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Haemostatic monitoring during postpartum haemorrhage and implications for management

C. Solomon[1]*, R. E. Collis[2] and P. W. Collins[3]

[1] Department of Anaesthesiology and Intensive Care, Salzburger Landeskliniken SALK, 48 Müllner Hauptstrasse, 5020 Salzburg, Austria
[2] Department of Anaesthesia, University Hospital of Wales, Cardiff, UK
[3] Department of Haematology, School of Medicine, Cardiff University, Cardiff, UK

* Corresponding author. E-mail: solomon.cristina@googlemail.com

Editor's key points

- Postpartum haemorrhage (PPH) is a major cause of maternal mortality worldwide.
- Monitoring of coagulation in PPH must take account of pregnancy-induced changes in coagulation status.
- Point-of-care testing may have advantages in guiding replacement therapy.
- There is a need for specific studies of haemostatic therapies in PPH.

Summary. Postpartum haemorrhage (PPH) is a major risk factor for maternal morbidity and mortality. PPH has numerous causative factors, which makes its occurrence and severity difficult to predict. Underlying haemostatic imbalances such as consumptive and dilutional coagulopathies may develop during PPH, and can exacerbate bleeding and lead to progression to severe PPH. Monitoring coagulation status in patients with PPH may be crucial for effective haemostatic management, goal-directed therapy, and improved outcomes. However, current PPH management guidelines do not account for the altered baseline coagulation status observed in pregnant patients, and the appropriate transfusion triggers to use in PPH are unknown, due to a lack of high-quality studies specific to this area. In this review, we consider the evidence for the use of standard laboratory-based coagulation tests and point-of-care viscoelastic coagulation monitoring in PPH. Many laboratory-based tests are unsuitable for emergency use due to their long turnaround times, so have limited value for the management of PPH. Emerging evidence suggests that viscoelastic monitoring, using thrombelastography- or thromboelastometry-based tests, may be useful for rapid assessment and for guiding haemostatic therapy during PPH. However, further studies are needed to define the ranges of reference values that should be considered 'normal' in this setting. Improving awareness of the correct application and interpretation of viscoelastic coagulation monitoring techniques may be critical in realizing their emergency diagnostic potential.

Keywords: blood coagulation tests; point-of-care systems; postpartum haemorrhage; thrombelastography

Postpartum haemorrhage (PPH) is excessive blood loss after childbirth, and has been defined as blood loss >500 ml within 24 h of normal vaginal delivery, or >1000 ml after Caesarean section,[1 2] although alternative definitions have been used to describe PPH and its severity.[3–6] Although PPH typically occurs within 24 h of childbirth (primary PPH), haemorrhage may occur any time up to 12 weeks postpartum (secondary PPH). PPH is the leading cause of maternal mortality worldwide, estimated to be responsible for around 143 000 deaths each year.[7] PPH also contributes significantly to maternal morbidity and is a major reason for intensive care admission and hysterectomy in the postpartum period.[8–10]

The causes of PPH are varied, and have been classified according to their underlying pathophysiology[11] (Fig. 1). Excessive bleeding is often exacerbated by acquired coagulation abnormalities, and coagulopathies vary markedly depending on underlying aetiology. Primary coagulation defects are occasionally direct causes of PPH. Although historically categorized under 'thrombin', recent studies suggest that acquired fibrinogen deficiency, rather than thrombin generation, may be the major coagulation abnormality associated with obstetric bleeding.[12–15] Similar observations have been made during blood loss in trauma[16] and major surgery.[17]

The diversity of potential triggers makes the occurrence and severity of PPH difficult to predict. Many cases have no identifiable risk factor.[3] However, episodes of PPH with differing causes may have common pathological progression, with measurement of haemostatic impairment potentially providing important information for diagnosis and therapeutic intervention. Bleeding leads to loss and consumption of coagulation factors, which may be exacerbated by dilutional coagulopathy after volume resuscitation. Coagulation defects may be compounded by hyperfibrinolysis. Rapid correction of coagulopathies that develop during PPH may be crucial for controlling bleeding and improving outcomes. However, appropriate haemostatic intervention may depend on the availability of tests which allow rapid diagnosis of the cause of bleeding. In this review, we discuss the normal changes in clotting factors during pregnancy, the importance of coagulation failure during major PPH, tests that

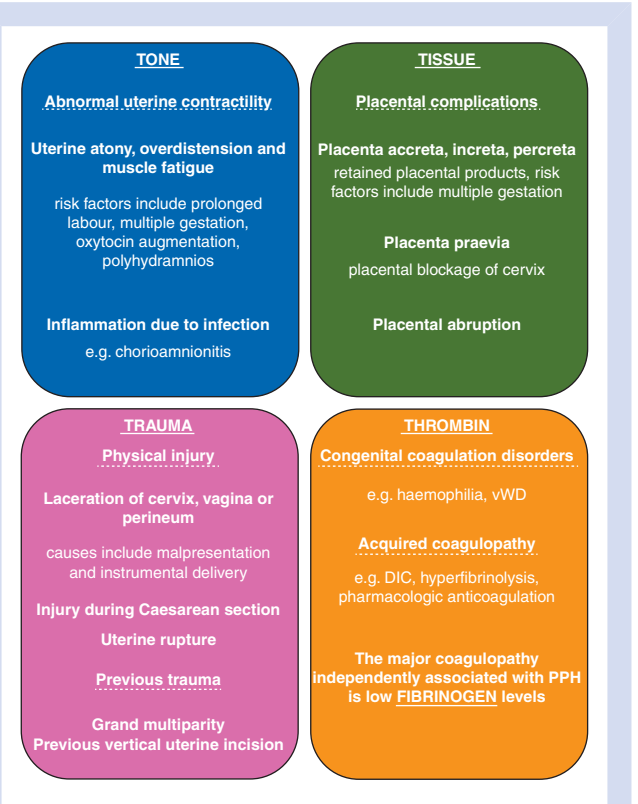

Fig 1 Major risk factors associated with PPH. Conditions are classified according to pathophysiology. DIC, disseminated intravascular coagulation; vWD, von Willebrand's disease; PPH, postpartum haemorrhage.

are available for monitoring haemostasis, and the implications of coagulation monitoring for PPH management strategies.

