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Transfusion and coagulation management in major obstetric hemorrhage

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Abstract

Purpose of Review—Major obstetric hemorrhage is a leading cause of maternal morbidity and mortality. We will review transfusion strategies and the value of monitoring the maternal coagulation profile during severe obstetric hemorrhage.

Recent Findings—Epidemiologic studies indicate that rates of severe postpartum hemorrhage (PPH) in well-resourced countries are increasing. Despite these increases, rates of transfusion in obstetrics are low (0.9% - 2.3%), and investigators have questioned whether a pre-delivery 'type and screen' is cost-effective for all obstetric patients. Instead, blood ordering protocols specific to obstetric patients can reduce unnecessary antibody testing. When severe PPH occurs, a massive transfusion protocol (MTP) has attracted interest as a key therapeutic resource by ensuring sustained availability of blood products to the labor and delivery unit. During early postpartum bleeding, recent studies have shown that hypofibrinogenemia is an important predictor for the later development of severe PPH. Point-of-care technologies, such as thromboelastography and rotational thromboelastometry, can identify decreased fibrin-clot quality during PPH, which correlate with low fibrinogen levels.

Summary—A MTP provides a key resource in the management of severe PPH. However, future studies are needed to assess whether formula driven vs. goal-directed transfusion therapy improves maternal outcomes in women with severe PPH.

Keywords

Postpartum hemorrhage; blood component therapy; coagulation management; massive transfusion protocol; blood ordering; Transfusion; Pregnancy; Anesthesia; Hemorrhage

INTRODUCTION

Obstetric hemorrhage is a leading cause of maternal death and morbidity worldwide. In Africa and Asia, obstetric hemorrhage accounts for more than 30% of all maternal deaths.[1] By comparison, obstetric hemorrhage is responsible for lower rates of maternal death in the

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developed world: 3.4% in United Kingdom between 2006–2008 [2] and 11.4% in the United States between 2006–2010 [3]. Despite the relatively low rates of death from hemorrhage in well-resourced countries, concern has been raised about the rising incidence of postpartum hemorrhage (PPH), driven by increases in PPH due to uterine atony [4–9]. Therefore, anesthesiologists are likely to be increasingly called upon to help manage the resuscitation of patients with major PPH, which include overseeing transfusion decision-making and the treatment of hemorrhage-related coagulopathy.

For this review, we will focus on key clinical aspects of transfusion and coagulation management in major obstetric hemorrhage, including: transfusion service support in obstetrics; fibrinogen as a predictor of major PPH; and the use of point-of-care devices for identifying alterations in maternal hemostasis.

OBSTETRIC HEMORRHAGE AND TRANSFUSION

Based upon population-wide data from developed countries, the rate of transfusion in obstetrics is relatively low (0.9% – 2.3%); however, transfusion rates have been increasing in recent years, likely due to the increases in rates of PPH.[7, 8, 10–12]. With transfusion identified as an important indicator of severe obstetric morbidity, obstetric experts in maternal safety have called upon hospitals to initiate quality improvement by reviewing case histories of women who received four or more units of blood products.[13] Furthermore, to optimize the quality of management during obstetric hemorrhage, the National Partnership for Maternal Safety has recommended that U.S. birthing facilities partner with local transfusion services to ensure rapid and sustained availability of blood products.[14] PPH guidelines from recognized state-wide or national obstetric bodies [15–18] and published hospital protocols[19] include blood component therapy as a key aspect of PPH management.

In some situations, patients with life-threatening hemorrhage can require large volumes of blood products (massive transfusion) during maternal resuscitation. Fortunately, massive transfusion of 10 or more units of red blood cells occurs rarely in obstetrics (6 of every 10,000 deliveries).[20] Among patients who receive massive transfusion, abnormal placentation is the most common etiology (27% of all cases). [20] This finding is concerning as rates of peripartum hysterectomy have been increasing in the U.S. (72 per 100,000 deliveries between 2006 and 2007).[21]

BLOOD ORDERING IN OBSTETRICS

Institutional policies for ordering a type and screen (T&S) may vary as health care and hospital providers attempt to adopt cost-effective approaches in order to maximize the highest degree of clinical impact.[22] The American Society of Anesthesiologists (ASA) Task Force on Obstetric Anesthesia practice guidelines[23] highlight the importance of blood transfusion management for hemorrhagic emergencies and include specific recommendations for ordering an intrapartum T&S based on: maternal history; anticipated hemorrhagic complications (e.g. placenta accreta); and local institutional policies. These practice guidelines also state that a routine blood cross-match is not necessary for healthy and uncomplicated parturients.

