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, although alternative definitions have been used to describe PPH and its severity. 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. PPH also contributes significantly to maternal morbidity and is a major reason for intensive care admission and hysterectomy in the postpartum period. The causes of PPH are varied, and have been classified according to their underlying pathophysiology (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. Similar observations have been made during blood loss in trauma and major surgery.

The diversity of potential triggers makes the occurrence and severity of PPH difficult to predict. Many cases have no identifiable risk factor. 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...
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)]; [blood coagulation tests (MeSH)] and [postpartum hemorrhage (MeSH)]; [thrombelastography (MeSH)] and [blood coagulation (MeSH)]; [thrombelastography (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 complications, 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. 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, although the clinical significance of this is uncertain.

Haemostasis can be further influenced by anaemia and pre-eclampsia. Anaemia (haemoglobin <11 or 10.5 g dl$^{-1}$ in second trimester) affects ~20% of pregnant women worldwide and is associated with increased blood loss and likelihood of transfusion during delivery. Similarly, pre-eclampsia, which occurs in 0.4–2.8% of births, is associated with haemostatic abnormalities including thrombocytopenia and disseminated intravascular coagulopathy.

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. 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. 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.

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 and other settings. 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. Pre-procedural coagulation screening is therefore not generally recommended unless a complication associated with haemostatic impairment.
(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 pregnancy.
genital tract bleeding.\textsuperscript{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\textsuperscript{3} recommend maintaining PT and aPTT at $\leq 1.5$ times normal control values, platelet count at $\geq 50 \times 10^9$ litre$^{-1}$, and plasma fibrinogen at $\geq 1$ g litre$^{-1}$, identical to the recommendations for non-pregnant populations.\textsuperscript{17}

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.\textsuperscript{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.\textsuperscript{16, 15} However, another retrospective multicentre validation study demonstrated that PT $>1.5$ times normal may predict the need for advanced intervention to control PPH.\textsuperscript{8} Current guidelines recommend using PT and aPTT to guide fresh-frozen plasma (FFP) transfusion,\textsuperscript{7} 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,\textsuperscript{19} 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.\textsuperscript{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\textsuperscript{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 $<100 \times 10^9$ litre$^{-1}$ on admission to the labour ward was associated with increased PPH incidence in some women.\textsuperscript{15} A large retrospective analysis also demonstrated an inverse association between lowest platelet count and red blood cell (RBC) transfusion requirement.\textsuperscript{12} Subsequent prospective studies showed that at diagnosis of haemorrhage, platelet counts in PPH patients were significantly lower than those in healthy parturients,\textsuperscript{13} and that decreasing platelet count during obstetric bleeding may be associated with progression to severe PPH.\textsuperscript{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 $\geq 100 \times 10^9$ litre$^{-1}$ during ongoing PPH,\textsuperscript{15} but a prospective analysis of 30 patients with coagulopathy after abruptio placentae had platelet counts $\sim 90 \times 10^9$ litre$^{-1}$ at 0 and 4 h postpartum.\textsuperscript{48} However, current PPH guidelines recommend platelet transfusion only when the platelet count decreases below $50 \times 10^9$ litre$^{-1}$, although in other massive haemorrhage guidelines, a trigger of $75 \times 10^9$ litre$^{-1}$ is recommended.\textsuperscript{69} 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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{13} and reporting lowest recorded fibrinogen level within 24 h of delivery as the variable best correlated with volume of blood-loss.\textsuperscript{12} These data cast doubt upon current guidelines which suggest fibrinogen replacement when plasma levels decrease below 1 g litre$^{-1}$ and suggest a trigger of $\geq 2$ g litre$^{-1}$ may be more appropriate.\textsuperscript{14} Coagulopathic bleeding has also been observed in abruptio placentae, despite postpartum fibrinogen levels of 1.5–1.6 g litre$^{-1}$.\textsuperscript{48} Studies evaluating the current approaches are urgently required.\textsuperscript{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.\textsuperscript{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$^{-1}$.\textsuperscript{1, 51, 52} The evidence supporting this change included prospective data in an obstetric setting.\textsuperscript{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.\textsuperscript{51–55} 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,\textsuperscript{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. In the UK and USA, cryoprecipitate provides a more concentrated alternative, although fibrinogen content remains variable (3.5–30 g litre⁻¹). Cryoprecipitate has been withdrawn in many European countries due to safety concerns, 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. Fibrinogen concentrate is highly purified, and since the introduction of pasteurization steps in the manufacturing process, no incidents of pathogen transmission have been reported. 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. 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). 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. 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 recommend that FFP is administered irrespective of PT/αPTT. UK PPH guidelines have similar recommendations. Haemostatic intervention is guided either by formulaic replacement or by clinical judgement alone. Such practice may result in unnecessary and/or inappropriate transfusions. 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%. 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 thrombelastometry. 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. 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.