Methodology

We conducted a literature search for articles describing haemostasis testing/coagulation monitoring in the obstetric setting, using PubMed with the following search terms with no filters applied: [blood coagulation tests (MeSH)] and obstetric; [thrombelastography (MeSH)] and obstetric; [blood coagulation tests (MeSH)] and [peripartum period (MeSH)]; [thrombelastography (MeSH)] and [peripartum period (MeSH)]; [blood coagulation tests (MeSH)] and [postpartum hemorrhage (MeSH)]; [thrombelastography (MeSH)] and [postpartum hemorrhage (MeSH)]; [postpartum hemorrhage (MeSH)] and [Blood coagulation (MeSH)]; [postpartum hemorrhage (MeSH)] and [Blood coagulation factors (MeSH)]. In total, 674 articles were retrieved. Articles published after 1991 were screened (abstract if available, whole article if not) and retained if the use of laboratory coagulation tests, point-of-care (POC) coagulation coagulation monitoring, or measurement of individual coagulation factors/inhibitors was reported during healthy pregnancy, obstetric complication, or PPH. After screening, 121 articles remained; these formed the evidence-base for the review and included review articles, *in vitro* and *ex vivo* experimental studies, case-reports, and prospective and retrospective clinical investigations. The evidence was supplemented with reports of interest known to the authors, and with references cited within articles used in the review.

Coagulation status during pregnancy and the peripartum period

Marked changes in haemostasis are observed during pregnancy.[18] In comparison with the non-pregnant state, procoagulant levels are generally elevated (Fig. 2), but antagonists of coagulation decrease or remain unchanged. This hypercoagulable state may reduce the risk of haemorrhage during delivery and the postpartum period. In contrast, platelet counts typically decrease during pregnancy,[19] although the clinical significance of this is uncertain.[15] Haemostasis can be further influenced by anaemia and pre-eclampsia. Anaemia (haemoglobin <11 or 10.5 g dl^{-1} in second trimester)[20] affects $\sim$20% of pregnant women worldwide[21] and is associated with increased blood loss and likelihood of transfusion during delivery.[22] Similarly, pre-eclampsia, which occurs in 0.4–2.8% of births,[23] is associated with haemostatic abnormalities including thrombocytopenia and disseminated intravascular coagulopathy.[24]

Standard coagulation tests; assessment of bleeding risk in obstetric patients

The routine coagulation screen

Laboratory-based screening is used routinely to assess coagulation status in obstetric patients. The tests consist of platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), with plasma fibrinogen levels also routinely determined in many centres.[12 15 25 26] Platelet count provides a measure of platelet concentration but not function. PT measures the extrinsic and common coagulation pathways, and is sensitive to levels of coagulation factors (F) II, V, VII, and X, whereas aPTT assesses coagulation via the intrinsic and common pathways and is sensitive to all coagulation factors except FVII and FXIII.[25 27] The aPTT is shorter in pregnancy because of the raised FVIII and so is relatively insensitive to haemostatic impairment. Both the PT and aPTT are relatively insensitive to plasma fibrinogen levels, which are typically measured indirectly using the Clauss assay.[28] In this method, fibrinogen concentration is inversely proportional to the time taken for the clot to form, and so gives a measure of functional fibrinogen (FF).

The value of routine full blood count and coagulation screening has been questioned in obstetrics[29 30] and other settings.[31 32] PT and aPTT may identify significant coagulation impairment, but they test limited parts of coagulation and do not help diagnose the underlying defect. These tests may also generate a high number of false-positive and false-negative results.[31] Pre-procedural coagulation screening is therefore not generally recommended unless a complication associated with haemostatic impairment

