Review Article

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The Utilization of Viscoelastic Testing to Guide Blood Component Therapy and Adjunctive Hemostatic Therapy for Postpartum Hemorrhage: A Narrative Review

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Abstract

This narrative review discusses the history of the pathophysiologic principles and utilization of point-of-care (POC) viscoelastic tests (VETs) in the definition and treatment of postpartum hemorrhage (PPH). This paper addresses the epidemiology of PPH, describes the hemostatic changes that occur in pregnancy and in PPH, and demonstrates the utilization of viscoelastic testing in the identification and treatment of patients with PPH. Additionally, a description of rotational thromboelastometry (ROTEM) and thromboelastography (TEG), the two most commonly used VETs, is detailed in this paper. VETs have only recently been used to guide blood component therapy (BCT) in trauma in the last decade. The recent increased utilization of VETs to guide BCT in PPH is following a similar trend with a delay of ten years. In a similar fashion to the trauma literature, which expanded greatly within this last decade, the literature concerning the use of VETs in PPH has also increased in the last few years. However, because of differing pathophysiologies associated with the coagulopathy of PPH verses traumatic-induced coagulopathy (TIC), utilization of VETs has been more refined and focused on the VETs' capacity to determine low fibrinogen and to guide the utilization of blood components and prohemostatic agents. The identification and treatment of PPH depends on clinical parameters, conventional coagulation tests (CCTs) including Clauss fibrinogen, and VETs. Successful treatment of PPH will no doubt include utilization of all three strategies with an increasing utilization of VETs in the future.

Keywords: Viscoelastic test, Thromboelastography, TEG, Rotational thromboelastometry, ROTEM, Postpartum hemorrhage, Obstetric, Blood component therapy, Resuscitation, Prohemostatic agents

Abbreviations: PPH: Postpartum Hemorrhage; VET: Viscoelastic Test; TEG: Thromboelastography; ROTEM: Rotational Thromboelastometry; BCT: Blood Component Therapy; CCT: Conventional Coagulation Test; PT: Prothrombin Time; aPTT: activated Partial Thromboplastin Time; POC: Point-of-Care; RBC: Red Blood Cell; AFE: Amniotic Fluid Embolism; DIC: Disseminated Intravascular Coagulation; R: Reaction time; K: Kinetics; MA: Maximum Amplitude; LY30/60: Lysis at 30/60 minutes; CT: Clot Time; CFT: Clot Formation Time; MCF: Maximum Clot Firmness; CA5/10: Clot Amplitude at

5/10 minutes; CLI30/60: Clot Lysis Index at 30/60 minutes; ML: Maximum Lysis; r-TEG: rapid Thromboelastography; EXTEM: Extrinsic Activator Thromboelastometry; FIBTEM: Fibrinogen Thromboelastometry; FFP: Fresh Frozen Plasma; TXA: Tranexamic Acid; RCT: Randomized Control Trial; TIC: Trauma-induced Coagulopathy; CRASH-2: Clinical Randomization of an Antifibrinolytic in Severe Hemorrhage; WOMAN: World Maternal Antifibrinolytic; MOH: Massive Obstetric Hemorrhage

Introduction

Epidemiology, definition, and utilization of VETs in PPH

Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide [1-3], and the incidence has increased in many countries despite improvements in obstetric protocols to prevent and treat severe hemorrhage [4-7]. Specific intervention points and management strategies to define and treat coagulopathy associated with PPH are not uniform [8]. Recently, the viscoelastic tests (VETs) thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been used to guide blood component therapy (BCT) and prohemostatic agents in PPH [9,10]. The nascent literature on the utilization of VETs in obstetric hemorrhage stems from guidelines and algorithms adapted from cardiothoracic surgery and trauma resuscitation [8,11,12].

