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Emerging Technology for Early Detection and Management of Postpartum Hemorrhage to Prevent Morbidity

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Title: Emerging Technology for Early Detection and Management of Postpartum Hemorrhage to Prevent Morbidity

Short Title: New Technology for PPH

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With regard to potential conflicts of interest:

- Dr. Lord has no financial conflicts of interest to disclose. Dr. Lord is involved in research on the AccuFlow sensor but has no financial relationship with the makers of that device. The AccuFlow sensor is discussed in this manuscript alongside its major competitors.
- Dr. Calderon has no conflicts of interest to disclose.
- Dr. Ahmadzia's research makes use of a ROTEM delta analyzer which is on loan from the device manufacturer, Instrumentation Laboratory. She does not receive any direct funding from Instrumentation Laboratory, nor are they involved in any way in the design or conduct of her research. ROTEM is discussed in this manuscript alongside its major commercial competitor (TEG), with equal time spent in discussion of both products. Dr. Ahmadzia also participated in consulting work for Hemosonics on one occasion in the past. No devices produced or designed by Hemosonics are discussed in this manuscript.
- Dr. Pacheco is part of the medical consultant board of Coagulant Therapeutics. No products produced or designed by Coagulant Therapeutics are discussed in this manuscript.

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Condensation: Emerging sensor and laboratory technology have the potential to improve early detection of hemorrhage and to facilitate targeted blood product transfusion.

AJOG at a Glance:

A. New technologies to detect and quantify postpartum hemorrhage can be classified into three categories: quantification of external blood loss, non-invasive measurement of serum hemoglobin, and detection of maternal physiologic compensation to hemorrhage. Devices in each category show promise but are not yet accurate enough for routine clinical use for the detection or management of postpartum hemorrhage.
B. Among patients with severe postpartum hemorrhage, targeted transfusion is associated with better outcomes than fixed-ratio transfusion.
C. Viscoelastic hemostasis assays (VHAs) such as TEG and ROTEM provide objective data on coagulation status at the point of care in as little as five minutes and can be used to guide targeted transfusion.
D. VHA-guided management of severe postpartum hemorrhage is associated with improved outcomes and decreased cost.

Keywords: postpartum hemorrhage, TEG, ROTEM, thromboelastometry, thromboelastography, viscoelastic hemostasis assays, postpartum hemorrhage detection, compensatory reserve

Abstract:

Despite advances in hemorrhage detection and management, postpartum hemorrhage remains the single leading cause of maternal death worldwide. Within the United States, hemorrhage is the leading cause of maternal death on the day of delivery and within the first week postpartum. Blood transfusion following hemorrhage represents a large proportion of severe maternal morbidity during and after delivery. Blood loss during delivery has historically been assessed visually by inspecting soiled pads, linens, and laparotomy sponges. These methods underestimate the volume of blood loss by as much as 40%, becoming increasingly inaccurate as blood loss increases. Young, healthy obstetric patients compensate for blood loss via peripheral vasoconstriction, maintaining heart rate and blood pressure in a normal range until over one liter of blood has been lost. A significant decrease in blood pressure along with marked tachycardia (>120bpm) may not be seen until 30-40% of blood volume has been lost, or 2-2.6L in a healthy term pregnant patient, after which the patient may rapidly decompensate. In resource-poor settings especially, the narrow window between the emergence of significant vital sign abnormalities and clinical decompensation may prove catastrophic. Once hemorrhage is detected, decisions regarding blood product transfusion are routinely made based on inaccurate estimates of blood loss, placing patients at risk of under-resuscitation (increasing the risk of hemorrhagic shock and end-organ damage) or over over-resuscitation (increasing the risk of transfusion reaction, fluid overload, and alloimmunization). We will review novel technologies which have emerged to assist both in the early and accurate detection of postpartum hemorrhage, and in decisions regarding blood product transfusion.

MAIN TEXT:

The scope of the problem

Postpartum hemorrhage remains the single leading cause of maternal death worldwide.[1] In the United States, obstetric hemorrhage is the primary cause of approximately 11% of maternal deaths overall, and is the leading cause of maternal death on the day of delivery and in the first week postpartum.[2,3] Severe hemorrhage of 1500mL or greater occurs in 0.4% of deliveries,[4] and is life-threatening in approximately 0.1% of deliveries.[5] Blood product transfusion is a major contributor to maternal morbidity.[6] Young, healthy patients compensate for hemorrhage via peripheral vasoconstriction; when volume loss is profound, the resulting hypoperfusion can lead to multiorgan failure, hemorrhagic shock, and pituitary necrosis.[7]