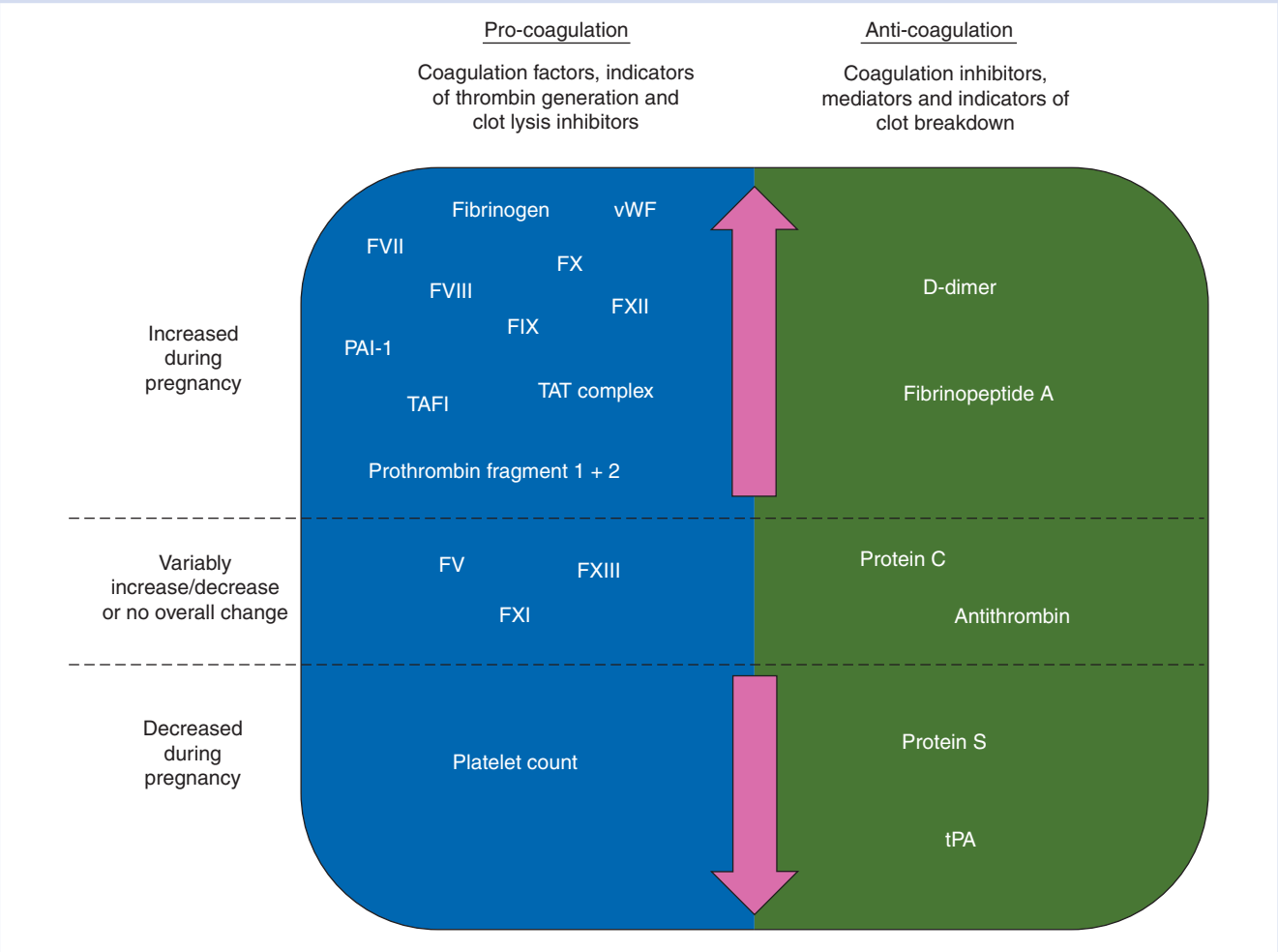

Fig 2 Changes in haemostatic variables observed during normal, healthy pregnancy. The overall increase in pro-coagulant factors results in a typically hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative 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; vWF, von Willebrand factor.

(e.g. placental abruption) is suspected. A comprehensive assessment of bleeding history and medication history is considered more accurate and cost-effective.[25 30 33–35]

If congenital haemostatic defects are suspected, tests may be conducted to identify specific coagulation factor deficiencies, so that appropriate prophylactic treatments can be incorporated into the plan for labour to minimize the risk of PPH. Typically, these tests are performed at 28–34 weeks gestation and should involve a multi-disciplinary team including a specialist in high-risk obstetrics and a haematologist.[36] Guidelines have been published for the management of obstetric patients with congenital bleeding disorders,[36 37] although a lack of data for many of the rarer conditions limits the possible recommendations specific to PPH. The recommendations are based on treatment of non-pregnant individuals, so do not account for the altered baseline coagulation status in pregnancy. To determine the true utility of antenatal coagulation testing, comprehensive reference ranges must first be established reflecting the normal physiology of pregnancy.

Standard coagulation tests; intraoperative testing and haemostatic therapy

The use of coagulation monitoring in obstetric patients raises an important question as to which reference values best represent 'normal' haemostasis in parturients and what values should trigger intervention. PT and aPTT can remain in the normal range even in severe PPH,[12] while thrombocytopenia is common during healthy pregnancy.[18] Maternal fibrinogen levels increase from a pre-pregnant median of 3.3–6.0 g litre^{-1} during the third trimester.[12 38] Fibrinogen levels below 2 g litre^{-1} (within the population normal range) potentially indicate the need for advanced intervention during

genital tract bleeding.[8 14] This again raises the question of what the appropriate target fibrinogen level should be during ongoing PPH and whether this should differ from other causes of massive haemorrhage. Current PPH management guidelines[3] recommend maintaining PT and aPTT at $\leq$1.5 times normal control values, platelet count at $\geq 50\times10^9$ litre^{-1}, and plasma fibrinogen at $\geq$1 g litre^{-1}, identical to the recommendations for non-pregnant populations.[37]

PT and aPTT during PPH

Both PT and aPTT appear to be of limited value for monitoring haemostasis during PPH. A recent review of 18 501 deliveries in the UK identified 456 cases complicated by blood loss $\geq$1500 ml.[12] PT did not correlate with the volume of haemorrhage and aPTT correlated weakly. The results were consistent with earlier studies which concluded that PT and aPTT are not useful for predicting PPH progression.[14 15] However, another retrospective multicentre validation study demonstrated that PT >1.5 times normal may predict the need for advanced intervention to control PPH.[8] Current guidelines recommend using PT and aPTT to guide fresh-frozen plasma (FFP) transfusion,[3] although there is no evidence to confirm that this practice is effective for the management of major bleeding. In addition, the transfusion trigger of >1.5 times normal is derived from trauma studies,[39] and may not be appropriate in PPH.

PT, aPTT, and international normalized ratio (INR) have been used to monitor the effects of recombinant activated FVII (rFVIIa) administered during refractory PPH.[40–47] However, the results are inconsistent and studies typically involve confounding factors. Conclusions cannot be drawn concerning the value of the tests until high-quality randomized controlled trials have been performed in this setting, and should not be used to assess the efficacy of rFVIIa. The lack of a test to discriminate between PPH patients who are likely to respond to rFVIIa and those who will not also limits the utility of this treatment option.