Research and management of PPH is thwarted by differing definitions and classifications of this clinical entity. In trauma, the initiation of bleeding is clear-cut. The definition of severe bleeding is also determined by vital signs, base deficits, and initial blood product utilization; therefore, resuscitation strategies are more straightforward. However, the definition and triggers of PPH severity are heterogeneous. For example, the most current American College of Obstetricians and Gynecologists Practice Bulletin defines PPH as either ≥ 1000 mL total blood loss or the signs and symptoms of hypotension within the first 24 hours postpartum, regardless of delivery method [13]. Many organizations consider "secondary" or "late" PPH a clinical diagnosis between 24 hours to 12 weeks postpartum [13,14]. Alternative definitions include blood loss of >500 mL post vaginal delivery or >1000 mL post cesarean delivery [8,13,15]. PPH is sometimes classified as moderate, 1000-2000 mL, or severe, ≥ 2000 mL [16]. PPH may also be defined as a fall in hemoglobin by 4 g, the need for transfusion of greater than 4 units, or the need for massive transfusion [9]. A major limitation for predicting PPH and its treatment is the inconsistent use of definitions making direct comparisons impossible [14,17]. A recent multidisciplinary consensus statement—developed by the Network of the Advancement of Patient

Blood Management, Haemostasis and Thrombosis—provided level 1B evidence guidelines recommending assessment of hemostatic competence in severe PPH. The consensus statement, additionally, advocates for the use of conventional coagulation tests (CCTs) and/or VETs to guide goal-directed use of hemostatic blood components and prohemostatic agents [18]. The CCTs that are used are prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and Clauss fibrinogen concentration; VETs include ROTEM and TEG [18].

Hemostatic changes in pregnancy

Hemostatic alterations that occur during pregnancy favor both coagulation and anticoagulation; however, the net effect is a hypercoagulable state near term. Figure 1 describes the changes in coagulation factors and proteins that occur near term in a normal pregnancy [19,20]. This hypercoagulable state of late pregnancy is reflected by altered CCTs and VET parameters [12,20-22]. A shorter PT/aPTT is noted as a reflection of the increased levels of procoagulant factors. Simultaneously, there is an increase in clot integrity as measured by the ROTEM/TEG parameters which will be discussed below [12,20,23-25].

Assessment and treatment strategies of severe PPH

Hemostasis in PPH is assessed by three different strategies. The first strategy is clinical observation paired with empirical blood product replacement. The second strategy is the assessment of the CCTs: PT/aPTT, Clauss fibrinogen, and platelet count. The third strategy is POC viscoelastic testing [10]. To date, however, it has been noted that there is no high level data suggesting that any single strategy is superior and that all three may be used simultaneously [10].

Clinical observation—such as risk factor assessment by vital signs, physical examination of the vulva, vagina, cervix, uterus, and perineum, quantification of blood loss, and use of multiple doses of uterotonics—is the first pillar of the identification of PPH [13]. The disadvantage of clinical observation alone is exemplified by the substantial variation of clinical parameters that have been used to define PPH as well as the heterogeneous

Figure 1: Hemostatic changes that occur during pregnancy can be seen above with preponderance of changes that can represent a hypercoagulable state.

Factors follow the format of "F" followed by a roman numeral, FII: Factor II, PAI-1: plasma activator inhibitor-1, TAFI: thrombin activatable fibrinolysis activator, TAT: thrombin antithrombin, tPA: tissue plasminogen activator, VWF: Von Willebrand Factor [20].

nature of the timespan during which PPH evolves [13,15].

The second pillar has traditionally been the CCTs which have been utilized to gauge the level of hemostatic competence during PPH. The advantage of the CCTs is the high level of reproducibility and quality control [20,26]. However, PT/aPTT has a very low sensitivity to determine the presence of coagulopathy. The failure of PT/aPTT to accurately assess coagulopathy has been well studied in trauma [27]. Clauss fibrinogen has recently been used to supplement the data, particularly for PPH [28-30].

VETs are point-of-care (POC) tests that are increasingly being used in various coagulopathic populations, including in the obstetric population. VETs are whole blood tests that analyze and graph the viscoelastic properties of a blood clot spanning from clot formation to fibrinolysis. This provides VETs with an advantage over other coagulation tests because it assesses the cumulative contribution of platelets, plasma clotting factors, and red blood cells (RBCs) throughout the entirety of the clotting cycle. Analysis of these tracings allows for rapid treatment during peripartum and postpartum management of PPH. Rapid turnaround time is essential, particularly in cases involving amniotic fluid embolism (AFE) because they are characterized by a sudden hemodynamic collapse. This hemodynamic collapse in AFE is caused by thromboplastin-mediated massive capillary leak, disseminated intravascular coagulation (DIC), renal failure, and potential cardiorespiratory collapse [16,20,31,32]. Use of a POC test, such as a VET, may provide early warning regarding hemodynamic collapse from coagulopathic etiologies such as DIC. POC assays can be used for the determination of coagulation factor

deficiencies, fibrinogen dysfunction, platelet impairment, and elevated fibrinolysis [24,27,33,34]. Because these tests are POC, they can be followed serially.

