Obstetric hemorrhage remains the leading cause of maternal morbidity and mortality worldwide. Thromboelastography and rotational thromboelastometry are laboratory methods of assessing the kinetics of blood clot formation through real-time measurement of viscoelastic clot strength and may aid in management of severe hemorrhage. Although first described more than 70 years ago, viscoelastic testing devices are now available that allow for rapid point-of-care use of this technology to aid in real-time management of blood product replacement in cases of severe hemorrhage. These devices can be used to visually estimate multiple facets of hemostasis—coagulation, platelet function, and fibrinolysis—within 10–20 minutes. They have been used successfully in cardiac surgery, trauma, and liver transplantation and have potential for use in management of obstetric hemorrhage. Goals with their use include targeted transfusion of blood and its components for specific coagulation deficiencies. To date, however, published experiences with the use of these viscoelastic tests for obstetric hemorrhage have been limited. Because of the increasing use of the point-of-care tests by anesthesiologists, surgeons, and intensivists, the purpose of this report is to familiarize obstetricians with the technology involved and its use in severe hemorrhage complicating pregnancy.

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Postpartum hemorrhage continues to be the leading preventable cause of maternal morbidity and death worldwide. In the United States, 10.7% of all pregnancy-related deaths during 2014–2017 were associated with postpartum hemorrhage. Owing to the significant contribution of postpartum hemorrhage to maternal morbidity and mortality, national organizations, including the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, now recommend a multidisciplinary approach to hemorrhage prevention and management. This approach includes safety bundles, stage-based protocols, and standardized checklists for treatment of maternal hemorrhage at the earliest stage possible. Existing efforts emphasize the need for early recognition and timely resuscitation, escalation of care, and, if necessary, deployment of a massive transfusion protocol to prevent hypoperfusion that can lead to multi-organ dysfunction and coagulopathy.

Laboratory assessment is an essential component of the management of obstetric patients with postpartum hemorrhage. This is especially true in the setting of large-volume blood loss requiring massive transfusion. The standard approach to laboratory testing has been the use of serial hematologic indices ordered emergently during the hemorrhage and transfusion therapy. Given the time-sensitive nature of responding to such life-threatening events, deployment of blood products often occurs before these studies are available owing to the time it takes to get the blood sample to the laboratory and for such testing to be performed.

Given the need for more timely information and a better understanding of the consequences of
coagulopathy, there has been a renewed interest in the availability of point-of-care hematologic testing in obstetric patients. Two viscoelastic methods, thromboelastography and rotational thromboelastometry, simultaneously measure multiple facets of hemostasis—coagulation, platelet function, and fibrinolysis—within 10–20 minutes. The goal with their use is to provide targeted transfusion of blood and blood components for specific coagulation deficiencies. These testing platforms have been employed successfully for cardiac surgery, trauma management, and liver transplantation. Although their application for management of obstetric hemorrhage has been championed, there have been only a few studies examining whether blood product utilization and outcomes are improved with their use in obstetrics.

The purpose of this report is to describe thromboelastography and rotational thromboelastometry technology, including their reporting parameters. We will also review the current evidence and limitations for use of such tests among obstetric patients in the setting of postpartum hemorrhage. Our goal is to provide context for this technology given its adoption in other specialties.

NORMAL AND ABNORMAL COAGULATION IN PREGNANCY

An understanding of coagulation—in both normal hemostasis and pathologic coagulopathies—is paramount in managing obstetric hemorrhage and the use of viscoelastic testing. By definition, coagulation is the process by which thrombin is activated and soluble plasma fibrinogen is converted into insoluble fibrin that polymerizes to form a clot. In the past, the coagulation process was described as a “cascade” or “waterfall.” It is now proposed that coagulation is normally initiated through tissue factor exposure and activation through the classic extrinsic pathway but with critically important amplification through elements of the classic intrinsic pathway.

In this simplistic scheme, coagulation is primarily initiated by tissue factor that forms complexes with factor VII or VIIa. In brief, the development of tissue factor–FVIIa complexes ultimately generates activated factor X to initiate clotting, and the previously labeled “intrinsic” pathway is responsible for the amplification of this process (Fig. 1). The product of this process is fibrin formation, which is then counterbalanced by the fibrinolytic system—dedicated to the removal of excess fibrin. Also shown in Figure 1 is the fibrinolytic system with plasminogen activated by tissue factor. This process is augmented by thrombin to produce plasmin, which lyses fibrin and fibrinogen. Viscoelastic testing evaluates both the timing and strength of clot formation, as well as fibrinolysis.