EARLY DETECTION OF POSTPARTUM HEMORRHAGE

The importance of early detection

While hemorrhage remains a leading cause of maternal death, 70% of maternal deaths from hemorrhage appear to be preventable.[8] Early hemorrhage detection, accurate quantification of blood loss, and early intervention are critical to improve maternal outcomes[9] -- coagulopathy is most likely when the diagnosis of postpartum hemorrhage is delayed or the volume of blood loss is underestimated.[10] Protocols have been developed to improve early recognition of postpartum hemorrhage and prioritize early transfusion to prevent end-organ damage and coagulopathy, but most continue to rely on visual estimation and/or changes in heart rate and blood pressure.[11–14]

The need for new tools for early detection

Blood loss at delivery or during surgery is routinely estimated visually by an obstetrician, midwife, obstetric nurse, or anesthesiologist. These estimates correlate with transfusion, perhaps because the decision to transfuse is often based on clinician estimates of cumulative blood loss. However, such estimates are only weakly correlated with changes in hematocrit,[15] often underestimating blood loss by at least 30%.[16–20] As blood loss increases, visual estimation becomes increasingly inaccurate.[17] Obstetricians, anesthesiologists, and obstetric nurses presented with conical drapes containing known volumes of blood consistently underestimated the amount of blood in each drape. With volumes of one liter or less they underestimated by less than 20%, but when the blood volume reached two liters the clinicians underestimated by 41%, or 830mL.[17] Nurses, obstetricians, and anesthesiologists were equally inaccurate, and years of training and experience appeared to have no effect.[17] Thus it appears that underestimation is most pronounced in cases of severe hemorrhage, when estimation of blood loss is most critical in planning interventions. Despite the established inaccuracy of visual estimation, this remains the most common method to estimate blood loss.[21]

New methods to measure external blood loss

Acknowledging the inaccuracy of visual estimation, new technologies have been developed to quantify blood loss. One such technology is the Triton system, which uses an Apple iPad with proprietary software to estimate the amount of blood in laparotomy sponges. Blood soaked laparotomy sponges are presented to the iPad camera one at a

time and the software calculates the amount of hemoglobin contained in each sponge.[22] A proprietary suction cannister with a calibration mark has been introduced for use with this system. A staff member enters the volume of fluid in the suction canister into the Triton software. The iPad is used to capture an image of the fluid in the suction canister and of a calibration marker. The app calculates the hemoglobin concentration of the fluid, the total amount of hemoglobin in the canister, and, by dividing by the patent's serum hemoglobin, the volume of blood lost.[23] Unfortunately, the Triton system's estimates of blood loss at cesarean do not correlate well with changes in hemoglobin (r= 0.26 and r= 0.29 in two studies),[24,25] and implementation of Triton for blood loss estimation at cesarean does not appear to impact rates of blood transfusion or length of stay.[26]

Non-invasive measurement of intravascular hemoglobin

Another approach, popularized my Masimo Corporation (Irvine, CA), uses a device similar to a fingertip pulse oximeter to provide continuous non-invasive estimates of serum hemoglobin, earning this technology the abbreviation SpHb (analogous to SpO2). These devices emit several wavelengths of light, measure the light returning to the sensors, and use this information to estimate hemoglobin concentration.[27] In orthopedic surgery, use of intraoperative SpHb has been associated with decreased packed red cell transfusion.[28]

Obstetric data are mixed. Kim et al compared laboratory hemoglobin to SpHb readings in patients undergoing cesarean for placenta previa and found a correlation coefficient of 0.877 between the two, with a mean difference between SpHb and

laboratory hemoglobin readings of of 0.3g/dL. The mean can be misleading, however – while the difference between SpHb and lab hemoglobin was less than 0.5g/dL in 65% of patients, laboratory hemoglobin and SpHb differed by at least 1.5g/dL in over 10% of patients.[29] In another study of pregnant and recently postpartum women, the device became increasingly inaccurate as pregnancy progressed: mean bias increased from -0.20 in nonpregnant patients to 1.32 in the third trimester. That is, the device overestimated hemoglobin levels by an average of 1.32g/dL in the third trimester. Among recently postpartum patients, another population of interest in postpartum hemorrhage research, the device continued to overestimate by an average of 1.10g/dL. Among those in the second or third trimester of pregnancy or within one week postpartum (a reasonable proxy for the patient population experiencing postpartum hemorrhage), the device overestimated hemoglobin by an average of 1.16g/dL. Confidence intervals did not cross the line of equality, suggesting a significant bias towards overestimation, and the correlation between SpHb and laboratory hemoglobin in this group was weak (r=0.087).[30]

Hadar and colleagues tested a different SpHb device, the NBM-200, and found a mean difference of only 0.1g/dL. The wide limits of agreement seen in that study, however, indicate significant variation in the difference between the non-invasive measurement and laboratory measurement with only 95% of SpHb readings falling within -1.59 to +1.79 g/dL of the laboratory value.[31–33] The authors were unable to locate any large, prospective, randomized trials of SpHb among patients experiencing postpartum hemorrhage, however it appears from the existing data that further refinements are needed. The accuracy of these devices is likely compromised in

ongoing obstetrical hemorrhage with significant vasoconstriction and decreased peripheral perfusion.