Several TEG®/ROTEM®-based tests have been described, with different activators and inhibitors used to make these tests sensitive to various aspects of haemostasis. 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. 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. 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. Selection of appropriate TEG®/ROTEM®-based tests, combined with awareness of
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® and ROTEM® can be used to demonstrate hypercoagulability in pregnancy. A case-matched study involving...
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. This corroborated an earlier study, which demonstrated significant differences in TEG®-recorded $r$, $k$, $\alpha'$, 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

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

| 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 |
| | $\alpha'$ (alpha angle) | $\alpha'$ (alpha angle) | Tangent of the slope between amplitude at 2 mm and at 20 mm |
| Clot strength/quality | MA (maximum amplitude) | MCF (maximum clot firmness) | Clot amplitude reached 5, 10, 15 min after CT has passed |
| | $G$ (clot rigidity) | MCE (maximum clot elasticity) | Maximum amplitude reached |
| 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 |
|-------------------|--------------------|---------------|
| (reagent name) | (reagent name) | (reagent name) |
| Test | Activator | Additional modifications* | Test | Activator | Additional modifications* |
| RapidTEG (RapidTEG™ reagent) | Kaolin + tissue factor | — | — | — | — |
| FF/functional fibrinogen test (FF reagent) | Tissue factor | Abciximab | FIBTEM (fib-tem®) | Recombinant tissue factor | Cytochalasin D |
| | — | — | APTEM (ap-tem®) | Recombinant tissue factor | Aprotinin |
| Kaolin-activated TEG®+heparinase | Kaolin | Heparinase | HEPTEM (hep-tem®) | Ellagic acid | Heparinase |
| Kaolin-activated TEG® | Kaolin | — | INTEM (in-tem®) | Ellagic acid | — |
| — | — | — | EXTEM (ex-tem®) | Recombinant tissue factor | — |
| NATEM (star-tem®) | None added | — | — | — | — |

Sensitive test measuring coagulation without added activator, although not applicable in emergencies due to slow clotting times

Defects in the intrinsic pathway of coagulation activation; heparin anticoagulation

Defects in the extrinsic pathway of coagulation activation; prothrombin complex deficiency; platelet deficiency (in parallel with FIBTEM)

Defects in the intrinsic and extrinsic pathways of coagulation activation; more rapid assessment than using kaolin activation alone

Fibrin-based clot defects, fibrin/fibrinogen deficiency

Hyperfibrinolysis (in comparison with EXTEM)

Heparin/protamine imbalance (in conjunction with INTEM or kaolin-activated TEG)
section with spinal anaesthesia. 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. These data again highlight the importance of establishing reference ranges for TEG®/ROTEM®-recordable parameters in pregnant women. 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. 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.

Evidence supporting the value of thrombelastography for treatment of acute obstetric haemorrhage has been available in German-language publications for more than 30 yr. Elsewhere, case-studies have reported successful use of TEG®/ROTEM® to guide intraoperative haemostatic treatment. 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. 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.

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

Fibrino(gen)olytic activity is generally diminished during pregnancy but may increase postpartum, peaking around 3 h postdelivery. Hyperfibrinolysis is also associated with complications including shock and amniotic fluid embolism. 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.

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. 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. Excessive fibrinolysis may be evident from prematurely declining clot amplitudes in INTEM/EXTEM tests or kaolin- or celite-activated TEG®.

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. A recent meta-analysis examined the use of tranexamic acid for controlling haemorrhage after Caesarean section or vaginal delivery. 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.

