/aPTT > 1.5 times normal [19], whilst another found a correlation between PT/aPTT with TEG-alpha angle and MA but did not investigate the utility of these parameters for triggering FFP infusion [53]. A moderate prolongation of CT/r may normalise when fibrinogen is replaced to >12 mm. [15]

CT/r within the non-pregnant normal range can be used to reassure clinicians that PT/aPTT will be normal and FFP is not required [15,18]. An observational study of 605 women found that if the Fibtem A5 was >15 mm, then it was safe to withhold FFP [44].

No definitive recommendations can be made about when to infuse FFP based on VHAs. A pragmatic approach is to infuse FFP when the CT/r times are prolonged above the non-pregnant normal range after fibrinogen has been replaced. It is feasible to replace fibrinogen first because fibrinogen concentrate can be given and repeat of VHAs performed within 20 min whilst FFP is thawing. With a markedly prolonged CT/r (for example >100 s), FFP is likely to be needed irrespective of fibrinogen replacement. Observational data show that very few women develop clinically significant depletion of coagulation factors when this approach is followed [46,48], and it is supported by some guidelines [5].

Prothrombin complex concentrates (PCC) have been suggested as a way to replace coagulation factors during PPH. PCC contains FII, FVII, FIX and FX but lack FV, FVIII, FXI, FXIII. Amniotic fluid embolus has been associated with reduced FV and normal levels of other coagulation factors [54], implying that PCC infusion is unlikely to be useful. The use of PCC in PPH has not been subjected to rigorous trials and may be associated with an increased risk of venous thrombosis. Guidelines recommend against their use in PPH outside of clinical trials [4,5]. There are no data to support the infusion of recombinant factor VIIa based on VHA parameters.

Deficiency of platelets

VHAs have been used to trigger platelet transfusion based on the calculations of Extem MCF-Fibtem MCF or Kaolin MA-FF MA, assuming that Fibtem/FF are above a predetermined level. One study investigated ExtemA10-FibtemA10 in 100 women with PPH and found a good correlation with platelet count [13]. However, another study did not find that these calculations are useful for directing platelet transfusion during PPH, possibly because clinically significant thrombocytopenia was uncommon [15]. A study with TEG reported that the Kaolin TEG-MA had good utility for detecting fibrinogen <2 g/L or a platelet count below 80×10^9/L, but thrombocytopenia was not reported separately. [19] A study using TEG reported a correlation between platelet count and TEG-MA and alpha angle but did not investigate whether these parameters could be used to direct platelet replacement [53]. At present, many obstetric units infuse platelets based on the full blood count or empirically.

Potential role of viscoelastic haemostatic assays in specific circumstances

Early haemostatic impairment during PPH may occur in situations associated with consumptive coagulopathies such as placental abruption, amniotic fluid embolus or sepsis. VHAs can identify women with significant haemostatic compromise and guide early proactive replacement.

Placental abruption may be complicated by early reduction in fibrinogen and platelets. Fibrinogen depletion may be present before delivery and identification, and replacement is likely to limit bleeding.

Case reports and series suggest that both Rotem and TEG have the potential to contribute to the diagnosis of placental abruption as well as guiding replacement therapy [26].

Amniotic fluid embolism is associated with a severe coagulopathy characterised by hyperfibrinolysis and very low, often undetectable, fibrinogen. Case reports suggest that other coagulation factors may be well preserved except for a marked decrease in factor V [54]. The haemostatic abnormalities can be readily identified using VHAs with excess fibrinolysis seen on the LY or LI parameters followed by a marked decrease in MCF/MA, especially in the Fibtem/FF assays. The CT/r time will be prolonged. Maternal collapse at the time of birth has a number of potential aetiologies, but severe haemostatic impairment suggests amniotic fluid embolus as a likely cause [27]. This means that VHAs support rapid diagnosis by identifying severe coagulopathy. In contrast, a normal Rotem/TEG trace makes amniotic fluid embolus less likely, and other causes for the symptoms should be considered. Resuscitation with fibrinogen and FFP and early infusion of tranexamic acid are necessary to control bleeding and can be guided by VHAs with the aim to increase the A5/MCF/MA with fibrinogen, reduce the CT/r time with FFP and correct the increased Li/Ly with tranexamic acid administration.

Algorithms for the use of viscoelastic assay during postpartum haemorrhage

Algorithms for the use of VHAs to guide blood component replacement during PPH have been published [10,47,49,50,55] and are supported by guidelines (Tables 2 and 3) [9]. There have been no high-quality trials that investigate whether VHAs are superior to laboratory coagulation tests or empirical blood component replacement.