Assessing maternal response to volume loss

Quantification of external blood loss via visual estimation,[24] camera-based systems such as the Triton system described above,[24,25,34] by weighing sponges,[24] or by using calibrated drapes[16,20] only account for blood that can be collected using such methods, and all appear to have limited ability to predict postoperative hemoglobin.[24,25,34] Intraperitoneal bleeding, concealed abruption, or blood lost prior to patient arrival to the hospital cannot be captured using these techniques. The SpHb technology described above appears unreliable in the delivering population.[29,30,33] Similarly, patient response to a set of volume of hemorrhage is quite variable – data from outside of pregnancy show that approximately one third of patients will progress to hypovolemic shock with much lower volumes of blood loss than the remainder of the population.[35] Thus, an interest has emerged in the use of maternal physiologic response to hemorrhage as the primary metric, rather than attempting to quantify blood on sponges, pads, or linens. Such methods correlate with need for transfusion in trauma patients,[36] but have not yet been studied in obstetric hemorrhage.

Peripheral vasoconstriction is a critical component of the physiologic response to hypovolemia,[37–39] and its quantitative assessment has emerged as a potential target for hemorrhage detection. The AccuFlow sensor (ThermaSENSE, Blacksburg, VA) is an investigational device which makes direct, quantitative measurements of perfusion at the skin surface. The device consists of sensors, applied to the skin, which heat up to

39C, then measure the rate at which the heat dissipates. Thermal readings are transmitted via Bluetooth or cellular data signals to an iPad or other smart device, where the ThermaSENSE AccuFlow app calculates perfusion, allowing the device to measure vasoconstriction in real time.[40–43] The AccuFlow and its predecessor, the CHFT+ sensor, detect altered perfusion in other conditions including in explanted organs[40] and in children with sickle cell disease.[44] The technology's ability to detect intrapartum hemorrhage has been assessed only in a small pilot of 25 patients undergoing cesarean section, which was presented at 2022 Society for Maternal Fetal Medicine Annual Pregnancy Meeting. An example of sensor readings taken throughout a cesarean delivery are shown in Figure 1. In the pilot, the change in perfusion at the wrist from delivery to the end of surgery was more strongly correlated with calculated blood loss than were the surgical team's blood loss estimates (r= -0.48 vs 0.087, p=0.03). Wrist perfusion at the end of the case was also correlated with blood loss (r= 0.22), suggesting that this approach may also be beneficial when patients present with a hemorrhage in progress.[45] Further studies are clearly needed and, as with other devices, the AccFlow is not yet ready for routine clinical use.

Another, related measure is the compensatory reserve, measured via either compensatory reserve index (CRI) or compensatory reserve measurement (CRM) algorithms.[46,47] These algorithms extract features of a pulse oximetry waveform which provide information about physiologic compensation for hypovolemia.[35] CRM has been shown to predict need for transfusion in emergency department trauma patients,[36] but its ability to detect obstetric hemorrhage has not been evaluated. Further studies are planned.

PREVENTING HEMORRHAGE-ASSOCIATED MORBIDITY: THE ROLE OF BLOOD PRODUCT TRANSFUSION

Fixed-ratio transfusion vs targeted transfusion for severe hemorrhage

Severe hemorrhage may result in massive transfusion (more than 4 units of packed red cells in an hour with ongoing bleeding, or more than 10 units of packed red cells within 24 hours).[12] In such cases, the use of fixed-ratio transfusion protocols such as a 1:1:1 ratio of packed red blood cells (RBC) to fresh frozen plasma (FFP) to platelets (PLT), has been recommended.[48–50] Early transfusion is a critical component of hemorrhage response;[21,51–53] transfusion maintains tissue oxygenation and prevents dilutional coagulopathy from large-volume crystalloid infusions.[52,54]

