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EDITORIAL

Point-of-care coagulation testing for obstetric hemorrhage: time for a theranostic approach?

Postpartum hemorrhage (PPH) is a leading source of preventable maternal morbidity and mortality, even in high-resource settings.[1,2] Low serum fibrinogen that occurs early in the course of bleeding correlates with PPH severity and morbidity,[3,4] thus a central tenet of care is to recognize and treat PPH-related coagulopathy without delay. Evidence is mounting for the utility of point-of-care (POC) coagulation tests such as rotational thromboelastometry (ROTEM®) and thromboelastography (TEG®) in the context of PPH. Coagulopathy associated with PPH can often be predicted from the etiology of the postpartum bleeding, but individuals vary significantly with regard to PPH onset, severity and resolution. The clinical complexity of PPH and its heterogeneous onset and resolution may warrant the use of POC ROTEM® to guide transfusion and treatment.

ROTEM® testing offers a theranostic approach to PPH management that has the potential to eclipse empiric or fixed-ratio transfusion approaches. The term "theranostic" refers to targeted therapy based on specific diagnostic tests. First coined by businessman John Funkhouser in the 1990s in the context of personalized medicine, theranostics had its oldest application in 1946 with the use of radioactive iodine to detect and treat thyroid cancer.[5] While modern theranostic medicine continues to refer largely to radionuclide-tagged molecular chemotherapy, it is not a novel concept in anesthesiology. A theranostic approach to transfusion has long been described in both the cardiac and liver transplant literature. Goal-directed, individualized hemostatic therapy has been reported during complex clinical bleeding associated with cardiopulmonary bypass, reperfusion and cirrhotic liver dysfunction.[6,7] A pertinent question therefore is "Why isn't POC testing a standard of care for PPH management?"

A reliable theranostic tool requires both precision and accuracy, and ROTEM for PPH has been hindered by deficiencies in these areas. In the current issue, Lee et al. report the largest investigation to date establishing normal ROTEM® reference ranges for pregnant women undergoing elective cesarean delivery at term gestation.[8] Previously reported reference ranges for pregnancy reflect the known hypercoagulable state during pregnancy compared to non-pregnant patients but these ranges show variability across studies.[9–11] This may indicate regional variation in patient demographics due to genetic or other factors, variability in coagulation status intrinsic to pregnancy, methodologic or operator differences, or an inadequate sample size. Determining a reference range specific to pregnant women is an important step for interpreting ROTEM® in the appropriate context. Ultimately, ROTEM® users should maintain stringent certification in precision testing and establish reference ranges locally to account for potential operator and population-related variability. Newer generation POC devices such as the ROTEM® sigma and TEG® 6S are cartridge-based which may lower the risk of operator error and yield greater precision and accuracy. However, a preliminary validation study reports inconsistency for FIBTEM assay values between the ROTEM® delta and the newer ROTEM® sigma and better correlation with Clauss serum fibrinogen using the ROTEM® sigma device.[12] Potentially distinct, device-specific ranges may be required. The onus on establishing pregnancy reference ranges, specific to the patient population and hospital and even between older and newer generation devices, is substantial.

A theranostic tool also requires a well-defined therapeutic target. For PPH, key markers of coagulopathy are a low serum fibrinogen and fibrinolysis. Fibrinogen is a central procoagulant that adaptively increases throughout pregnancy and is the first variable to fall below a normal threshold during PPH and coagulopathy.[13] Pregnant women with low serum fibrinogen early in the course of PPH are likely to benefit most from targeted hemostatic treatment.[14] Measurement of Clauss serum fibrinogen content can take up to one hour before a result is available. In contrast, ROTEM® FIBTEM amplitudes can be determined at 5 and 10 minutes, correlate with serum fibrinogen and can be used as surrogate measurements.[10] A low serum fibrinogen (<2 g/L) early in PPH is associated with continuation to severe PPH[3,4] but thresholds for fibrinogen replacement and a therapeutic target for serum fibrinogen continue to be refined. The OBS2 study suggests that a FIBTEM A5 >12 mm or a serum fibrinogen level of >2 g/L are adequate for hemostasis during PPH.[15] This information indicates reasonable therapeutic targets for fibrino-

gen replacement during PPH, and the rapidity of fibrinogen level assessment by ROTEM® gives it theranostic value.