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

Plasma fibrinogen levels correlate with the incidence and severity of PPH. ROTEM®-based measurements of fibrin-based clot quality (FIBTEM MCF) have been shown to correlate with laboratory fibrinogen measurements, 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 MCF without abnormal bleeding, 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. The FIBTEM test enables diagnosis of fibrinogen deficiency within 10 min (including sample acquisition and setup) of
Haemostatic monitoring and management of PPH

drawing blood, whereas laboratory measurements typically take 30–50 min. 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. Dilution with a gelatin and HES combination has less impact on ROTEM®-recorded parameters than HES alone.

A TEG®-based FF test, based on the same principle as the FIBTEM test (Table 2), uses abciximab to inhibit platelet activation. Abciximab has been added to celite-activated TEG® assays to distinguish between platelet and fibrin(ogen) components of clotting in pregnant patients, to demonstrate elevated fibrin-based clot formation after in vitro fertilization, and to dissect the effects of contaminating blood with amniotic fluid in vitro. 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 use of TEG®-based monoaalysis. Promotional material for the TEG® device (http://www.haemonetics.com/site/pdf/AnalysisTree-Koalin.pdf) describes a haemostatic algorithm guided by kaolin-activated TEG® alone, in which each parameter indicates a different therapeutic intervention, and similar practice has been reported. 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. For example, αx is used to guide fibrinogen replacement and MA to guide platelet transfusion. Although αx has been described as dependent upon the rate of fibrin accumulation, and representative of fibrinogen concentration, thrombus formation in kaolin-activated tests also involves platelets. Therefore, αx may be primarily dependent upon fibrinogen but may also indicate thrombocytopenia. Consistent with this, platelet count correlates strongly with αx and platelet transfusion elevates αx during PPH.

On current evidence, the most reliable approach for distinguishing fibrinogen deficiency from thrombocytopenia is parallel EXTEM and FIBTEM analysis. For this purpose, CT, CFT, and αx 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. 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. 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, 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.

**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). 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. 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. Thus, the FF assay produces consistently higher values than the FIBTEM assay, and could potentially overestimate fibrinogen 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. 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. 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
The authors have the following conflicts of interests to declare: C.S. has received travel support from Haemoscope Ltd (former manufacturer of TEG®), and speaker honoraria and/or research support from Tem International and CSL Behring. R.E.C. has received speaker honoraria from CSL Behring and Novo Nordisk and research support from Tem International. P.W.C. has received speaker honoraria from CSL Behring and Novo Nordisk and research support from Tem International.

Funding
Editorial assistance with manuscript preparation was provided by Meridian HealthComms, funded by CSL Behring. Funding to pay the Open Access publication charges for this article was provided by CSL Behring.