Platelet count in PPH

The clinical significance of gestational thrombocytopenia and whether decreases in platelet number are counterbalanced by increased platelet reactivity[15] are not fully understood. One study has suggested low platelet count to be an independent risk factor for PPH. A retrospective analysis of 797 pregnancies found that a platelet count $<100\times10^9$ litre^{-1} on admission to the labour ward was associated with increased PPH incidence in some women.[15] A large retrospective analysis also demonstrated an inverse association between lowest platelet count and red blood cell (RBC) transfusion requirement.[12] Subsequent prospective studies showed that at diagnosis of haemorrhage, platelet counts in PPH patients were significantly lower than those in healthy parturients,[13] and that decreasing platelet count during obstetric bleeding may be associated with progression to severe PPH.[14]

These findings suggest that platelet transfusion or desmopressin may be valid haemostatic therapies for PPH. However, they raise concerns about recommended transfusion triggers. Data suggest that platelet count should be maintained $\geq100\times10^9$ litre^{-1} during ongoing PPH,[15] but a prospective analysis of 30 patients with coagulopathy after *abruptio placentae* had platelet counts $\sim90\times10^9$ litre^{-1} at 0 and 4 h postpartum.[48] However, current PPH guidelines recommend platelet transfusion only when the platelet count decreases below 50×10^9 litre^{-1},[3] although in other massive haemorrhage guidelines, a trigger of 75×10^9 litre^{-1} is recommended.[49] Studies are required to confirm the validity of current approaches.

Plasma fibrinogen levels in PPH

Fibrinogen concentration correlates with the incidence and severity of bleeding.[12 14 15] In a prospective study involving 128 patients, decreasing plasma fibrinogen during early PPH was the only variable independently associated with progression to severe PPH (requiring RBC or invasive intervention).[14] Fibrinogen >4 g litre^{-1} had a negative predictive value of 79% for severe haemorrhage, whereas fibrinogen $\leq$2 g litre^{-1} had a positive predictive value of 100%. The data corroborated large retrospective studies reporting fibrinogen levels on admission to the labour ward as the factor most significantly correlated with the incidence of PPH,[15] and reporting lowest recorded fibrinogen level within 24 h of delivery as the variable best correlated with volume of blood-loss.[12] These data cast doubt upon current guidelines which suggest fibrinogen replacement when plasma levels decrease below 1 g litre^{-1} [3] and suggest a trigger of $\geq$2 g litre^{-1} may be more appropriate.[14] Coagulopathic bleeding has also been observed in *abruptio placentae*, despite postpartum fibrinogen levels of 1.5–1.6 g litre^{-1}.[48] Studies evaluating the current approaches are urgently required.[50] Plasma fibrinogen trigger levels have been discussed in other therapy areas. Recent guidelines for the management of massive haemorrhage acknowledge that target fibrinogen levels of 1 g litre^{-1} are usually insufficient and that plasma fibrinogen >1.5 g litre^{-1} is more likely to improve haemostasis.[49] Notably, the European Guideline for the management of bleeding after major trauma has updated its recommended trigger level for fibrinogen replacement from <1 to <1.5–2.0 g litre^{-1}.[51 52] The evidence supporting this change included prospective data in an obstetric setting.[14] In the light of these changing guidelines, the current recommended trigger of only 1 g litre^{-1} for PPH warrants reconsideration.

The data associating fibrinogen depletion with PPH progression suggest that fibrinogen replacement therapy may be an important early step in PPH management, with one option being administration of FFP. Fibrinogen concentrations can vary from 1.6 to 3.5 g litre^{-1} in FFP.[53–55] However, as plasma fibrinogen levels are typically around 3.5–6 g litre^{-1} at term and 1.5–4 g litre^{-1} in PPH,[12] adequate replacement of fibrinogen using FFP may not be achieved,

and FFP transfusion may dilute already depleted fibrinogen levels. It has been shown that even after extensive FFP transfusion, declining fibrinogen levels persisted in PPH patients.[12] In the UK and USA, cryoprecipitate provides a more concentrated alternative, although fibrinogen content remains variable (3.5–30 g litre^{-1}).[55–58] Cryoprecipitate has been withdrawn in many European countries due to safety concerns,[59] so use as the first-line replacement therapy could be considered unethical. Recent reports have described fibrinogen concentrate infusion as an effective therapy for controlling PPH concurrent with low fibrinogen levels.[60 61] Fibrinogen concentrate is highly purified, and since the introduction of pasteurization steps in the manufacturing process, no incidents of pathogen transmission have been reported.[62] Prospective data supporting the use of fibrinogen concentrate in PPH are limited, although a retrospective analysis of French PPH episodes indicated that fibrinogen concentrate was co-administered with platelets in 47% of cases.[63] There is a lack of studies of fibrinogen replacement therapy in obstetric patients, and in view of the increasing evidence linking fibrinogen levels with PPH progression, such studies should be a matter of priority.

Limitations of standard coagulation tests

Despite the potential of plasma fibrinogen concentration and platelet count as targets for haemostatic therapy, their utility in PPH management is hampered by long assay turnaround times (typically 30–60 min).[27 38 64 65] Slow turnaround is incompatible with efficient management of bleeding in PPH, particularly as the result will not reflect the current haemostasis and delayed treatment is a strong predictor of poor outcome, including maternal death.[66] Rapid POC tests such as the CoaguChek device (Roche Diagnostics Ltd, Basel, Switzerland) monitor parameters including PT and INR. However, they do not assess the dynamics of whole blood clotting, and their use is not yet widespread.

Where test results are not returned in a reasonable timeframe, Italian Guidelines for bleeding management[67] recommend that FFP is administered irrespective of PT/aPTT. UK PPH guidelines have similar recommendations.[3] Therefore, haemostatic intervention is guided either by formulaic replacement or by clinical judgement alone. Such practice may result in unnecessary and/or inappropriate transfusions.[12] A retrospective analysis reported that 72% of FFP transfusions would not have been given if transfusion guidelines had been adhered to, but it is not possible to define whether inappropriate transfusion triggers were used, or if delays in obtaining test results led to inappropriate treatment. Moreover, depleted fibrinogen levels in many patients suggested that alternative replacement therapy may have been more effective than FFP.