Principles of ROTEM/TEG

TEG: TEG was first employed on whole blood samples to demonstrate hemostatic function. Citrated whole blood is added to a cup which rotates independently of a pin submerged into the blood. As the blood begins to coagulate, a "clot bridge" is generated between the rotating cup and the stationary pin which places torque on the pin which is transmitted to a transducer to synthesize a TEG tracing. The normal or physiologic TEG tracing is shown in Figure 2. The TEG tracing parameters are abbreviated as follows: the time to reach an amplitude of 2 mm is reaction time (R), the time to create a certain level of clot is kinetics or clot formation (K), the rate of clot formation is the α -angle, the maximum clot strength is maximum amplitude (MA), and the percent decrease in maximum amplitude after 30/60 minutes is lysis at 30/60 minutes (LY30/60) [35-42].

ROTEM: The main difference between TEG and ROTEM is that the ROTEM has a stationary cup with a rotating pin (Figure 2). While both machines take the same measurements and create the same curve, the ROTEM uses different nomenclature: clot time (CT) matches TEG's R, clot formation time (CFT) matches TEG's K, and maximum clot firmness (MCF) matches TEG's MA. The clot amplitude (CA5/10) is the amplitude reached 5/10 minutes after CT and is exclusive to ROTEM. The clot lysis index (CLI30/60) does not exactly match TEG's LY30/60. The CLI30/60 refers to residual clot firmness at 30/60 minutes after CT, described as a percentage of MCF.

Specific comparison of the times to CLI30/60 and LY30/60 are beyond the scope of this paper. Finally, the maximum lysis (ML) is the lysis detected as a percentage of the MCF during the run time and at the end of the run [37,38].

Tissue factor initiates coagulation for the Rapid TEG (r-TEG) and for the extrinsic activator thromboelastometry (EXTEM) for ROTEM. The r-TEG and EXTEM are more commonly used to assess hypo-coagulopathic patients. Also, kaolin is used to activate the TEG in whom a hypercoagulable state is suspected as well [39-42].

A recent refinement of ROTEM that has been applied most successfully to PPH is the fibrinogen thromboelastometry (FIBTEM) which represents a whole blood POC assay for fibrinogen levels within a channel and cup where platelet function is inhibited and the hemostatic integrity of fibrin without platelet contribution is measured. The curve is similar in shape to the ROTEM tracing but more narrow and recent literature has determined specific thresholds that predict early coagulopathy in PPH with greater reliability than other ROTEM parameters [43,44].

Figure 2: Depiction of a normal or physiologic ROTEM/TEG tracing. As illustrated on the left-hand side of the figure, citrated blood is placed into a warmed cup into which a pin descends. In ROTEM, the pin oscillates within the stationary cup. As the clot forms in the cup, a force is transduced to the pin which deflects the pin and results in a characteristically shovel-shaped graph. In comparison, for a TEG, the cup oscillates, and the pin remains stationary. As the clot forms, the torque on the pin registers as the characteristic shovel-shaped graph. ROTEM and TEG use equivalent but independently labeled parameters. ROTEM parameters are labeled in red and TEG parameters are labeled in blue. Clot Time (CT) and Reaction Time (R) refer to the amount of time required for the amplitude to grow to 2 mm during clot formation. These correlate with the PT/aPTT for the CCTs. Clot Formation Time (CFT) and Kinetics (K) refer to the amount of time required for the amplitude to grow to 20 mm and are a measure of clot formation kinetics and initial clot strength. α -angle, a parameter that is used by both ROTEM and TEG, is the angle formed between the horizontal axis and the sloped line formed between 0 mm and 20 mm of amplitude and measures the rate of clot formation. The CFT, K, and α -angle broadly correlate with fibrinogen level. Clot Amplitude (CA5/10) is amplitude reached at 5/10 minutes after CT. Maximum Clot Firmness (MCF) and Maximum Amplitude (MA) refer to the maximum amplitude reached and are a measure of the maximum clot strength. MCF and MA correlate with maximum clot retraction and are generally a reflection of crosslinking of fibrin with platelets. Clot Lysis Index (CLI30/60) is the residual clot remaining 30/60 minutes after CT measured as a percentage of MCF. Maximum Lysis (ML) is the maximum lysis at the end of the run measured as a percentage of MCF. Lysis at 30/60 minutes (LY30/60) is the percent decrease in amplitude 30/60 minutes after achieving MA. CLI30/60, ML, and LY30/60 are measures of fibrinolysis [36-38].