VHAs play two main roles during PPH. The first is to identify abnormal coagulation and guide replacement of fibrinogen and coagulation factors. The second is to avoid unnecessary transfusion and inform the clinical team that a cause for bleeding, other than haemostatic impairment, needs to be identified and treated. To achieve this, VHAs should be performed early during the bleed. VHAs should be repeated if bleeding is ongoing, and testing every 30 min after each 500 mL blood loss has been suggested [4,55]. Blood product replacement is not required if bleeding has stopped.

It has been established that a Fibtem A5 above 12 mm (equivalent to a TEG6s FF A5 of about >16 mm [18]) is adequate for haemostasis and fibrinogen and FFP infusions are not needed [31], and this is reflected in most algorithms.

An observational study described an algorithm that infused fibrinogen concentrate if the Fibtem A5 was <7 mm or 7–12 mm with ongoing bleeding. This equates to Clauss fibrinogen of roughly 1.2 and 1.2–2 g/L, respectively. If the Extem CT was >100 s, FFP was infused. Outcomes were compared to the previous practice of infusing empirical shock packs. There was a reduction in RBC and FFP transfusion and fewer women had circulatory overload and intensive care admission decreased [47,48].

A national quality improvement programme called OBS Cymru introduced objectively measured blood loss from deliver, escalation to more senior staff at specific bleed volumes and VHAs performed after 1 L PPH, or earlier for clinical concern to detect and guide early fibrinogen replacement (Fig. 4) [55]. The VHA algorithm recommended fibrinogen infusion if the Fibtem A5 was <12 mm and FFP if the Extem CT was >75 s (an equivalent TEGs6 algorithm is supplied, Fig. 4). The initiative resulted in a 22% decrease in the proportion of women receiving RBC transfusion and 23% reduction in the rate of massive PPH (bleeds ≥2.5 L) [46]. Two years later, the improvements in national outcomes have been sustained (unpublished data).

A retrospective, observational cohort study compared treatment guided by Rotem Delta (n = 28) with a massive transfusion protocol (n = 58) in severe PPH. Cryoprecipitate was administered if Fibtem A5 was <5 mm (Clauss fibrinogen <1 g/L) with the aim of achieving A5 >10 mm if bleeding was ongoing. If the Extem CT was >80 s, 2 units of FFP were given, and if the Extem MCF was <45 mm (with a normal Fibtem), one pool of platelets was given. Women managed with VHAs experienced smaller bleeds (2 L vs 3 L), were less likely to need a hysterectomy and were transfused fewer RBC, FFP and platelets [49].

Algorithms for Rotem, TEG and standard laboratory tests have been developed and introduced in Italy. Infusion triggers for fibrinogen, FFP and platelets are described (Table 2), but no outcome data have been published [50]. A further algorithm for both TEG and Rotem has been proposed as part of a literature review [10].

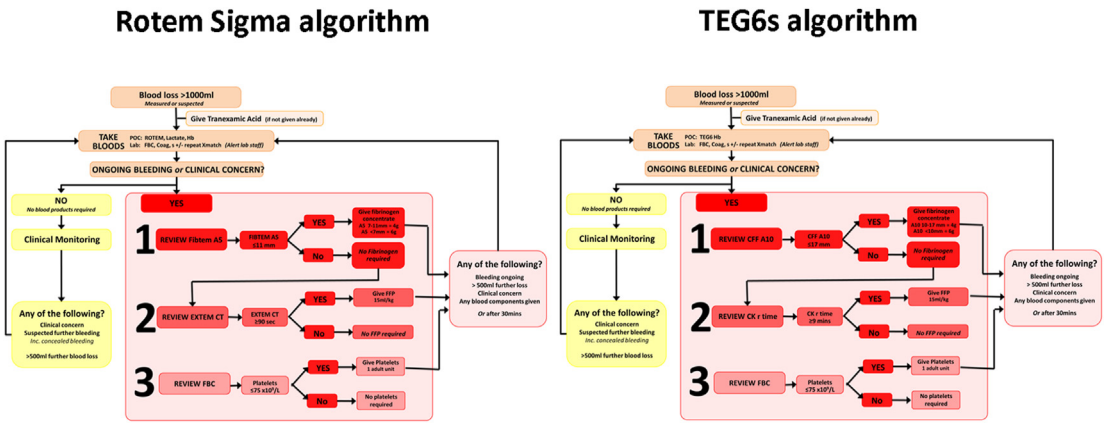

Fig. 4. OBS Cymru algorithms for Rotem Sigma and TEG6s.
Legend: Possible algorithms for managing haemostatic impairment for use during postpartum haemorrhage. The Rotem algorithm was validated during the OBS Cymru quality improvement initiative [46] and the TEG6s algorithm uses equivalent triggers. POC is point-of-care, lab is laboratory tests, FBC is full blood count and coag is coagulation screen. Fibrinogen concentrate can be replaced by cryoprecipitate; 4 g is 2 pools and 6 g is 3 pools.