Doubts also exist about the precision of Clauss fibrinogen measurement after volume replacement with hydroxyethyl starch (HES). Haemodilution using HES can lead to the overestimation of Clauss plasma fibrinogen levels by 120%.[68] The amount of HES used appeared more influential than molecular size; 50% haemodilution resulted in greater fibrinogen overestimation than 30% dilution. Compared with haemodilution using isotonic saline or albumin, HES also decreases fibrin-based clot firmness measured using thromboelastometry.[69] Thus, HES provides a twin hazard by compromising clot quality while over-representing plasma fibrinogen.

Obstetric coagulation monitoring using thrombelastography and thromboelastometry

TEG® and ROTEM®; principles, parameters, and tests

Thrombelastography (TEG®; Haemonetics Corp., Braintree, MA, USA) and thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany) are increasingly used at the POC for clinical coagulation assessment. Compared with laboratory coagulation assessment, TEG®- and ROTEM®-based tests have increased sensitivity for identifying some abnormalities in the coagulation process.[70] Laboratory tests are typically performed on plasma and end with formation of the first fibrin strands, whereas TEG®/ROTEM®-based monitoring is performed in whole blood, and assess the process from coagulation initiation through to clot lysis, including clot strength and stability. TEG®/ROTEM®-based assessment can therefore provide a sensitive assessment of how changes in haemostatic balance impact upon coagulation. This allows a more complete diagnosis of coagulopathy, and rapid evaluation of the effects of haemostatic intervention on coagulation.

TEG®/ROTEM®-based monitoring can be performed at the POC. Viscoelastic properties of the sample are recorded to produce a profile of coagulation dynamics (Fig. 3), which is used to generate values indicating the speed and quality of clot formation (Table 1). Importantly, several of these values can be obtained within minutes (e.g. CT, A5, A10) and are therefore potentially useful for guiding rapid haemostatic intervention.[13 71–74]

Several TEG®/ROTEM®-based tests have been described, with different activators and inhibitors used to make these tests sensitive to various aspects of haemostasis.[75–80] The most commonly used tests are the commercially available assays (Table 2). The benefit of performing multiple parallel assays has been highlighted by comparing monoanalysis using kaolin-activated TEG® with a panel of ROTEM® tests for diagnosis of different coagulopathies.[76] TEG® monoanalysis could not distinguish between dilutional coagulopathy and thrombocytopenia, establishing the potential for platelet transfusion when another therapy may be more appropriate. Clinical use of TEG® monoanalysis to guide intervention has been reported to increase platelet transfusions.[81] In contrast, in cardiovascular surgery, the use of multiple ROTEM® assays has been shown to reduce transfusion of allogeneic blood components, while increasing targeted administration of coagulation factor concentrates.[71 82] Selection of appropriate TEG®/ROTEM®-based tests, combined with awareness of