References
1 WHO guidelines for the management of postpartum haemorrhage and retained placenta. World Health Organization, 2009
2 Wise A, Clark V. Strategies to manage major obstetric haemorrhage. Curr Opin Anaesthesiol 2008; 21: 281–7
3 Arulkumaran S, Mavrides E, Penney GC. Prevention and management of postpartum haemorrhage. Royal College of Obstetricians and Gynaecologists Green-top Guideline 52, 2009
4 Combs BA, Murphy EL, Loros RK Jr. Factors associated with hemorrhage in cesarean deliveries. Obstet Gynecol 1991; 77: 77–82
5 Combs BA, Murphy EL, Loros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol 1991; 77: 69–76
6 Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case–control study. Br Med J 2001; 322: 1089–93
7 Dolea C, AbouZahr C, Stein C. Global burden of maternal haemorrhage in the year 2000. Geneva: Evidence and Information for Policy (EIP), World Health Organization, 2003. Available from http://www.who.int/healthinfo/statistics/bod_maternalhaemorrhage.pdf. Accessed June 2012
8 Gayet E, Resche-Rigon M, Morel O, et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Med 2011; 37: 1816–25
9 Zeeman GG. Obstetric critical care: a blueprint for improved outcomes. Crit Care Med 2006; 34: S208–14
10 Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A, Group M-B. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. BJOG 2005; 112: 89–96
11 Devine PC. Obstetric hemorrhage. Semin Perinatal 2009; 33: 76–81
12 de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth 2011; 20: 135–41
13 Huissoud C, Carrobin N, Audibert F, et al. Bedside assessment of fibrinoid level in postpartum haemorrhage by thrombelastometry. BJOG 2009; 116: 1097–102
14 Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007; 5: 266–73
15 Simon L, Santi TM, Sacquin P, Hamza J. Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implications. Br J Anaesth 1997; 78: 678–83
16 Dunbar NM, Chandler WL. Thrombin generation in trauma patients. Transfusion 2009; 49: 2652–60
17 Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995; 81: 360–5
18 Franchini M. Haemostasis and pregnancy. Thromb Haemost 2006; 95: 401–13
19 Pitkin RM, Witte DL. Platelet and leucocyte counts in pregnancy. J Am Med Assoc 1979; 242: 2696–8
20 Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. World Health Organization, 2001
21 Goonewardene M, Shehata M. Anaemia in pregnancy. Best Pract Res Clin Obstet Gynaecol 2012; 26: 3–24
22 Kavle JA, Stoltzfus RJ, Witter F, et al. Association between anaemia during pregnancy and blood loss at and after delivery among women with vaginal births in Pemba Island, Zanzibar, Tanzania. J Health Popul Nutr 2008; 26: 232–40
23 Dolea C, AbouZahr C. Global burden of hypertensive disorders of pregnancy in the year 2000. Geneva: Evidence and Information for Policy (EIP), World Health Organization, 2003. Available from http://www.who.int/healthinfo/statistics/bod_hypertensivedisordersofpregnancy.pdf. Accessed June 2012
24 Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. Hypertens Pregnancy 2003; 22: 203–12
25 Orlikowski CE, Rocke DA. Coagulation monitoring in the obstetric patient. Int Anesthesiol Clin 1994; 32: 173–91
26 Wong CA, Liu S, Glassenberg R. Comparison of thrombelastography with common coagulation tests in pre eclamptic and healthy parturients. Reg Anesth 1995; 20: 521–7
27 Kozek-Langenecker SA. Perioperative coagulation monitoring. Best Pract Res Clin Anaesthesiol 2010; 24: 27–40
67 Liumbruno GM, Bennardello F, Lattanzio A, et al. Recommendations for the transfusion management of patients in the perioperative period. II. The intra-operative period. Blood Transfus 2011; 9: 189–217
68 Adam S, Karger R, Kretschmer V. Influence of different hydroxyethyl starch (HES) formulations on fibrinogen measurement in HES-diluted plasma. Clin Appl Thromb Hemost 2010; 16: 454–60
69 Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sørensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 2010; 50: 2571–6
70 Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA. Comparison of thrombelastography with common coagulation tests. Thromb Haemost 1981; 46: 752–6
71 Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology 2011; 115: 1179–91
72 Ogawa S, Szlam F, Chen EP, et al. A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 2011; 52: 14–22
73 Schöchl H, Cotton B, Inaba K, et al. FIBTEM provides early prediction of massive transfusion in trauma. Crit Care 2011; 15: R265
74 Schöchl H, Nienaber U, Maegle M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011; 15: R83
75 Cookley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 2006; 20: 548–53