Analysis of ROTEM/TEG: Using the tracing values from ROTEM/TEG, therapeutic measures can be tailored to a patient's specific needs and adjusted accordingly. Fresh frozen plasma (FFP) is used for a long CT/R in hyperfibrinolysis, cryoprecipitate or fibrinogen concentrate is used for a decreased α -angle, platelets are used for a narrow MCF/MA, and tranexamic acid (TXA) is used for an increased CLI30/60 and LY30/60 [44,45]. Adding the CT/R, CFT/K, α -angle, and MCF/MA values together results in the coagulation index which has been suggested as a possible way to evaluate a patient's thrombotic or hemorrhagic risk [46,47].

The use of ROTEM/TEG to guide BCT in patients with PPH

ROTEM and TEG, are gaining popularity in the area of guiding BCT and diagnosing a coagulopathy associated with PPH. Even though the first paper describing the utilization of VETs to diagnose and treat PPH was published more than 30 years ago, ROTEM and TEG have only recently been studied with increasing numbers in the diagnosis and treatment of PPH [8,9,24,38,43].

VETs are advantageous because of their ability to allow adequate resuscitation while reversing the patient's coagulopathy. VETs also assist practitioners avoid volume overload which may exacerbate a coagulopathy, particularly in a patient with shock [4,8,9,16,18,20,32,38,48].

The recommendations for predicting or treating PPH based on ROTEM and TEG parameters vary significantly due to the lack of concrete studies using VETs. The sections below outline the various heterogeneous recommendations that have emerged using VET-directable blood components and prohemostatic agents.

Fibrinogen: With the advent of rapid POC VETs for fibrinogen, it has been appreciated that high levels of fibrinogen are required to establish a return to hemostatic competence in severe PPH. Specifically, it has been recently recommended that Clauss fibrinogen levels approaching 400 mg/dL are required to reverse the coagulopathy of PPH [49].

To maintain hemostasis during PPH, Collis et al. suggest a Clauss fibrinogen level of 300 mg/dL which corresponds to a FIBTEM of ≥ 16 mm. At these levels, it is assumed that coagulation parameters will be normal and that no blood components other than blood cells will need to be administered [16].

FFP and cryoprecipitate: Traditionally, FFP has been used to correct fibrinogen deficiencies in PPH and for volume resuscitation. Recent editorials are suggesting the early administration of cryoprecipitate for PPH rather than FFP because FFP contains lower concentrations of fibrinogen compared to cryoprecipitate and also causes hemodilution [20,50-55]. The reasoning behind this shift in protocol is that the quantity of fibrinogen in a single unit of FFP is about half of the median concentration of fibrinogen in a patient in the third trimester of pregnancy [49]. The utilization of fibrinogen concentrate and/or cryoprecipitate diminishes the likelihood of volume overload as compared to the utilization of FFP. Rather than broad administration of FFP, the targeted administration of specific coagulation factors, such as fibrinogen, can be accomplished. In Europe, cryoprecipitate has been withdrawn due to safety concerns whereas soluble fibrinogen concentrate has been adopted widely. In the United States, cryoprecipitate is the standard mode of replacing fibrinogen [52,53]. Numerous studies out of Europe indicate that the use of fibrinogen concentrate can result in a decrease of blood product use [9,56-58]. However, it is important to note that the efficacy of fibrinogen concentrate use still needs to be investigated more thoroughly via randomized control trials (RCTs) [8,9,43,56].

Fibrinogen, FFP, and POC testing: POC testing with VETs allows for bedside monitoring and for goal-directed approaches to coagulation management. This POC data allows obstetricians to not only focus on resuscitation with the volume of FFP and RBCs, but also to assess the adequacy of fibrinogen levels in patients with PPH. Recently, it has been suggested that FFP be administered to replenish volume after patients have had their fibrinogen levels brought up to adequate levels greater than at least 200 mg/dL who also have a prolonged clotting time based on EXTEM [9]. Implicit in this strategy is the importance of fibrinogen in the PPH patient. In comparison to trauma-induced coagulopathy (TIC), inadequate levels of fibrinogen play the primary role in PPH coagulopathy [59]. This strategy elevates FIBTEM CA5 and EXTEM CA5 (which are both ROTEM parameters measured five minutes after CT) to the first two ROTEM parameters that should be analyzed in the PPH patient. When identifying and treating PPH, other aspects of coagulopathy such as volume depletion can be managed with FFP rather than crystalloid. However, these studies do not measure platelet function, while studies concerning TIC have demonstrated the importance for monitoring platelet function [8,60].