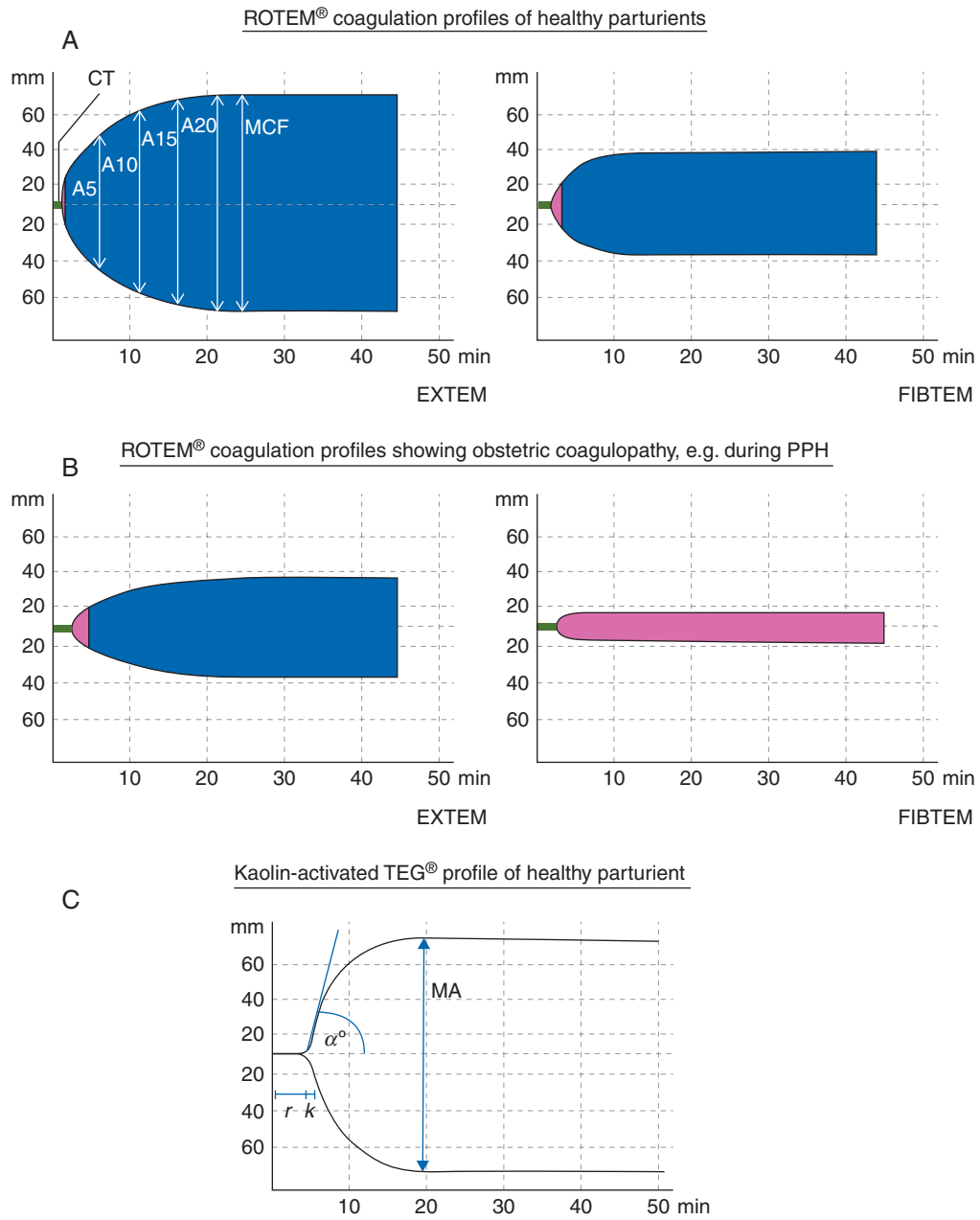

Fig 3 ROTEM®- and TEG®-based coagulation profiles in the peripartum period. Schematic representation of healthy (A) and coagulopathic (B) obstetric coagulation profiles for EXTEM and FIBTEM tests. Coagulation parameters which are typically reported for these tests are indicated in the top-left panel. The profiles reflect EXTEM and FIBTEM test results reported for healthy patients around the time of delivery,[29 38 87] and for patients with PPH associated with poor fibrin-clot quality.[13 90] Clot lysis parameters are not indicated; if (hyper)fibrinolysis is suspected, an APTEM test can be performed. APTEM profiles mirror EXTEM profiles under healthy conditions, and show enhanced coagulation *vs* EXTEM during fibrinolysis.[76] Also presented (C) is a healthy, obstetric coagulation profile for kaolin-activated thrombelastography, with typically reported parameters indicated for this test. The profile reflects kaolin-TEG® values observed for healthy patients in the third trimester,[86] and before elective Caesarean delivery.[114] Owing to the lack of available evidence for typical test results, profiles are not presented for kaolin-TEG® during PPH, or for other TEG®-based tests in obstetric patients. α°, alpha angle; A5–A20, clot amplitude at 5–20 min after CT; CT, clotting time; MA, maximum amplitude; MCF, maximum clot firmness; PPH, postpartum haemorrhage; *r*, reaction time.

the diagnostic utility of each assay in different clinical situations, may be critical for correct, timely diagnosis of coagulopathy during haemorrhage.

TEG® and ROTEM® for antenatal assessment

TEG®[25 83] and ROTEM®[29] can be used to demonstrate hypercoagulability in pregnancy. A case-matched study involving

Table 1 Parameters recordable using TEG® and ROTEM®-based tests. *$G = (5000 \times MA)/(100 - MA)$;[127] $MCE = (100 \times MA)/(100 - MA)$[130]

Parameter recorded	TEG® value	ROTEM® value	Description
Coagulation initiation	*r* (reaction time)	CT (clotting time)	Time taken to reach an amplitude of 2 mm
Clot formation	*k*	CFT (clot formation time)	Time taken for amplitude to increase from 2 to 20 mm
	α° (alpha angle)	α° (alpha angle)	Tangent of the slope between amplitude at 2 mm and at 20 mm
Clot strength/quality		A5, A10, A15, etc.	Clot amplitude reached 5, 10, 15 min after CT has passed
	MA (maximum amplitude)	MCF (maximum clot firmness)	Maximum amplitude reached
	G (clot rigidity)	MCE (maximum clot elasticity)	Calculable from MA and MCF values*
Clot lysis	LY30 (lysis)	LI30 (lysis index)	% of MA/MCF remaining 30 min after MA/MCF has been reached
		MI (maximum lysis)	Greatest % decrease in MCF observed during assay period

Table 2 Commercially available TEG®- and ROTEM®-based coagulation tests. Analogous tests for the different devices are presented side-by-side in the same row. Details of the assay principles and applications of TEG®-based tests can be found at http://www.haemonetics.com/site/pdf/teg-product-brochure.pdf. Similar details for ROTEM®-based tests are available at http://www.rotem.de/site/. *Tests are typically performed using recalcified, citrated blood. FII, factor; FV, factor V; FVIII, factor VIII; FIX, factor IX; FXI, factor XI; FXII, factor XII; FF, functional fibrinogen

TEG®-based tests			ROTEM®-based tests			Diagnostic use
Test (reagent name)	Activator	Additional modifications*	Test (reagent name)	Activator	Additional modifications*	
—	—	—	NATEM (star-tem®)	None added	—	Sensitive test measuring coagulation without added activator, although not applicable in emergencies due to slow clotting times
Kaolin-activated TEG®	Kaolin	—	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)
RapidTEG (RapidTEG™ reagent)	Kaolin + tissue factor	—	—	—	—	Defects in the intrinsic and extrinsic pathways of coagulation activation; more rapid assessment than using kaolin activation alone
FF/functional fibrinogen test (FF reagent)	Tissue factor	Abciximab	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)
Kaolin-activated TEG® + heparinase	Kaolin	Heparinase	HEPTEM (hep-tem®)	Ellagic acid	Heparinase	Heparin/protamine imbalance (in conjunction with INTEM or kaolin-activated TEG)

INTEM, EXTEM, and FIBTEM testing of 120 women, either pregnant and undergoing elective Caesarean section or non-pregnant and undergoing elective surgery, found that for all tests, the time of coagulation (CT and CFT) was reduced, and clot firmness (MCF) was increased, in the pregnant group.[29] This corroborated an earlier study[83] which demonstrated significant differences in TEG®-recorded *r*, *k*, α°, and MA values between healthy non-labouring pregnant women and non-pregnant women, and a later study establishing TEG®-based reference ranges in parturients undergoing Caesarean

section with spinal anaesthesia.[84] ROTEM®-based analysis has shown that hypercoagulability is not limited to the pre-delivery period; low CT and CFT, and elevated α°, A20, and MCF, can persist up to 3 weeks postpartum.[85] These data again highlight the importance of establishing reference ranges for TEG®/ROTEM®-recordable parameters in pregnant women.[13 29 38 86 87]

When attempting to use coagulation status to predict PPH, it is important to remember that, unlike many clinical settings, substantial blood loss may be considered 'normal' in obstetric patients. Blood loss of 500 ml may occur before PPH is suspected and up to 1000 ml may be tolerated in women without underlying medical disorders.[88] It can be argued that 'baseline' assessment of haemostatic activity postpartum should not be measured pre-delivery, but instead taken after 500–1000 ml blood loss. Assessment of coagulation dynamics after this initial bleed may provide a more reliable indication of coagulation abnormalities which may develop postpartum, and thus may better reflect the risk of imminent progression to PPH.