During pregnancy, there is augmented production of most procoagulants (Table 1). Importantly, fibrinogen concentration increases approximately 50% above values for nonpregnant individuals; during late pregnancy, it ranges from 375 to 620 mg/dL. At the same time, there is a reduction in levels of natural anticoagulants, including protein C and S and tissue-factor pathway inhibitor-1, as well as an acquired resistance to protein C. These changes that occur in pregnancy affect the interpretation of viscoelastic testing parameters.

The standard approach for laboratory testing for coagulopathy in pregnant women is to obtain five tests: hematocrit, platelet count, international normalized ratio–prothrombin time, activated partial thromboplastin time, and fibrinogen. These tests can be used to guide product administration and have been incorporated into various scoring systems for disseminated intravascular coagulation; however, the clinical utility of these tests in the midst of an active obstetric hemorrhage is debatable. It is problematic that these tests are plasma-based and ignore the dynamic interaction among platelets, procoagulants, and fibrinolytic factors, as well as inhibitors. Thus, they measure clot initiation but do not necessarily assess the quality and strength of the clot. Because these standard tests are plasma-based, centrifugation to remove cellular elements is necessary and turnaround times of 30–60 minutes render results irrelevant during a rapidly evolving hemorrhage. These challenges are eliminated with thromboelastography and rotational thromboelastometry viscoelastic testing as adjunct point-of-care tests during an obstetric hemorrhage, because they can be used to quickly assess multiple facets of hemostasis, including coagulation, platelet function, and fibrinolysis.

VISCOELASTIC TECHNOLOGY

Thromboelastography was initially described by Hertel in 1948. A later modification of the technology was termed rotational thromboelastometry. Both methods measure similar functions of clot formation kinetics by real-time assessment of the viscoelastic clot strength in whole blood. This is done by a visual graphic assessment of clot function under low shear conditions similar to those in the vena cava and below shear stress conditions characteristic of those in venules, large veins, and arteries.
Thromboelastography and rotational thromboelastometry devices assess clot kinetics by computerized measurement and display of the amount of a continuously applied rotational force transmitted to an electromechanical transduction center by the developing clot. A schematic composite of these devices is shown in Figure 2. An electronic tracing called the temogram is then visualized on a screen. Although the information gathered by both techniques is identical, their nomenclature of clot kinetics is different (Table 2). At our hospital, we use the rotational thromboelastometry device; thus, to avoid confusion, all descriptions and nomenclature of clot kinetics that follow are those obtained using rotational thromboelastometry technology.

**Rotational Thromboelastometry Technique**

A whole blood specimen is collected in a vacutainer containing sodium citrate as an anticoagulant. The blood is then placed in a cup made of acrylic polymer, and calcium chloride is added to reverse the citrate anticoagulant. The device is then activated, and the pin begins to oscillate. As the clot forms, the factors listed in Table 2 are measured and graphically depicted and recorded as the temogram. Figure 3 is an illustration of the composition of a clot as ascertained by rotational thromboelastometry.

In the initial phase, the blood is still liquid and offers no resistance to the rotating pin. As shown in Figure 3, this is represented as a flat line—the clotting time. As clotting proceeds, thrombin is generated and clot formation begins; this is represented by an increase in amplitude. With thrombus formation, platelets and fibrin interact and the clot gains strength—depicted as the clot function time and alpha angle (α). Next, the amplitude of the clot graph is measured at time points designated as A10, A15, and A20. In the event of hypercoagulability, such as with normal pregnancy, the time to clot initiation is shorter, the alpha angle is increased, and the maximum amplitude is higher.

The final interaction of platelets and fibrin constitutes the maximum clot firmness. After clotting, some fibrinolysis begins as part of normal physiology, but it usually is not apparent with the 30-minute rotational thromboelastometry assay. If abnormal fibrinolysis is present, the clot undergoes lysis sooner, as depicted in Figure 3, in which clot lysis is evident by 30 minutes (LY30) and complete by 60 minutes.

**Rotational Thromboelastometry Assays**

There are several rotational thromboelastometry assays that are used to test clotting of the specimen. These assays are performed in parallel to clearly outline coagulation abnormalities. For an individual patient, each assay is performed after the addition of various analytes. These are defined as follows:

- INTEM—intrinsic clotting; clot activation is stimulated by reagents with phospholipid and ellagic acid.