Several studies have assessed the cost-effectiveness and clinical value of pre-delivery routine T&S. Ransom et al.[24] performed a retrospective study assessing institutional transfusion rates in patients undergoing cesarean delivery and observed that only 132/3962 (3.3%) patients required transfusion. A cost saving of $135,000 over 3 years was calculated, based on the assumption that >60% of patients did not have any pre-determined obstetric risk factors for transfusion on admission. In a similar study, Cousins et al.[25] observed a transfusion rate of 1.7% among patients undergoing cesarean delivery, yet a T&S test was performed for 82% of patients. The authors recommended a “hold clot” (current clot tube in blood bank) order for patients at low risk for transfusion with a negative prenatal antibody screen. Dilla et al. [26] performed a retrospective study at a single center to examine whether risk stratification for peripartum hemorrhage, based on guidelines from California Maternal Quality Care Collaborative[15], accurately predicted the risk of PPH. Rates of hemorrhage requiring one unit or more of red blood cells (RBC) were low for women at low-risk, medium-risk and high-risk for hemorrhage (0.8%, 2% and 7.3% respectively). Furthermore, 98% patients who had a T&S test did not receive a RBC transfusion.

Prior to 2009, our institution (Stanford Medical Center) had no standardized approach on our labor and delivery service for blood ordering. Therefore a working group was formed, which included obstetricians, obstetrical anesthesiologists, and transfusion medicine specialists, to develop an institution-specific blood ordering protocol for obstetrics based on literature review and expert consensus.[27] Details of the protocol are described:

- **a.** For patients identified as ‘low risk’ for transfusion, blood type testing for ABO system and Rhesus system only was recommended.
- **b.** For patients deemed ‘moderate risk’ for transfusion, testing for T&S was recommended.
- **c.** For patients considered ‘high risk’ for transfusion, a ‘type and cross’ (T&C) or cross-match to set up RBCs was recommended.

Implementation of these strategies resulted in a 55% reduction in antibody testing.[27] Since it is not feasible to provide support with antigen negative, Coomb’s crossmatched RBCs during the resuscitative phase for hemorrhaging obstetric patients, the institution-specific massive transfusion protocol (MTP) was included in each category of blood ordering. The implementation of these transfusion algorithms (i) consolidates important transfusion medicine resources; (ii) more clearly defines ‘at risk’ patient groups; (iii) reduces inconsistencies in transfusion ordering practices; and (iv) reduces the overall costs related to blood ordering.

MASSIVE TRANSFUSION PROTOCOL FOR POSTPARTUM HEMORRHAGE

The process of obtaining RBC and other blood products for emergent transfusion in the management of severe, unanticipated obstetric hemorrhage can be logistically challenging and time-consuming. The time table for issuing blood emergently depends on whether type-specific, crossmatched RBC can be provided within an acceptable turnaround time[28], based on the diagnostic antibody screen results (Table 1). We have developed a standardized MTP for women with an emergent need for blood transfusion, including those whose

antibody screen evaluation was positive or unknown upon admission.[27, 29, 30] Figure 1 illustrates our algorithm for blood transfusion therapy during the MTP.[29]

The MTP have been advocated as an essential tool for facilitating the early transfusion of sufficient volume and types of blood products for patients with massive obstetric hemorrhage.[27, 31] Implementation of an MTP has been shown to improve the timeliness of blood transfusion (compared to historical controls) and to be cost-effective (due to a lower overall usage of blood products).[32] In addition, access to the MTP improves lines of communication for ordering and transportation of blood products from the transfusion services department to the labor and delivery unit, and ensures ongoing availability of blood products until surgical and hemostatic control of bleeding has been achieved.[27] Verbal and electronic orders are needed to initiate the preparation and issue of MTP blood products. The transfusion services department will issue a pack containing MTP blood products to a courier within 5–10 minutes of receiving the verbal order.

The MTP comprises: six O negative uncrossmatched blood products, 4 units of AB plasma, and 1 apheresis platelet unit. Thawed group A plasma may be an acceptable alternative to liquid AB plasma as the first option for plasma therapy in emergencies.[33] Plasma and platelets are important in the correct of coagulopathy (discussed later) and thrombocytopenia that can occur in the setting of obstetric hemorrhage. In a retrospective review of blood component therapy used at a single obstetric center for PPH management, plasma, cryoprecipitate, and/or platelets were required by 12%, 46% and 100% of women transfused with 0 to 3 units of RBCs, 4 to 7 units of RBCs, and 8 or more units of RBCs respectively for the treatment of PPH.[34] Although the ideal ratio of plasma to RBC for obstetric hemorrhage remains uncertain, the ratios of the blood products components of our MTP were designed to be in proportion to whole blood with the goal of minimizing the effects of dilutional coagulopathy and hypovolemia.[35]

There is currently no national data on the availability and utilization rates of an MTP within U.S. maternity units. However, a survey of sixty directors of academic obstetric anesthesia units reported that an MTP was present in 95% and 90% of units with and without a PPH hospital-wide protocol respectively.[36] Despite the lack of studies comparing outcomes between women receiving MTP-based therapy versus ‘usual care’, the high rate of MTP availability among centers in this survey suggests that providers appreciate the potential clinical value of an institution-specific MTP. The MTP provides a feasible solution for preventing system delays and inefficiencies in the ordering, processing and transporting blood products that may influence the severity of hemorrhage-related morbidity and mortality. [37, 38]