TEG® and ROTEM®; intraoperative assessment and haemostatic therapy

TEG® and ROTEM® can enhance coagulation management algorithms

POC coagulation monitoring is of greatest value when patients are bleeding and in procedures with a risk of major bleeding. However, there are few studies in obstetric patients. It is important to establish whether TEG®- and ROTEM®-recorded transfusion triggers in PPH should differ from other clinical situations to reflect the difference in 'normal' ranges of coagulation parameters seen at delivery. To reduce treatment delay, it is important that POC devices are available to the labour ward at all times.[89]

Evidence supporting the value of thrombelastography for treatment of acute obstetric haemorrhage has been available in German-language publications for more than 30 yr.[89] Elsewhere, case-studies have reported successful use of TEG®/ROTEM® to guide intraoperative haemostatic treatment.[90–97] In addition, two prospective trials have shown the potential benefit of using viscoelastic testing for monitoring coagulation defects and guiding therapy in the labour ward. In 30 women with *abruptio placentae*, the *r*, *k*, and MA values from TEG® analyses performed immediately before, after 4 h, and after 24 h postpartum correlated with laboratory coagulation test results. A study of 54 healthy parturients and 37 women during early PPH showed that A5, A10, and MCF indicated decreased fibrin-clot quality during PPH and all three parameters correlated with plasma fibrinogen measurement.[13] These findings reflect the findings of prospective, randomized studies in cardiovascular surgery where TEG®/ROTEM®-based transfusion triggers as part of pre-defined algorithms for the management of bleeding have helped to restrict blood loss and transfusion requirements.[98 99]

Use of TEG® and ROTEM® to diagnose hyperfibrinolysis in PPH

Fibrino(geno)lytic activity is generally diminished during pregnancy[100] but may increase postpartum, peaking around 3 h postdelivery.[101] Hyperfibrinolysis is also associated with complications including shock and amniotic fluid embolism.[90] Hyperfibrinolysis counteracts clot formation and may lead to consumption and depletion of coagulation factors, particularly fibrinogen. Limiting hyperfibrinolysis has been suggested as the first step in a therapy algorithm for acquired coagulopathy in PPH.[90]

Conventional laboratory tests for hyperfibrinolysis include measurement of plasma D-dimer levels (from breakdown of cross-linked fibrin) or fibrin/fibrinogen degradation products. These tests are indirect measures, reflecting past rather than current events, and recently their utility has been questioned.[102 103] Conventional tests of hyperfibrinolysis also have poor turnaround times. In contrast, TEG®/ROTEM®-based tests facilitate rapid diagnosis of ongoing hyperfibrinolysis. The ROTEM® APTEM assay has been reported for diagnosis of hyperfibrinolysis in amniotic fluid embolism.[90] Excessive fibrinolysis may be evident from prematurely declining clot amplitudes in INTEM/EXTEM tests or kaolin- or celite-activated TEG®.[97]

Once hyperfibrinolysis is diagnosed, antifibrinolytic therapy provides a stable platform for subsequent coagulation factor replacement. Currently, the drug of choice is tranexamic acid, whose efficacy is proven in surgical settings.[104 105] A recent meta-analysis examined the use of tranexamic acid for controlling haemorrhage after Caesarean section or vaginal delivery.[106] The evidence from 34 studies (five randomized trials) suggested that tranexamic acid is safe and effective in reducing blood loss during PPH. This agrees with an earlier, smaller analysis of tranexamic acid use in preventing PPH.[107]

Use of TEG® and ROTEM® to diagnose defects in fibrin-based clot quality

Plasma fibrinogen levels correlate with the incidence and severity of PPH.[12 14 15] ROTEM®-based measurements of fibrin-based clot quality (FIBTEM MCF) have been shown to correlate with laboratory fibrinogen measurements,[13] although the involvement of other proteins, for example, FXIII, means that FIBTEM MCF should not be considered as an alternative method of measurement of fibrinogen concentration. Nevertheless, impaired fibrin-based clotting can be used to determine whether fibrinogen supplementation is required. In a prospective observational comparison of 37 parturients with PPH and 54 without abnormal bleeding,[13] FIBTEM MCF values were lower in the haemorrhage group [median (IQR)=15 (9–19) mm] than in the non-bleeding group [19 (17–23) mm]; the latter were consistent with independently reported FIBTEM MCF values [22 (18–25) mm] recorded 1–2 h after non-haemorrhagic delivery.[87] The FIBTEM test enables diagnosis of fibrin(ogen) deficiency within 10 min (including sample acquisition and setup) of

drawing blood, whereas laboratory measurements typically take 30–50 min.[13] Thus, fibrinogen replacement therapy in PPH may be better guided by viscoelastic clot measurement than absolute quantification of fibrinogen levels. The FIBTEM test also highlighted the coagulopathic potential of obstetric volume resuscitation. *In vitro* tests using blood from healthy parturients showed that FIBTEM MCF decreased from 20.3 mm (mean) to 9.1 or 3.3 mm after 60% haemodilution using lactated Ringer's or 1:1 lactated Ringer's:HES, respectively.[108] Dilution with a gelatin and HES combination has less impact on ROTEM®-recorded parameters than HES alone.[109]

A TEG®-based FF test, based on the same principle as the FIBTEM test (Table 2), uses abciximab to inhibit platelet activation.[110] Abciximab has been added to celite-activated TEG® assays to distinguish between platelet and fibrin(ogen) components of clotting in pregnant patients,[111] to demonstrate elevated fibrin-based clot formation after *in vitro* fertilization,[112] and to dissect the effects of contaminating blood with amniotic fluid *in vitro*.[113] However, no evidence was identified for the use of platelet-inhibited TEG® assays during PPH.