Platelet function: The function of platelets in PPH is not well studied in the literature [61]. Furthermore, traditional platelet analysis measures platelet counts (typically 50,000-75,000 μ L) rather than platelet function as is measured by ROTEM/TEG. Platelet dysfunction determined by a prolonged CFT or a low α -angle has been noted [8]. However, a few recent studies have utilized ROTEM/TEG with platelet mapping to demonstrate platelet-sparing strategies that allow for lower platelet levels in bleeding associated with PPH. It has been proposed that the TEG-aggregation test platelet mapping assay and other parallel assessments of platelet function with POC assays could improve diagnosis, although their role in PPH has yet to be determined [20]. In particular a very recent development in peripartum management has been the utilization of the EXTEM CA10, which represents the entire extrinsic pathway, and the FIBTEM CA10, which represents the same pathway but without the contribution by platelets [62]. This particular study has proposed that EXTEM CA10 and FIBTEM CA10 can supplement other parameters of ROTEM, such as the MCF [62]. A proposed parameter that defines platelet functionality has been called the PLTEM which is calculated as the difference between the EXTEM CA10 and the FIBTEM CA10 [62].

Prohemostatic therapy: Utilization of prohemostatic therapy has been of great interest since the Clinical Randomization of an Antifibrinolytic in Severe Hemorrhage (CRASH-2) Trial in 2010 and World Maternal

Antifibrinolytic (WOMAN) Trial in 2016. These large well-designed RCTs suggest that the utilization of TXA within 3 hours of bleeding, either from trauma or PPH, improved mortality. Subsequent studies have suggested that knowledge gaps in the CRASH-2 Trial and problems in defining PPH have made these trials a source of considerable and interesting discussion [7,63-77]. For the other prohemostatic agents, the utilization of soluble fibrinogen in Europe and cryoprecipitate in the United States is guided by VETs and Clauss fibrinogen [10]. Prothrombin Complex Concentrate has been used as a prohemostatic supplement for hemostatic resuscitation, and its use can also be directed by VETs [10]. Recent papers have suggested that prohemostatic agents, such as desmopressin and Factor VIIa, can be guided by VETs and used for prohemostatic therapy in select patients with PPH. However, most recently, it has been suggested that VET parameters of fibrinolysis should not be relied upon in order to deliver TXA to patients with PPH [9,10,43,44,61]. The heterogeneous nature of recommendations regarding the utilization of prohemostatic therapy in PPH represents a function of the nascent state of the application of the VETs in peripartum and postpartum management. The future of VETs to monitor BCT and prohemostatic therapy in PPH may well lead to a concept of precision-based medicine, whereby therapy is guided by a microfluidic assay determined by a hemostatic phenotype [66,69,78,79].

Figure 3: Comparison of the timelines of major publications for the utilization of VETs in trauma and surgery and in obstetrics.

Table 1: A chronology of the literature since 2002 describing VET findings in patients with PPH.