Though lifesaving in the right clinical setting, massive transfusion does carry some risk. Hyperkalemia risk is related to the number of units transfused, and hyperkalemic arrests have been reported.[12,55–57] Citrate, used as anticoagulant in blood products, binds serum calcium resulting in hypocalcemia and, potentially, hypotension and cardiac conduction abnormalities.[12,58–60] Transfusion of large volumes of refrigerated blood products without warming can also trigger hypothermia, which is associated with coagulopathy and worse outcomes following traumatic hemorrhage.[58] Transfusion reactions are also more common with transfusion reactions occurring in up to 2% of patients receiving massive transfusion.[61] Rates of transfusion-related acute lung injury (TRALI) increase with the quantity of blood products transfused.[62] Women receiving blood transfusions at delivery are at an approximately twofold increased risk of

transfusion reaction[61] and sixfold increased risk of TRALI[62] when compared to nonpregnant women receiving blood transfusions. Many massive transfusion protocols also result in transfusion of un-crossmatched red cells, increasing the risk of red cell alloimmunization and hemolytic disease in future pregnancies.[63] These risks have prompted a renewed interested in targeted transfusion; that is, transfusing products individually based on predicted patient needs, rather than transfusing set ratios of products to mimic whole blood. Massive transfusion protocols with set ratios of blood products remain a critical component of early response to hemorrhage, but there may be a role for targeted transfusion in the ongoing response to hemorrhage.

The importance of fibrinogen

Studies of targeted transfusion have revealed a critical role for fibrinogen in postpartum hemorrhage. Severe postpartum hemorrhage is associated with decreased fibrinogen levels,[64,65] and fibrinogen replacement is associated with improved outcomes.[66,67] Transfusion to a target fibrinogen level of 200mg/dL has been proposed for patients with postpartum hemorrhage.[10,68] Early fibrinogen replacement is associated with decreased need for packed red cell transfusion.[50,69,70] Obstetric patients may even benefit from empiric transfusion of fibrinogen concentrates in cases of severe hemorrhage.[53] Fibrinogen concentrates are also stored at room temperature,[70] do not require crossmatching,[70] contain no red cells and thus carry no risk of red blood cell alloimmunization,[70] and are associated with only negligible risks of transfusion-related morbidity.[71] Given the importance of fibrinogen replacement in hemorrhage response, and the favorable safety profile of fibrinogen replacement, some sources suggest that

targeted blood product transfusion with an emphasis on replacement of fibrinogen and clotting factor replacement should be preferred over fixed-ratio transfusion.[53]

THE ROLE OF VISCOELASTIC HEMOSTATIC ASSAYS

Point of care viscoelastic hemostatic assays

First described in 1948,[72,73] viscoelastic hemostatic assays (VHAs) have gained widespread attention, with applications in liver transplantation,[74–76] cardiac surgery,[75–80] and trauma.[49,81–84] Using whole blood, VHAs assess the kinetics of coagulation at multiple stages from the initiation of clot formation until its proper lysis, providing a real-time computerized graphical representation and readout of critical parameters (Table 1).[11,75,83,85] The two most common assays, thromboelastography (TEG) and rotational thromboelastometry (ROTEM), offer similar performance, though the reagents used and exact output parameters vary (Tables 1 and 2).[82] In the laboratory version of both systems, a pin moves through a sample of whole blood in a cup, and sensors detect changes in resistance to the movement of the pin, similar to the process first described in 1948.[69,72,73,86] In ROTEM, a pin moves through blood in a stationary cup,[69,73] while in TEG analyzers the cup moves and the pin remains stationary.[69,73]

VHAs are moving out of the laboratory and to the point of care (POC), providing real-time information without the need to send specimens to a laboratory. Both of the major producers of VHA analyzers, ROTEM and TEG, have developed point of care analyzers for use as close to the patient as possible: in the operating room, in the trauma bay, or on labor and delivery.[82,86,87] Automated cartridge systems eliminate the

need for manual pipetting or reagent mixing.[73,88] The TEG 6s analyzer applies vibration, using LEDs and infrared sensors to measure the resulting deflection of the blood in the cartridge.[86] This system has been shown to provide results equivalent to those obtained from the original cup-and-pin systems.[88] ROTEM's cartridge-based POC system, ROTEM Sigma, is pending FDA approval but is in use in other countries. To use this system, a tube of blood is placed into a cartridge containing reagents, which is inserted into the machine and subjected to the same cup-and-pin technique used in previous machines.[86] Other point of care devices have been developed by other manufacturers, but as only limited data are available on these devices, they are not discussed in detail in this document.[86]

POC VHAs allow clinicians to test at the bedside, with results available in real time. The first clinically meaningful results are available in 5-10 minutes, though additional results can continue for up to 90 minutes with some systems.[11,82] In contrast, traditional laboratory coagulation profiles provide no results for 40-90 minutes.[65,82,89] With VHAs available at the point of care, clinicians can use these results to guide resuscitation during an acute hemorrhage.[65] In fact, some evidence suggests that alterations in viscoelastic testing may also occur before changes in fibrinogen levels,[65] potentially allowing clinicians to intervene earlier in cases of severe hemorrhage with emerging coagulopathy. These advantages have led to the rapid uptake of VHA in non-obstetric massive hemorrhage settings including cardiac surgery and trauma.[75,90]