The need for validation of the FF test is heightened by widespread practice of TEG®-based monoanalysis.[65 81 114–116] Promotional material for the TEG® device (http://www.haemonetics.com/site/pdf/AnalysisTree-Kaolin.pdf) describes a haemostatic algorithm guided by kaolin-activated TEG® alone,[117] in which each parameter indicates a different therapeutic intervention, and similar practice has been reported.[81 96 118–121] These algorithms treat TEG® parameters as isolated elements of the coagulation system, rather than recognizing that viscoelastic measurements monitor interactions between plasmatic coagulation and platelets in whole blood.[122] For example, α° is used to guide fibrinogen replacement and MA to guide platelet transfusion. Although α° has been described as dependent upon the rate of fibrin accumulation, and representative of fibrinogen concentration,[117 123] thrombus formation in kaolin-activated tests also involves platelets. Therefore, α° may be primarily dependent upon fibrin(ogen) but may also indicate thrombocytopenia.[124] Consistent with this, platelet count correlates strongly with α°,[125] and platelet transfusion elevates α° during PPH.[94]

On current evidence, the most reliable approach for distinguishing fibrin(ogen) deficiency from thrombocytopenia is parallel EXTEM and FIBTEM analysis. For this purpose, CT, CFT, and α° are not useful, and measures of clot quality are the most clinically informative parameters. The sensitivity of this approach may be increased by using the maximum clot elasticity (MCE; Table 1) rather than MCF to measure clot quality. Relative differences in FIBTEM MCF between non-pregnant, pregnant, and coagulopathic populations are typically greater than those in EXTEM MCF values.[13 29 38] One explanation for this is that EXTEM MCF is typically around three times greater than FIBTEM MCF, and clot firmness is a non-linear measurement. Although less commonly used, MCE has a curvilinear relationship with MCF so may be more useful for comparisons.[126] It seems intuitive that dual TEG® analysis using rapidTEG and FF tests would provide a similar diagnosis to EXTEM and FIBTEM. However, the diagnostic performances of FIBTEM and FF differ,[110] so further validation of the FF test is required. The argument for using MCE over MCF in ROTEM analysis also applies to using clot rigidity (*G*) in place of MA for TEG®-based tests.[127]

Limitations of coagulation monitoring using TEG® and ROTEM®

The utility of viscoelastic coagulation assessment is limited by several practical considerations. By direct addition of an activator, such as tissue factor or kaolin, ROTEM® and TEG® automatically by-passes primary haemostasis, therefore cannot detect disorders of primary haemostasis. Most viscoelastic tests also cannot diagnose the cause of coagulopathy involving platelet function defects; for example, abnormal/deficient von Willebrand factor function and the effect of anti-platelet drugs such as clopidogrel (except for the novel TEG aggregation test Platelet Mapping Assay).[128] Parallel assessment using POC platelet function assays may therefore improve diagnosis, although their role in PPH has yet to be established.

Importantly, results from ROTEM® FIBTEM and TEG® FF assays are not directly comparable, as the different devices and use of different reagents yields distinct reference ranges.[129] Additionally, cytochalasin D used in the FIBTEM assay appears to be more effective at inhibiting the contribution of platelets to clot formation than equivalent levels of abciximab used in the FF assay.[110 130] Thus, the FF assay produces consistently higher values than the FIBTEM assay, and could potentially overestimate fibrin(ogen) levels. Threshold values for haemostatic interventions may need to be defined separately for the two devices.

As TEG®- and ROTEM®-based tests are most effective when performed at the POC, they may be conducted by obstetricians, anaesthetists, or nurses rather than diagnostic laboratory staff.[27] Correct application and interpretation of the various assays and parameters requires that individuals performing the assessment are appropriately trained and experienced, and that sufficient quality control procedures are in place. This raises concern especially at night or on weekends, when staff trained in the use of ROTEM®/TEG® may not be present. A recent UK audit of test results from 18 TEG® and 10 ROTEM® users, in different centres, found sufficient variation in results to suggest that differences in therapy would have resulted.[49] It was concluded that routine external quality assessment and proficiency testing is required.

In conclusion, PPH remains a major cause of maternal morbidity and mortality worldwide, but is difficult to predict due to the diversity of causal factors. Rapid diagnosis and correction of coagulopathic bleeding is therefore important. Current approaches to PPH management are hampered by limitations of laboratory coagulation assessment, poor familiarity with TEG®/ROTEM®-based monitoring, and our limited understanding of the complex coagulopathies that underlie PPH.

Owing to the lack of studies directly relating to PPH, much of the data covered in this review are necessarily extrapolated from other settings, such as trauma or cardiac surgery. However, not all massive haemorrhage is the same, and the haemostatic derangements seen in these settings are likely to differ from those in PPH. High-quality studies are needed to examine these differences. Current PPH management guidelines do not account for the altered baseline coagulation status in obstetric patients. Future studies should address the need for reference values and triggers for haemostatic therapy in patients with PPH. POC tests are more suitable in PPH due to their faster turnaround time. By improving awareness of the correct application and interpretation of these tests, we can make better use of their emergency diagnostic capabilities and increase our understanding of the most appropriate haemostatic interventions for the management of obstetric bleeding. Data regarding the efficacy of haemostatic therapies in PPH are sparse. Studies of fibrinogen replacement therapies should be prioritized, as decreasing fibrinogen levels have been linked with PPH progression.

Declaration of interest

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