76 Larsen OH, Fenger-Eriksen C, Christiansen K, Ingerslev J, Sørensen B. Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology 2011; 115: 294–302
77 Michelson AD, Frelinger AL III, Furman MI. Current options in platelet function testing. Am J Cardiol 2006; 98: 4–10N
78 Schroeder V, Chatterjee T, Kohler HP. Influence of blood coagulation factor XIII and FXIII Val34Leu on plasma clot formation measured by thrombelastography. Thromb Res 2001; 104: 467–74
79 Sørensen B, Johansen P, Christiansen K, Woelke M, Ingerslev J. Whole blood coagulation thromboelastographic profiles employing minimal tissue factor activation. J Thromb Haemost 2003; 1: 551–8
80 Thai J, Reynolds EJ, Natalia N, et al. Comparison between Rapid-TEG® and conventional thromboelastography in cardiac surgery patients. Br J Anaesth 2011; 106: 605–6
81 Johansson PI, Stensballe J. Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study. Vox Sang 2009; 96: 111–8
82 Spalding GJ, Hartrumpf M, Sierig T, et al. Cost reduction of perioperative coagulation management in cardiac surgery: value of ‘bedside’ thrombelastography (ROTEM). Eur J Cardiothorac Surg 2007; 31: 1052–7
83 Steer PL, Krantz HB. Thromboelastography and Sonoclot analysis in the healthy parturient. J Clin Anesth 1993; 5: 419–24
84 Macafee B, Campbell JP, Ashpole K, et al. Reference ranges for thromboelastography (TEG®) and traditional coagulation tests in term parturients undergoing caesarean section under spinal anaesthesia. Anaesthesia 2012; 67: 741–7
85 Saha P, Stott D, Atalla R. Haemostatic changes in the puerperium ‘6 weeks postpartum’ (HIP Study)—implication for maternal thromboembolism. BJOG 2009; 116: 1602–12
86 Polak F, Kolnikova I, Lips M, et al. New recommendations for thromboelastography reference ranges for pregnant women. Thromb Res 2011; 128: e14–7
87 Oudghiri M, Keita H, Kouamou E, et al. Reference values for rotation thromboelastometry (ROTEM®) parameters following non-haemorrhagic deliveries. Correlations with standard haemostasis parameters. Thromb Haemost 2011; 106: 176–8
88 McIntosh C, James AH. Obstetric hemorrhage. J Thromb Haemost 2011; 9: 1441–51
89 Riedel H, Burket W. Determination of blood coagulation in acute obstetrical and gynecologic hemorhages by means of the Hellige direct writing thrombelastograph. Fortschr Med 1978; 96: 1800–3
90 Annecke T, Geisenberger T, Kurzl R, Penning R, Heinbl B. Algorithm-based coagulation management of catastrophic anhemitic fluid embolism. Blood Coagul Fibrinolysis 2010; 21: 95–100
91 Clements A, Jindal S, Morris C, et al. Expanding perfusion across disciplines: the use of thrombelastography technology to reduce risk in an obstetrics patient with Gray Platelet Syndrome—a case study. Perfusion 2011; 26: 181–4
92 Monte S, Lyons G. Peripartum management of a patient with Glanzmann’s thrombasthenia using Thrombelastograph. Br J Anaesth 2002; 88: 734–8
93 Przkora R, Euliano TY, Roussos-Ross K, Zumberg M, Robicsek SA. Labor and delivery in a patient with hemophilia B. Int J Obstet Anesth 2011; 20: 250–3
94 Rajpal G, Pomerantz JM, Ragni MV, Waters JH, Vallejo MC. The use of thromboelastography for the peripartum management of a patient with platelet storage pool disorder. Int J Obstet Anesth 2011; 20: 173–7
95 Sharma SK, Vera RL, Steggal WC, Whitten CW. Management of a postpartum coagulopathy using thrombelastography. J Clin Anesth 1997; 9: 243–7
96 Steer PL, Finley BE, Blumenthal LA. Abruptio placentae and disseminated intravascular coagulation: use of thrombelastography and sonoclot analysis. Int J Obstet Anesth 1994; 3: 229–33
97 Whitta RK, Cox DJ, Mallett SV. Thrombelastography reveals two causes of haemorrhage in HELLP syndrome. Br J Anaesth 1995; 74: 464–8
98 Ak K, Isibir CS, Tetik S, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg 2009; 24: 404–10
99 Girdauskas E, Kempfert J, Kunze T, et al. Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. J Thorac Cardiovasc Surg 2010; 140: 1117–24 e2
100 Maki M, Soga K, Seki H. Fibrinolytic activity during pregnancy. Tokohu J Exp Med 1980; 132: 349–54
101 Gerbasi FR, Bottoms S, Farag A, Mamment EF. Changes in hemostasis activity during delivery and the immediate postpartum period. Am J Obstet Gynecol 1990; 162: 1158–63
102 Lang T, von Depka M. Possibilities and limitations of thrombelastometry-/-graphy. Hamostaseologie 2006; 26: 520–9
103 Nordenholz KE, Naviaux NW, Stegelmeier K, et al. Pulmonary embolism risk assessment screening tools: the interrater reliability of their criteria. Am J Emerg Med 2007; 25: 285–90
104 Adler Ma SC, Brindle W, Burton G, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis. J Cardiathorac Vasc Anesth 2011; 25: 26–35