Viscoelastic profiles of obstetric patients

VHAs have been well-validated outside of pregnancy,[82] yet as with other devices, obstetric data are somewhat more limited. TEG[91–94] and ROTEM[93–95] profiles of non-laboring pregnant patients are notably different from those observed in non-pregnant women. Key differences in TEG output between pregnant and non-pregnant subjects include a shorter R time (shorter time to begin clot formation),[91,96,97] shorter K time (shorter time until the clot reaches a fixed strength),[91,96,97] steeper alpha angle (faster fibrin accumulation),[91,93,96,97] and increased MA (clot strength).[91,93,96,97] Similar findings were noted with ROTEM,[93,98] and are consistent with the prothrombotic state observed in pregnancy.[99] These differences between pregnant and non-pregnant patients are summarized in Figure 2. In patients with emerging coagulopathy in other settings, the opposite changes are noted: R and K times increase (reflecting slower clot initiation and formation), alpha angle decreases as fibrin accumulation slows, and clot strength is decreased.[93] These relationships appear to persist in pregnancy; patients experiencing postpartum hemorrhage have higher R and K times and lower alpha angle on TEG than patients delivering without hemorrhage, but this gap narrows when the hemorrhaging patients receive blood product transfusions.[100] Researchers have sought to develop pregnancy-specific normal ranges for TEG to parallel the existing pregnancy-specific normal ranges for fibrinogen,[97] but these have not yet been widely adopted.

Correlation between VHA results and laboratory assays in obstetric hemorrhage

Traditional laboratory assays may require up to 60-90 minutes.[65,89] Thus, tools which can rapidly identify hypofibrinogenemia are of critical importance. TEG 6s cartridge system results appear to correlate with laboratory fibrinogen results in

obstetric hemorrhage.[101] Results obtained on the ROTEM Sigma device are also highly correlated with laboratory fibrinogen levels (r=0.85).[102] When the ROTEM Delta was evaluated in a similar study population, FIBTEM results were only moderately correlated with laboratory fibrinogen (r = 0.59). However, FIBTEM and laboratory fibrinogen had similar positive predictive values for progression to transfusion,[103] possibly since VHA findings precede abnormalities on standard laboratory assays.[65] Thus, although VHA results do not correlate exactly with laboratory fibrinogen levels, VHAs appear as useful in identifying need for fibrinogen replacement, in a fraction of the time needed for traditional assays. Given the morbidity associated with over-transfusion, determining who should *not* be transfused is equally valuable. In 5 minutes, ROTEM can identify patients with postpartum hemorrhage who do not benefit from fibrinogen replacement,[104] and 10-minute TEG readings are 74% sensitive and 97% specific (area under the curve 0.95) for a laboratory fibrinogen level below 200.[101] Unfortunately, assessment of other coagulation parameters has been less reliable. TEG 6s had a sensitivity of only 50% for platelets <75,000, and less than 30% sensitivity for prolonged PT/aPTT.[101] Thus it appears that in the setting of pregnancy and postpartum hemorrhage, VHAs are most reliable for fibrinogen assessment.

Improved outcomes in VHA-managed hemorrhage

When compared to standard laboratory analysis or clinician discretion, use of POC VHAs in cardiac surgery was associated with decreased blood transfusion,[82,105,106] decreased mortality,[76] and shorter hospital stays.[76] Among liver transplant patients, TEG-guided transfusion decreased the use of fresh frozen plasma,[107] postoperative

ROTEM was superior to plasma fibrinogen to predict postoperative bleeding,[108] and ROTEM-based transfusion was associated with decreased re-operation due to bleeding, postoperative hemodynamic instability, re-transplantation, and acute kidney injury.[109] In trauma, VHA-guided transfusion is associated with increased fibrinogen replacement, decreased RBC and PLT transfusion, and decreased risk of multi-organ failure and hemorrhage-related mortality, without changing post-trauma hemoglobin.[110]

Though prospective, randomized controlled trials are lacking, retrospective studies indicate that total blood loss, time to cessation of bleeding, and total blood products transfused appear to be decreased when VHAs are used to guide hemorrhage management.[4,100] Rates of hysterectomy and ICU admission are also decreased with VHA-guided management.[4] Interestingly, while total blood product transfusions decreased, fibrinogen replacement increased,[4] supporting the theory that pregnant patients with hemorrhage need fibrinogen in greater quantities than other blood components, that continued use of a set 1:1:1 ratio may result in over-transfusion of other components, and that VHAs can aid clinicians in selecting appropriate products for transfusion.