Study	Test	Findings
Monte et al., 2002 [80] (Case Report)	TEG	TEG was used to monitor and guide the treatment of a 31-year-old patient with Glanzmann's thrombasthenia who inevitably developed PPH following an emergency c-section. TEG results demonstrate an ↑R time, indicating delayed clot initiation, and a ↑α-angle and ↑MA, indicating reduced clot strength. TEG can be used as a predictor to diagnose and treat future hemorrhaging.
Hunt et al., 2005 [81] (Review)	ROTEM/ TEG	ROTEM/TEG is underused. It has been shown to reduce inappropriate transfusions.
Huissoud et al., 2009 [82] (Case Series; n = 91)	ROTEM/ FIBTEM	PPH correlates with ↓fibrinogen, ↓CA5, ↓CA15, ↓MCF, and ↑CT as demonstrated by ROTEM/FIBTEM. Allows for early detection of coagulopathy disorders.
Rajpal et al., 2011 [83] (Case Report)	TEG	TEG was used to monitor and guide treatment of a 26-year-old patient with platelet storage pool disorder who developed PPH; patient presented with ↑R, ↓α-angle, and ↓MA. PT/aPTT test can take 30 to 60 minutes, meanwhile, TEG with its increased sensitivity and decreased callback time allows for a more up to date results.
Armstrong et al., 2011 [12] (Case Series; n = 120)	ROTEM	ROTEM quickly identified hypercoagulability in women before pregnancy, with ↓CT, ↓CFT, and ↑MCF.
de Lange et al., 2012 [24] (Review)	ROTEM/ FIBTEM/ TEG	Patients at fibrinogen levels of ≤400 mg/dL and FIBTEM MCF ≤19 mm are prone to developing PPH while patients at ≤200 mg/dL and ≤19 mm are susceptible to a higher risk of PPH.
Solomon et al., 2012 [20] (Review)	ROTEM/ FIBTEM/ TEG	ROTEM/FIBTEM has been used to monitor and guide treatment of patients presenting with PPH. Patients with PPH have ↓fibrinogen, ↑CT, ↓CA5, ↓CA15, and ↓MCF. Literature concerning the use of TEG to treat PPH is limited, but TEG has heightened reactivity letting it narrow down the many triggers of PPH.
Karlsson et al., 2014 [34] (Case Series; n = 94)	TEG	Massive obstetric hemorrhage (MOH) patients had ↓R, ↑K, ↓α-angle, ↓MA, and ↓LY30. MOH patients had a decline of 36% in platelet count, 39% in fibrinogen, and 38% in antithrombin.
Collins et al., 2014 [30] (Case Series; n = 356)	ROTEM/ FIBTEM	FIBTEM is useful in predicting the progression of PPH as ↓fibrinogen levels are associated with more severe PPH.
Mallaiah et al., 2015 [56] (Case Series; n = 93)	ROTEM/ FIBTEM	Using fibrinogen concentrate in combination with RBCs lowered the overall cost of blood products used. Approximately 47% of patients had a normal MCF at 15 mm p<0.001. Correlations between FIBTEM MCF and CA5 values were observed. A correlation was also found between FIBTEM CA5 values and fibrinogen levels.
McNamara et al., 2015 [84] (Case Series; n=4)	ROTEM/ FIBTEM	Patients presenting with hypofibrinogenemia detected by FIBTEM with ↓fibrinogen, ↑CT, and ↓CA5 are at risk of developing severe PPH. Early detection of hypofibrinogenemia can prevent the development of severe PPH, and a ROTEM-guided administration of fibrinogen concentrate reduced the need for other blood products.
Pavord et al., 2015 [45] (Case Study)	TEG	27-year-old patient presented with ↓fibrinogen levels and developed PPH. TEG was used to monitor the patient throughout treatment. ↑R and ↑K indicated that there was a significantly reduced number of clotting factors, and the ↓α-angle and ↓MA indicated reduced clot strength.