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This assay provides information similar to that of the activated partial thromboplastin time. It is most often prolonged with heparin therapy, and treatment is with fresh-frozen plasma.

- **EXTEM**—extrinsic clotting: activated by recombinant tissue factor. This assay provides information similar to that of the prothrombin time. Prolongation suggests a deficiency of coagulation factors in the extrinsic pathway, for example, with vitamin K antagonists.

- **FIBTEM**—fibrinogen assay: cytochalasin D is added to inhibit polymerization of actin to block platelet contribution to clot formation. This assay is used to identify hypofibrinogenemia, and it is used most often in obstetric hemorrhage.

- **APTEM**—aprotinin fibrinolysis: aprotinin inhibits fibrinolysis, and it is used in conjunction with tissue factor and compared with EXTEM analysis to assess fibrinolysis.

### Table 1. Normal Nonpregnant and Third-Trimester Reference Ranges for Procoagulants

<table>
<thead>
<tr>
<th>Function</th>
<th>Nonpregnant Adult</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III, functional (%)</td>
<td>70–130</td>
<td>82–116</td>
</tr>
<tr>
<td>D-dimer (micrograms/mL)</td>
<td>0.22–0.74</td>
<td>0.13–1.7</td>
</tr>
<tr>
<td>Factor V (%)</td>
<td>50–150</td>
<td>60–88</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>50–150</td>
<td>149–211</td>
</tr>
<tr>
<td>Factor VIII (%)</td>
<td>50–150</td>
<td>143–353</td>
</tr>
<tr>
<td>Factor IX (%)</td>
<td>50–150</td>
<td>164–235</td>
</tr>
<tr>
<td>Factor XI (%)</td>
<td>50–150</td>
<td>65–123</td>
</tr>
<tr>
<td>Factor XII (%)</td>
<td>50–150</td>
<td>129–194</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>233–496</td>
<td>373–619</td>
</tr>
<tr>
<td>Homocysteine (micromoles/L)</td>
<td>4.4–10.8</td>
<td>3.2–21.4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.9–1.04</td>
<td>0.80–0.94</td>
</tr>
<tr>
<td>Partial thromboplastin time, activated (sec)</td>
<td>26.3–39.4</td>
<td>24.7–35.0</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>12.7–15.4</td>
<td>9.6–12.9</td>
</tr>
<tr>
<td>Protein C, functional (%)</td>
<td>70–130</td>
<td>67–135</td>
</tr>
<tr>
<td>Protein S, total (%)</td>
<td>70–140</td>
<td>33–101</td>
</tr>
<tr>
<td>Protein S, free (%)</td>
<td>70–140</td>
<td>20–65</td>
</tr>
<tr>
<td>Protein S, functional activity (%)</td>
<td>65–140</td>
<td>16–42</td>
</tr>
<tr>
<td>Tissue plasminogen activator (ng/mL)</td>
<td>1.6–13</td>
<td>3.3–9.2</td>
</tr>
<tr>
<td>Tissue plasminogen activator inhibitor-1 (ng/mL)</td>
<td>4–43</td>
<td>67–92</td>
</tr>
<tr>
<td>von Willebrand factor (%)</td>
<td>75–125</td>
<td>121–260</td>
</tr>
</tbody>
</table>

Data compiled from References 14–16.

### Table 2. Terminology Used in Thromboelastography and Rotational Thromboelastometry

<table>
<thead>
<tr>
<th>Function</th>
<th>Definition Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time</td>
<td>R (reaction time) CT (clotting time)</td>
</tr>
<tr>
<td>Clot kinetics</td>
<td>K (kinetics) CFT (clot formation time)</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>α (alpha) Estimates rapidity of clot formation; prolongation suggests platelet dysfunction or deficiency, fibrinogen deficiency, or both; shortening may indicate hypercoagulability</td>
</tr>
<tr>
<td>Clot strength</td>
<td>MA (maximum amplitude) MCF (maximum clot firmness)</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>CL30, CL60 LY30, LY60 Indicates clot lysis at time X in minutes, eg, LY30, LY60, and possible need for antifibrinolytic agents</td>
</tr>
</tbody>
</table>

TEG, thromboelastography; ROTEM, rotational thromboelastometry.
One perceived drawback was that Nelson et al. At this time, we continue to support application of massive transfusion protocols in response to obstetric hemorrhage.