While promising, further data is needed before VHAs are widely adopted into obstetrical hemorrhage protocols. We recommend that in the presence of severe active obstetrical hemorrhage, activation of massive transfusion protocols should not be delayed while awaiting results of any coagulation assessment, including VHAs. During the resuscitation process, VHAs may guide clinicians in targeting transfusion of blood products.

Cost effectiveness of VHAs

Use of POC VHAs in trauma saves over $900 per patient, largely in transfusion-associated costs.[82] In obstetrics, ROTEM-guided transfusion resulted in a cost savings of over $8,000 per patient when compared to routine laboratory monitoring.[4] With a startup cost of approximately $25,000-40,000 and a severe hemorrhage rate of 0.4%, VHAs produce a net cost savings after 1,000 deliveries.[82]

THE ROLE OF NOVEL TECHNOLOGY IN REDUCING DISPARITIES

Black women experiencing postpartum hemorrhage in the United States are at increased risk of severe maternal morbidity and mortality when compared to white women,[111,112] and their deaths are more likely than those of white women to be identified as preventable,[113,114] with implicit bias likely contributing to these disparate outcomes.[115] Black women have lower mean hemoglobin in pregnancy[116] and are more likely to experience disseminated intravascular coagulation (DIC) or to require blood transfusion or hysterectomy following postpartum hemorrhage.[112] Implementation of hemorrhage protocols appears to reduce or even eliminate Black-white disparities in severe maternal morbidity, suggesting benefit from the use of objective measures rather than clinician impression.[111] VHAs have decrease the rates of complications for which Black women are particularly at risk: transfusion and hysterectomy.[4] By providing early, objective data to guide transfusion, implementation of VHA-based protocols may be able to reduce disparities in maternal outcomes after postpartum hemorrhage.

CONCLUSIONS

Despite many promising technologies on the horizon for early detection of postpartum hemorrhage, none yet meet the standards of reliability needed for clinical application beyond a research setting. This remains an active area of research, as techniques in use in other surgical fields are translated into obstetrics. While the exact role of VHAs in obstetrical hemorrhage remains to be determined, it appears that they may aid clinicians in targeting transfusion of blood products after a MTP has been activated during severe acute bleeding episodes.

Table 1: Normal ranges and recommended next steps in management of common viscoelastic hemostatic assays (TEG and ROTEM)

	Method	Sample type	Parameter (normal values)				
			Time to start forming a clot	Time until the clot reaches a fixed strength	Speed of fibrin accumulation	Clot strength	Fibrinolysis: reduction in clot amplitude from maximum
TEG-5000	Cup and pin	Fresh or citrated whole blood	Reaction time, R (5-10min) [1-13min]	Kinetics, K (1-3min) [0.2-3.8min]	Alpha (53-72°) [47-82°]	Maximum amplitude, MA (50-70mm) [65-86mm]	Lysis at 30 minutes, LY30 (0-8%) [0-9%]
TEG-6s	Cartridge and vibration	Citrated whole blood	Reaction time, R (5-9min)	Kinetics, K (1-2min)	Alpha (63-78°)	Maximum amplitude, MA (52-69mm)	Lysis at 30 minutes, LY30 (0-3%)
ROTEM Delta[a]	Cup and pin	Citrated whole blood	Clotting time, CT (38-79 sec) [41-50sec]	Clot formation time, CFT (34-159) [62-81sec]	Alpha (<52°) [74-79°]	Maximum clot firmness, MCF (50-72mm) [69-74mm]	Clot lysis at 30 minutes, CL30 (<10%) [4-12%]
ROTEM Sigma[a]	Cartridge cup and pin	Citrated whole blood	Clotting time, CT (50-80 sec) [41-50sec]	Clot formation time, CFT (46-149) [62-81sec]	Alpha (<52°) [74-79°]	Maximum clot firmness, MCF (55-72mm) [69-74mm]	Clot lysis at 30 minutes, CL30 (<10%) [4-12%]
Abnormal result indicates			Low clotting factors	Low fibrinogen	Low fibrinogen	Low platelets	Excess fibrinolysis
Next step			Give FFP	Give cryoprecipitate	Give cryoprecipitate	Give platelets or DDAVP	Give tranexamic acid

Reported ranges are (non-pregnant normal range) provided by the device manufacturer and validation studies[87,117] and [proposed third trimester normal range] for TEG from Macafee et al,[92] and for ROTEM from de Lange et al.[118] ROTEM normal Ranges provided are for EXTEM. Pregnancy-specific normal ranges are not available for the TEG-6s.