Study	Test	Findings
Butwick et al., 2015 [85] (Review)	ROTEM/ TEG	Altered clot formation and lysis information, occurring in obstetric hemorrhage, can be obtained from ROTEM/TEG.
Collis et al., 2015 [16] (Review)	ROTEM/ TEG	A review of the literature concerning the use of ROTEM/TEG in the treatment and early detection of PPH found that studies have shown that the use of VET-guided administration of fibrinogen concentrate to treat PPH-related complications has reduced overall blood product usage and is useful in the early detection and treatment of PPH-related complications by guiding the administration of appropriate blood products.
Lockhart et al., 2015 [2] (Review)	ROTEM/ FIBTEM/ TEG	FIBTEM's ability to detect hypofibrinogenemia allows it to predict severe PPH. ROTEM and TEG can identify excessive fibrinolysis more rapidly than CCTs.
Mallaiah et al., 2015 [86] (Reply)	ROTEM	ROTEM allows for a reduction in costs of blood products. This reply asks how to improve on a return of salvaged blood as their unit yielded a 3% return while Dr. Ralph's unit, to which they are comparing against, yielded a 19% return in operative procedures.
Collins et al., 2016 [10] (Review)	ROTEM/ TEG	To monitor hemostasis during PPH, both VETs and PT/aPTT with Clauss fibrinogen are good options. VETs are better in cases of severe bleeding because they are faster but are not sensitive enough for lower severity cases.
Shreeve et al., 2016 [21] (Case Series; n=112)	TEG	As pregnancy duration increases, ↓K, ↑α-angle, ↑MA, ↓LY30, and ↓LY60.
Guasch et al., 2016 [87] (Review)	ROTEM/ FIBTEM	Severe PPH conditions: FIBTEM CA5 <7 mm, EXTEM CA5 <47 mm or FIBTEM CA5 <7-12 mm and EXTEM CA5 <47 mm, active bleeding.
Gehrie et al., 2016 [88] (Review)	ROTEM/ TEG	VETs provide results at the bedside in less time than CCTs and provide vital information for earlier intervention.
Hurwich et al., 2016 [33] (Case Study)	TEG	35-year-old Caucasian female survived birth of second child due to use of TEG values which led to goal-directed BCT rather than 1:1:1 ratio care.
Collins et al., 2017 [43] (Case Series; n=55)	ROTEM/ FIBTEM	FIBTEM-guided administration of PPH is feasible, but the study does not support nor negate the cost effectiveness. Early infusion of fibrinogen concentrate based on a FIBTEM CA5 of <15 mm did not significantly reduce blood loss.
Gillissen et al., 2018 [6] (Cohort Study; n=1312)	N/A	Of the women included in the study, those with low fibrinogen levels and prolonged aPTT developed severe PPH. The authors acknowledged that traditional assessments limit the amount of time to administer targeted hemostatic therapy, thus VETs may be more effective in the management of PPH.
Collins et al., 2018 [9] (Review)	ROTEM/ FIBTEM	A review of the literature concerning the use of VET-guided algorithms in the treatment of PPH confirmed that ↓fibrinogen (<200 mg/dL) and a FIBTEM ↓CA5 (<12 mm) were associated with progression to severe PPH. Correction of hypofibrinogenemia with fibrinogen concentrate at levels <200 mg/dL and 12 mm has been shown to be advantageous, but larger prospective trials are necessary to confirm this. Also presents the need for a large study establishing the effectiveness of early viscoelastic testing in conjunction with CCTs in the treatment and prevention of severe PPH.

Study	Test	Findings
Snegovskikh et al., 2018 [8] (Case Series; n=54)	ROTEM/ FIBTEM/ TEG	Patients treated with the guidance of VETs had lower received blood products, blood loss, occurrence of puerperal hysterectomy, rate of ICU admission, time hospitalized postpartum, and cost of hospitalization.
Peng et al., 2018 [89] (Review)	ROTEM/ TEG	Coagulation requires fibrinogen. VETs can detect fibrinogen deficiency and direct transfusion to aid in the coagulation process.
McNamara et al., 2019 [57] (Case Series; n=52)	ROTEM/ FIBTEM	FIBTEM CA5 ≤ 12 mm was used to define coagulopathy in pregnant patients; a ROTEM/FIBTEM algorithm was used to guide administration of fibrinogen concentrate in 52 women. The algorithm resulted in a statistically significant reduction in morbidity amongst patients presenting with low fibrinogen and severe PPH.
Toffaletti et al., 2019 [62] (Retrospective Study)	ROTEM	FIBTEM CA10 and EXTEM CA10 values can replace MCF results in patients with PPH.
Muñoz, 2019 [18] (Review)	ROTEM/ FIBTEM	Discourages preemptive fibrinogen supplementation. Suggests monitoring fibrinogen levels early in severe PPH to guide BCT with cryoprecipitate or fibrinogen concentrate at plasma fibrinogen level < 200 mg/dL or FIBTEM CA5 < 12 mm.
McNamara and Mallaiah, 2019 [58] (Review)	ROTEM/ FIBTEM	FIBTEM and ROTEM are useful in providing quick assessment of low fibrinogen levels which has been shown to be associated with the development of severe PPH; further RCTs are required to evaluate the effectiveness of ROTEM-guided administration of fibrinogen concentrate to treat hypofibrinogenemia.

Summary of literature concerning VETs and PPH:

In spite of the increasing frequency of PPH, defined triggers for initiating massive transfusion protocol are lacking. Part of the problem is that, by definition, PPH evolves over 24 hours, and “secondary PPH” evolves over an even longer time period. Additionally, the methods of quantifying blood loss during childbirth are often inaccurate and inconsistent with low inter-rater reliability. Further, relying on CCTs to predict the need for massive transfusion has been unreliable and they cannot offer POC guidance.