There have been few studies evaluating outcomes related to obstetric hemorrhage when using viscoelastic rotational thromboelastometry result–guided transfusion of blood products.\(^{28,29}\) One perceived drawback was that these point-of-care studies had different reference values than what should be used for pregnant women. In a study of 132 obstetric patients undergoing elective cesarean delivery, rotational thromboelastometry reference ranges for uncomplicated pregnancies were noted to have higher amplitudes and shorter clotting times compared with these values in nonpregnant patients.\(^ {24}\) Specifically, compared with nonpregnant women, the EXTEM clotting time was shorter, the FIBTEM maximum clot firmness amplitude was higher, and the INTEM and EXTEM amplitudes were higher.\(^ {24}\) These investigators also showed that women in active labor had higher amplitudes for clot firmness and faster clot formation than nonlaboring women.\(^ {25}\) Although these data illustrate the protective hyperfibrinogenemia of pregnancy, they do not appear to be otherwise clinically significant for accurate rotational thromboelastometry interpretation when evaluating patients for immediate fibrinogen replacement.

There have also been studies examining the role of FIBTEM and plasma fibrinogen levels to predict progression of postpartum hemorrhage to quantities exceeding 2,500 mL or the number of blood products transfused.\(^ {28}\) Women with a low FIBTEM A5 amplitude were reported to be more likely to have a postpartum hemorrhage greater than 2,500 mL and to be transfused with more units of blood. In addition, prolonged bleeding was reported in patients with low FIBTEM amplitudes and low fibrinogen levels. To evaluate thresholds of rotational thromboelastometry values warranting clinical response, in the OBS-2 trial, Collins and colleagues\(^ {29}\) quantified the FIBTEM A5 level at which transfusion of fibrinogen concentrate improved outcomes in women with postpartum hemorrhage. Use of a FIBTEM A5 value of 15 mm or less to trigger fibrinogen transfusion did not improve outcomes in postpartum hemorrhage. Prespecified subgroup analysis showed that, when FIBTEM A5 is greater than 12 mm, fibrinogen replacement is not required. These findings have led some to conclude FIBTEM A5 may be valuable as an early identifier of women who can benefit from fibrinogen replacement at the onset of postpartum hemorrhage. In another study, patients with severe postpartum hemorrhage managed with a point-of-care viscoelastic test had fewer transfusions of red blood cells, fresh frozen

Fig. 2. Schematic of the thromboelastography or rotational thromboelastometry devices. The sensor pin is immersed in 0.36 mL of blood, and the pin oscillates 4–5˚ every 5 seconds. Subsequent rotation of the pin is inversely related to the changes in viscoelastic clot strength, which are transmitted to an electromechanical transducer. The image sensor system is connected to the data processing unit. LED, light-emitting diode.


- HEPTEM—heparin neutralization: heparinase is added to neutralize unfractionated heparin and used with INTEM reagent and compared with INTEM analysis to assess heparin effects on clotting. Without heparinase, unfractionated heparin-treated samples will result in a flat line. This assay is used principally in patients given unfractionated heparin while undergoing cardiopulmonary bypass.\(^ {23}\)

Of these assays, the most commonly used in obstetrics are estimating the plasma fibrinogen content and detecting accelerated fibrinolysis. Importantly, these tests are not a substitute for quantitative measurement of plasma fibrinogen concentration. Shown in Figure 4 are examples of temograms that depict a normal clotting profile and some of the pathologic states. With accelerated fibrinolysis, abnormal values may prompt consideration for treatment with tranexamic acid or epsilon-aminocaproic acid to inhibit plasminogen activators.\(^ {11}\)

**USE IN MANAGEMENT OF BLOOD PRODUCT TRANSFUSION**

On some obstetric services, severe postpartum hemorrhage is treated with fixed-ratio blood component transfusions, and a predetermined ratio of red blood cells, fresh frozen plasma, platelets, and fibrinogen are transfused.\(^ {26}\) Because point-of-care viscoelastic tests have successfully replaced these fixed transfusion protocols for management of hemorrhage in cardiac surgery, trauma, and liver transplantation, their use has now been recommended for obstetric hemorrhage as well. That said, application of this technology for obstetric hemorrhage needs further study.\(^ {7,8,23,27}\) At this time, we continue to support application of massive transfusion protocols in response to obstetric hemorrhage.
plasma, and platelets and lower rates of postoperative intensive care unit admission. Finally, rotational thromboelastometry–guided algorithms for coagulopathy treatment in obstetric hemorrhage have been reported to reduce morbidity due to transfusion-associated circulatory overload. Well-conducted prospective studies are still needed to examine whether the use of thromboelastography or rotational thromboelastometry improves outcomes in the setting of obstetric hemorrhage.