Table 2. Viscoelastic hemostatic assays available

		Measures effect of heparin [Reagent]	Evaluation of intrinsic pathway (PTT) [Reagent]	Evaluation of extrinsic pathway (PT/INR) [Reagent]	Evaluation of platelet function [Reagent]	Evaluation of fibrinogen (with a platelet inhibitor) [Reagent]	Time to fastest result	Time to standard full result (minutes)
TEG-5000		Heparinase TEG (hTEG) [Heparinase]	Standard TEG [Kaolin]	Rapid TEG (rTEG) [Kaolin, TF]	CFF	Functional fibrinogen (FF) [TF, Reopro]	rTEG (15min)	30-60
TEG 6s	Global hemostasis cartridge	CKH [Heparinase, Ca]	CK [Kaolin, Ca]	CRT [Kaolin, TF, Ca]		CFF [TF, Reopro, Ca]	CRT (5 min)	Max 90
	Platelet mapping cartridge	HKH			ActF [ADP, AA]			
ROTEM Delta		HEPTEM [Heparinase]	INTEM [Ellagic acid]	EXTEM [TF]		FIBTEM [cytochalasin D]	EXTEM (10min)	45-60
ROTEM Sigma complete cartridge		HEPTEM [Heparinase]	INTEM [Ellagic acid]	EXTEM [TF]		FIBTEM [cytochalasin D]	EXTEM (10min)	60

Table 3. Final recommendations:

Topic of Interest	**Recommendations**
Novel sensors for early detection of postpartum hemorrhage	Though many sensors are under investigation, no commercially available technology provides sufficiently accurate estimates of blood loss to justify routine clinical use.
	Further studies should be performed, and the algorithms behind these technologies may be able to be refined to improve test performance in an obstetric population.
	Since obstetric hemorrhage outcomes depend not only on the actual volume of blood loss or the hemoglobin nadir, but on the patient's response to hemorrhage, alternative endpoints should be considered in such studies.
Application of viscoelastic tests to guide management of postpartum hemorrhage	Pregnancy-specific reference ranges should be established for the existing viscoelastic assays.
	Prospective, randomized trials are needed to confirm the clinical utility and cost savings associated with this technology.
	If viscoelastic hemostatic assays are used, fibrinogen assessment appears to be more reliable in obstetric hemorrhage than other viscoelastic parameters.
	In case of heavy bleeding, hypotension, or tachycardia, massive transfusion protocols should be initiated and blood products transfused while awaiting results of further testing. Once available, the results of viscoelastic hemostatic assays may be used to guide transfusion of additional blood products.

Figure Legends:

Figure 1. Sample of sensor readings obtained during cesarean delivery using the AccuFlow sensor, demonstrating changes in perfusion at multiple sites.

Figure 2. Illustration of differences in viscoelastic hemostatic assay parameters between pregnant and non-pregnant individuals.