Hence, there has been a recent increase in the world's literature concerning the utilization of VETs to identify, anticipate, and guide BCT and prohemostatic therapy in PPH. Much of the literature concerning the application of VETs in guiding BCT in PPH has been derived from the trauma literature. In spite of the recent shift favoring the application of VETs to guide BCT in trauma resuscitation, the use of these VETs is far from uniform. Because adoption of VETs in the setting of PPH by the obstetrical community is in its nascent form, there has been a delay with significant increase in appearance of studies that describe utilization of these tests. Figure 3 and Table 1 provide a chronological description of significant papers covering the use of VETs for PPH resuscitation.

Conclusion

The management of patients with PPH is characterized by the heterogeneity of published parameters that define and guide treatment for PPH. The three pillars upon which identification and treatment of PPH are clinical prediction guidelines, CCTs, and viscoelastic testing. The coagulopathy associated with PPH is multifactorial and cannot be identified solely by CCTs. In particular, the literature has established a clear link between low fibrinogen and development of PPH; however, the lack of sensitivity and prolonged turnaround time of CCTs make it difficult to guide BCT in patients with low fibrinogen that are at risk of developing PPH [12,28,29]. The obstetrics literature has adopted much of its strategy for utilizing VETs to diagnose and treat PPH by referring to the trauma literature. The trauma literature has grown exponentially in the last decade as traumatologists have discovered the benefits of POC testing to identify coagulopathy and aid in goal-directed BCT and prohemostatic therapy necessary to treat and prevent TIC. The most recent literature has shown a much slower growth in the description of the utilization of VETs in obstetrics compared to trauma. The challenge for the obstetrics community is that there is a significant heterogeneity of the definition and pathophysiology of PPH. Unlike trauma and the subsequent TIC, which occur

in a matter of seconds to hours, PPH evolves over a longer period of time and therefore requires early recognition and treatment [10,13]. For example, the immediate coagulopathy associated with AFE is identified and treated in a completely different way than the less fulminant coagulopathy associated with the more common cause of severe PPH: uterine atony [20]. Nevertheless, these two examples demonstrate the need for an immediately available POC test that provides obstetricians with real-time data on developing coagulopathies. Therefore ROTEM/TEG will see growth of studies in this area of research and clinical practice that most likely will lead to refinement in the accuracy of prediction, identification, and treatment of PPH. This paper introduced early-adopters in obstetrics who recognize the value of VETs in PPH and recommendations from those early-adopters can serve as a roadmap for additional investigation and recommendations.

Much as in the early days of trauma literature, the first obstetrics papers described parameters for ROTEM and TEG that have been adopted by various practitioners and institutions. However, there are still no internationally

recognized values that allow for the uniform application of triggers for identifying severe PPH or for providing standardized goal-directed therapy for hemostasis in PPH. Progress is being made by instituting local standards with local experts such that VETs have been found useful and have been included in large studies demonstrating that VET goal-directed therapy, particularly in severely injured patients with high severity scores, translates into patient outcome benefits.

Review of obstetric-related publications reveals great variability in proposed VET thresholds for identifying patients with severe PPH. The agreed upon strategy has been to rely on clinical evaluation paired with empiric blood management, the CCTs including Clauss fibrinogen, and viscoelastic testing. By combining all three, the consensus is that patients can be more effectively identified and treated. Implicit in the literature is that the utilization of VETs in PPH is in a nascent state which is reminiscent of the utilization of the VETs to guide resuscitation of trauma more than a decade ago.

Figure 4 summarizes the most recent thought by

Figure 4: General algorithm utilizing Clauss fibrinogen levels, FIBTEM, and EXTEM to guide treatment of PPH [9].

leading experts regarding the utilization of ROTEM and fibrinogen levels to guide blood component therapy in PPH.

Declarations

Ethics approval and consent to participate

See note about IRB approval below.

Consent for publication

The authors have IRB approval for publications related to this area of research.

Availability of data and material

No original data for this review article.

Competing interests

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Authors' contributions

All authors participated in writing, reviewing, and approving of the entire manuscript as well as in the collection of bibliographies; SB, MW, SVL, RM, AG, and FS conceptualized the manuscript; FS, NZ, SP, SZ, AS, and AVT collected the literature for the formation of Table 1; DH, AVT, SZ, AS, and SP produced and formatted the figures; all authors reviewed the final manuscript and figures and approved the submission.

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