An algorithm has been described that used a hybrid of a massive transfusion protocol and TEG 5000 guided treatment. The aim was to maintain kaolin r time <6 min, MA >57 mm and alpha angle >50. If the r time was 6–8 min, 2 units FFP were infused, and if >8 min, 4 FFP and 2 pools of cryoprecipitate were given. MA 50–57 mm triggered a pool of platelets and for <50 mm, 2 pools of platelets and 2 pools of cryoprecipitate [56].

These algorithms have many similarities, especially regarding the indications to transfuse fibrinogen where the evidence base is strongest, but there are also similarities around FFP and platelet transfusion. It is important to recognise that introducing a VHA-based algorithm is unlikely to be effective unless it is part of a structured multidisciplinary approach to PPH.

Clinical guidelines

Table 3 summarises professional guideline documents. The Network for Advanced Transfusion Alternatives recommend infusion of fibrinogen if Clauss fibrinogen is <2 g/L, Fibtem A5 <12 mm or FF MA <14 mm. FFP is recommended if there is prolongation of the CT/r time or if PT/aPTT are >1.5 times normal. Platelets should be infused if $<75 \times 10^9$/L and also if "reduced clot strength related to impaired platelet function as measured by TEG or Rotem", but no cut-offs are stated [5].

British Society of Haematology suggests the trigger for fibrinogen infusion during PPH, with either fibrinogen concentrate or cryoprecipitate, should be Fibtem A5 <12 mm (equivalent to TEG6s FF of 16 mm). No recommendation is given about infusion of FFP, but the importance of early tranexamic acid administration, irrespective of the lysis parameters, is highlighted [9].

Royal College of Obstetrics and Gynaecology in the UK [4] and International Society on Thrombosis and Haemostasis [3] support the use of VHAs if there is a locally agreed algorithm, but intervention triggers are not described. They both state that FFP should be given to maintain PT/aPTT <1.5 times normal and platelets infused $<75 \times 10^9$/L.

Summary

The use of VHAs to guide treatment during postpartum haemorrhage is expanding. There is good evidence to support the use of Rotem and TEG to detect and treat clinically significant hypofibrinogenaemia, but it remains unproven whether this improves outcomes. Evidence to support the role of VHAs for guiding FFP and platelet transfusion is less clear. A normal Rotem/TEG trace should reassure clinicians that haemostasis is normal, blood products are not needed and another cause for bleeding needs to be found and treated. Guidelines support the use of VHAs during postpartum haemorrhage if they are supported by locally agreed algorithms. Algorithms for the use of Rotem and TEG have been published, and there is a high level of agreement between authors that fibrinogen infusion should be given if the Fibtem A5 is <12 mm and bleeding is ongoing. Guidelines recommend against using VHAs to guide the need for tranexamic acid, and this drug should be given as soon as bleeding is recognised, irrespective of the Rotem/TEG traces. The cost effectiveness of VHAs during postpartum haemorrhage needs to be addressed.

Practice points

- Viscoelastic haemostatic assays (VHAs) provide rapid information about clot development and fibrinolysis during postpartum haemorrhage.
- To date, no high-quality trials show that VHAs are superior to laboratory coagulation tests during postpartum haemorrhage, but the results are known sooner, thus facilitating earlier intervention.
- Fibrinogen falls to critically low levels before other coagulation factors, and VHAs can be used to detect hypofibrinogenaemia and guide early replacement.
- VHAs can be used to reassure clinicians that haemostasis is normal and other causes of bleeding need to be identified and treated.
- Professional management guidelines support the use of VHAs during postpartum haemorrhage if they are underpinned by a locally agreed algorithm.

Research agenda

- Research is needed to compare the effectiveness of VHAs with standard coagulation tests on maternal morbidity and blood product usage during postpartum haemorrhage.
- The optimum timing of VHAs during postpartum haemorrhage should be established.
- The role of VHAs to guide FFP and platelet transfusion needs to be investigated.
- The cost-effectiveness of VHAs needs to be evaluated.

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