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Figure 1

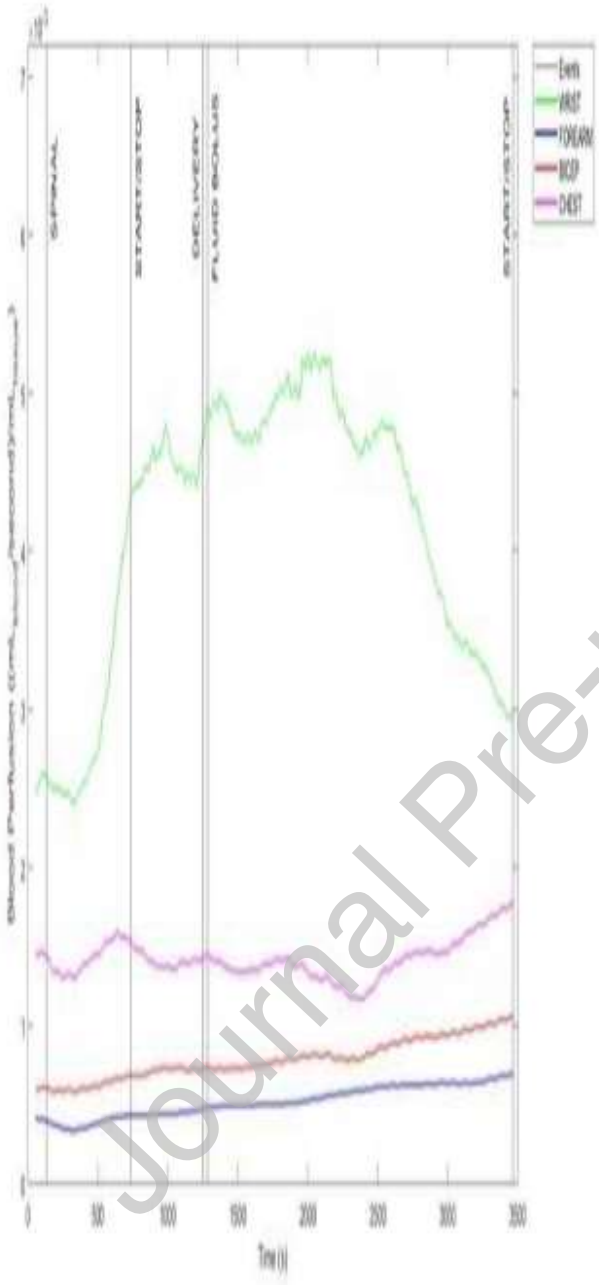

Figure 2

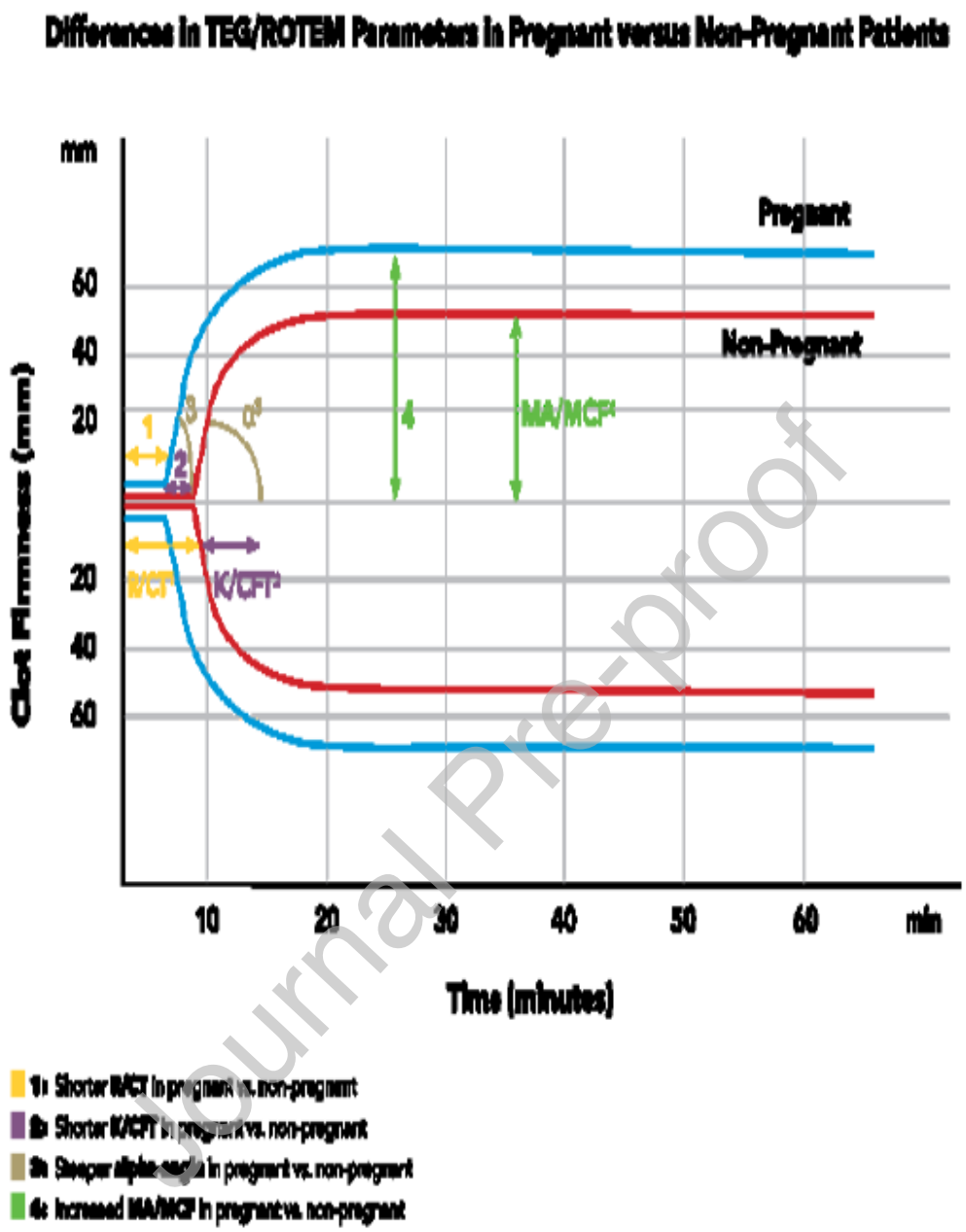

Figure 3