Serious causes of obstetric hemorrhage are placental abruption and postpartum hemorrhage due to uterine atony, placenta accreta spectrum disorder, and ruptured uterus. Examples of rotational thromboelastometry results are shown for some of these obstetric complications in Figure 5A and B and Figure 6.

**Advantages**

Using this point-of-care testing modality can facilitate determining whether hemorrhage is due to surgical or coagulopathic bleeding. With a quick turnaround time, the results can be applied real-time in clinical situations. If coagulation test results are abnormal, the correct blood products can be given early and limit unnecessary transfusion of other blood products. The other advantages of point-of-care testing in other fields include shorter hospital stays, lower costs, and reduced need for re-operation. Finally, rotational thromboelastometry analysis allows for the evaluation of several coagulation pathways simultaneously using multiple chambers.

**Limitations**

Viscoelastic testing has several limitations. Most recommend that baseline testing begins at the onset of hemorrhage. Importantly, however, if massive transfusion protocol has been deployed, rotational thromboelastometry testing should not be measured during rapid hemorrhage with ongoing blood and component replacement. These tests are more useful when active bleeding and resuscitation have been paused. At that time, they can be used to direct transfusions of blood components and antifibrinolytic agents on an as-needed basis.

Another drawback is that the vascular endothelium, which plays a significant role in hemostasis, is not assessed by standard viscoelastic tests. Disorders of primary hemostasis cannot be detected owing to the addition of activators to viscoelastic assays bypassing primary hemostasis. Current testing is also insufficient at detecting low-grade hyperfibrinolysis.
These point-of-care tests also cannot detect some coagulation disorders, such as von Willebrand disease and hemophilia. Viscoelastic assays lack sensitivity to antiplatelet drugs and cannot detect platelet dysfunction. Viscoelastic testing is also limited by incomplete inhibition of platelet aggregation in fibrinogen-based assays affecting the interpreted results. For example, incomplete platelet inhibition can influence maximum clot firmness of fibrinogen polymerization assays. When addressing the correlation between different tests to evaluate clotting and need for blood product replacement, viscoelastic testing is good in general, but no fixed conversion factors are available to compare rotational thromboelastometry results directly with Clauss fibrinogen assays.

There are no standardized reference ranges for viscoelastic testing in pregnancy. Patient
demographics, regional variation, trimester of pregnancy, and prolongation of labor can affect reference values. Different devices have specific ranges for "normal," and standardized hospital-specific reference ranges need to be established. Performance by personnel who are not properly trained often leads to incorrect interpretation of the temograms. Quality control of the viscoelastic devices, device maintenance, and trained personnel required to run the test may prove cost prohibitive for some birth settings.

CONCLUSIONS

Viscoelastic point-of-care testing has been reported to be useful in management of severe hemorrhage encountered with cardiac surgery, trauma, and liver transplantation. Such testing is now being used by anesthesiologists and intensivists for postpartum hemorrhage. Two of these devices—thromboelastography and rotational thromboelastometry—are currently available for this purpose. At this time, published experience with these tests in the obstetric setting is limited, and we find that application is best suited for hemorrhage cases after control of active, ongoing bleeding. Although evidence for point-of-care coagulation testing is mounting, prior reports have appeared in journals of laboratory science or anesthesia, and management of severe postpartum hemorrhage requires a multispecialty team including obstetricians, anesthetists, intensivists, and hematologists. Although these point-of-care test show promise for obstetric hemorrhage, more experience is needed before they are widely adopted, given the limited published studies available and limitations noted. If the technology is deployed, a comprehensive understanding of the utility and application is necessary, as well as availability of appropriately trained personnel. We look forward to additional published evidence in obstetric patients for using this unique hematologic point-of-care test as an opportunity to reduce maternal morbidity and tests mortality due to obstetric hemorrhage.

REFERENCES

Point-of-Care Viscoelastic Tests


CME FOR THE CLINICAL EXPERT SERIES

Learning Objectives for “Point-of-Care Viscoelastic Tests in the Management of Obstetric Hemorrhage”

After completing this continuing education activity, you will be able to:

• Describe rotational thromboelastometry and thromboelastography point-of-care viscoelastic tests;
• Discuss the information provided by real-time measurement of viscoelastic clot strength; and
• Outline ways that this form of testing can aid in clinical decision making in the face of obstetric hemorrhage.

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