105 Sukey M, Alshyrdy S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br 2011; 93: 39–46

106 Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother 2011; 12: 503–16

107 Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2010: CD007872

108 Ansari T, Riar W. The effect of haemodilution with 6% hydroxyethyl starch (130/0.4) on haemostasis in pregnancy: an in-vitro assessment using thromboelastometry. Eur J Anaesthesiol 2010; 27: 304–5

109 Fries D, Innerhofer P, Klingler A, et al. The effect of the combined administration of colloid and lactated Ringer's solution on the coagulation system: an in vitro study using thrombelastograph coagulation analysis (ROTEG). Anesth Analg 2002; 94: 1280–7

110 Solomon C, Sørensen B, Hochleitner G, et al. Comparison of whole blood fibrin-based clot tests in thromboelastography and thromboelastometry. Anesth Analg 2012; 114: 721–30

111 Gottumukkala VN, Sharma SK, Philip J. Assessing platelet and fibrinogen contribution to clot strength using modified thromboelastography in pregnant women. Anesth Analg 1999; 89: 1453–5

112 Harnett MJ, Bhavani-Shankar K, Datta S, Tsen LC. In-vitro assessment using thrombelastometry. Eur J Anaesthesiol 2010; 27: 304–5

113 Harnett MJ, Bhavani-Shankar K, Datta S, Tsen LC. In vitro fertilization-induced alterations in coagulation and fibrinolysis as measured by thromboelastography. Anesth Analg 2002; 95: 1063–6

114 Butwick A, Ting V, Ralls LA, Harter S, Riley E. The association between thromboelastographic parameters and total estimated blood loss in patients undergoing elective cesarean delivery. Anesth Analg 2011; 112: 1041–7

115 Chan KL, Summerhayes RG, Ignjatovic V, Horton SB, Monagle PT. Reference values for kaolin-activated thromboelastography in healthy children. Anesth Analg 2007; 105: 1610–3

116 White H, Zollinger C, Jones M, Bird R. Can Thromboelastography performed on kaolin-activated citrated samples from critically ill patients provide stable and consistent parameters? Int J Lab Hematol 2010; 32: 167–73

117 Cohen E, Navickas IA. Method and apparatus for hemostasis and blood management. Office USPaT. USA: Haemoscope Corporation, 2002

118 Thrombelastography test—any value for assessing hemostasis during surgery? California Blood Bank Society. Available from http://www.cbbsweb.org/enf/2001/teg_bleeding.html. Accessed January 2012

119 Allen SR, Kashuk JL. Unanswered questions in the use of blood component therapy in trauma. Scand J Trauma Resusc Emerg Med 2011; 19: 5

120 Dries DJ. The contemporary role of blood products and components used in trauma resuscitation. Scand J Trauma Resusc Emerg Med 2010; 18: 63

121 NHS UK. Blood and Transplant Matters. Summer 2010, issue 31

122 Koster A, Kukuccka M, Fischer T, Hetzer R, Kuppe H. Evaluation of post-cardiopulmonary bypass coagulation disorders by differential diagnosis with a multichannel modified thrombelastogram: a pilot investigation. J Extra Corpor Technol 2001; 33: 153–8

123 Jeger V, Zimmermann H, Exadaktylos AK. Can RapidTEG accelerate the search for coagulopathies in the patient with multiple injuries? J Trauma 2009; 66: 1253–7

124 Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thrombelastography. Anesth Analg 1987; 66: 856–63

125 Roeloffzen WW, Kluin-Nelemans HC, Mulder AB, de Wolf JT. Thrombocytopenia affects plasmatic coagulation as measured by thromboelastography. Blood Coagul Fibrinolysis 2010; 21: 389–97

126 Lang T, Bauters A, Braun SL, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005; 16: 301–10

127 Nielsen VG, Geary BT, Baird MS. Evaluation of the contribution of platelets to clot strength by thromboelastography in rabbits: the role of tissue factor and cytochalasin D. Anesth Analg 2000; 91: 35–9

128 Mousa SA, Forsythe MS. Comparison of the effect of different platelet GP IIb/IIIa antagonists on the dynamics of platelet/fibrin-mediated clot strength induced using thromboelastography. Thromb Res 2001; 104: 49–56

129 Venema LF, Post JW, Hendriks HG, et al. An assessment of clinical interchangeability of TEG and RoTEM thromboelastographic variables in cardiac surgical patients. Anesth Analg 2010; 111: 339–44

130 Lang T, Toller W, Gut M, et al. Different effects of abciximab and cytochalasin D on clot strength in thrombelastography. J Thromb Haemost 2004; 2: 147–53