In addition to the detection and treatment of a low fibrinogen state, management of ongoing hyperfibrinolysis is a therapeutic goal in PPH. The current reports in this volume of the journal by Loughran et al.[16] and Pujolle et al.[17] demonstrate cases of severe hyperfibrinolysis detected by ROTEM®, both with effective clinical and ROTEM®-derived responses on repeat testing after therapy with fibrinogen concentrate and tranexamic acid. Diagnosis of such rare but potentially catastrophic obstetric events may be first suspected based on ROTEM®-derived coagulopathy that is not explained by any other cause, for example rapid hemorrhage with hemodilution.[18,19] The coagulopathy that is pathognomonic for amniotic fluid embolism (AFE) can help to differentiate AFE from pulmonary embolism, an event that may manifest with similar cardiopulmonary symptoms but without associated coagulopathy. As the therapies for AFE and pulmonary embolism have opposing goals of hemostasis, rapid determination of coagulation status by ROTEM® can procure a swift diagnosis for timely and appropriate therapy. As such cases of hyperfibrinolysis detection and treatment accumulate in the literature, the theranostic value of ROTEM® will increase.

In addition to precision, accuracy and a well-defined therapeutic target, a valuable theranostic tool should demonstrate favorable impact from its use. Since the vast majority of patients with PPH have no coagulopathy, a substantial value of ROTEM®-based management is the avoidance of unnecessary transfusion of procoagulant therapy such as fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate or platelets. By utilizing FIBTEM A5-guided fibrinogen concentrate therapy instead of a fixed ratio transfusion approach of 1:1:1 (packed red blood cells: FFP: platelets) for PPH, Mallaiah et al. demonstrated a reduction in transfusion requirements and associated morbidity.[20] There is mounting evidence that FFP administration is not necessary or even beneficial in the majority of cases of PPH.[21] Seto et al. describe algorithmic dosing of fibrinogen concentrate and FFP for PPH according to serum fibrinogen levels and prothrombin time, respectively. With this algorithm, pregnant women received less FFP and had lower recorded blood loss.[22] In the OBS2 study, withholding FFP when FIBTEM A5 levels were $\geq$15 did not impair hemostasis.[15] Wikkelso et al. found that pre-emptive treatment with fibrinogen concentrate for PPH in patients with normal-range serum fibrinogen did not result in a lower blood transfusion requirement.[23] Taken together, these studies suggest that a one-size-fits-all approach to PPH should not be used and the studies support a theranostic approach for detecting and treating low-fibrinogen states during PPH. However, evidence of reduced mortality from viscoelastic testing is still lacking.[24] Large randomized controlled trials comparing ROTEM®-based therapy to empiric or generalized therapy during PPH may help further define the benefit of POC coagulation testing as a theranostic tool in PPH management.

Logistical factors must be considered before theranostic POC testing is implemented on a large scale for PPH. The cost may be prohibitive in centers where PPH occurs infrequently due to lower numbers of births. The manpower required to run, interpret and perform quality control on viscoelastic devices may not be feasible in all labor units, however advances in cartridge-based POC devices may streamline use and cost. A preliminary cost analysis suggests that ROTEM®-based PPH management is associated with lower hospitalization costs.[25] Research comparing alternate coagulation assessments to POC testing may define surrogate tests for centers where POC is not available. Finally, further research refining triggers for component therapy administration and demonstrating benefit in randomized studies will drive the use of POC coagulation testing in obstetric patients.

The evidence is mounting for POC coagulation testing as theranostic tool for PPH management as a result of its targeted evaluation of fibrinogen status, the early detection of coagulopathy and for assessment of the efficacy of therapeutic interventions. This theranostic approach to PPH has benefit along the entire spectrum of postpartum bleeding, from avoiding therapy in the vast majority of patients who have no associated coagulopathy to the earliest detection and aggressive management when profound coagulopathy occurs. This has been demonstrated by the cases described by Loughran et al. and Pujolle et al.[16,17] Point-of-care testing allows obstetric and anesthesia physicians to be engaged and communicate rapidly at the bedside, to distinguish surgical versus coagulopathic bleeding and to respond in a targeted and appropriate way.[26] High-volume tertiary centers caring for women at the greatest risk for PPH can, and should, continue to pursue research in the theranostic value of POC testing for PPH management. Until PPH is no longer a preventable source of maternal morbidity and mortality, striving for a more effective and sophisticated theranostic approach to transfusion is warranted.

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