FIBRINOGEN AND POSTPARTUM HEMORRHAGE

Pregnancy is associated with a hypercoagulable state. Teleogically, these changes occur in preparation for blood loss at the time of parturition. During pregnancy, there is an increase in procoagulant activity (characterized by increases in factors V, VII, VIII, IX, X, XII and XII, von Willebrand factor, fibrinogen), decreases in endogenous anticoagulant activity (characterized by increases in heparin cofactor II, a_1 antitrypsin, protein S activity and

activated protein C resistance), and depressed fibrinolytic activity.[39, 40] Of note, fibrinogen levels increase with advancing gestation and in the third-trimester are higher than those in non-pregnant women (Table 2).[41–47]

Coagulopathy can accompany a number of obstetric morbidities. Obstetrical disseminated intravascular coagulation (DIC) is an acute, severe complication linked to placental abruption, amniotic fluid embolism, and dead fetus syndrome.[48] Although obstetrical DIC may secondarily result in obstetric hemorrhage, it has been less clear whether and to what degree the maternal coagulation profile is altered during the period of acute and ongoing blood loss, in the absence of pre-existing DIC.

Recently, investigators have focused their attention on profiling changes in the maternal coagulation profile during the course of obstetric hemorrhage. Specifically, a low fibrinogen level has been identified an important predictor for severe PPH.[49] Charbit et al. examined coagulation profiles among 128 patients with atonic PPH (after administration of a second-line uterotonic) upto 24 hr after bleeding onset.[50] The maternal fibrinogen level was independently associated with severe PPH; for each 1g/L decrease in fibrinogen, there was a 2.6 fold increased odds of severe PPH. A baseline fibrinogen level ≤2g/L taken at the time of bleeding onset had a positive predictive value of 100%. These findings signify that a low fibrinogen level during the early phase of postpartum bleeding can predict the later development of severe PPH. Similar findings have been observed in other observational studies. In a secondary analysis of a population-wide study in France, Cortet et al. observed that women who developed PPH post-vaginal delivery who had fibrinogen levels <2g/L within 2 hr of PPH diagnosis were independently associated with severe PPH (adjusted OR=12).[51] In a retrospective study of 456 patients with severe PPH, de Lloyd et al. also found nadir fibrinogen levels were inversely correlated with post-delivery blood loss values ($r = -0.48$).[52] In another retrospective study examining 257 women with PPH, low fibrinogen levels (<2 g/L) predicted the need for an advanced intervention (uterine artery embolization, intra-abdominal packing, vessel ligation or hysterectomy).[53] These data provide strong evidence of an association between low fibrinogen levels with severe PPH. However, it is unclear whether this relationship is purely associative or causative. In a large, multicenter study of women with early PPH, the effect of pre-emptive treatment with 2 g fibrinogen concentrate as a measure to reduce RBC transfusion compared with placebo.[54] No between-group differences were observed in the rate of postpartum transfusion (fibrinogen group (20%) vs. placebo group (22%)), therefore fibrinogen concentrate given pre-emptively for patients with PPH and normofibrinogenemia may not be advantageous. However, for women who develop severe PPH, the use of purified virally inactivated fibrinogen concentrates may be as efficacious as cryoprecipitate in correcting hypofibrinongenemia and, if introduced into an algorithm for treating PPH-related coagulopathy, may reduce the need for massive transfusion of RBCs, plasma and platelets.[55, 56] Further studies of fibrinogen concentrate in the setting of PPH are needed, and we await the results of another randomized trial using fibrinogen concentrate for the early treatment of PPH.[57]

POINT-OF-CARE DEVICES FOR ASSESSING COAGULOPATHY

Standard laboratory tests of coagulation (prothrombin time, activated partial thromboplastin time (APTT), international normalized ratio (INR)) have become indoctrinated into clinical practice as tests for determining the presence and severity of coagulopathy. More recently, questions have been raised about the clinical utility of these tests in the management of coagulopathic bleeding. As these tests can have long turnaround times (occasionally >60 mins), many providers may decide to transfuse based on a protocol-based approach or clinical judgement. Furthermore, INR and APTT were originally intended to monitor vitamin K antagonists and heparin effects,[58] not for predicting bleeding or the management of coagulopathic bleeding. Haas et al. recently confirmed that there is no data from randomized controlled trials to support the use of these laboratory tests as tools for assessing coagulopathy or transfusion decision-making in the setting of severe hemorrhage.[59]

Point-of-care technologies, notably thromboelastography (TEG®;Haemonetics Corp, Braintree, MA) and thromboelastometry (ROTEM®; Tem International GmbH; Munich; Germany), can assess and graphically display the visco-elastic properties of clot formation through to clot lysis.[60–62] Key parameters measured by these technologies include: the time to initial fibrin formation (reaction time (TEG®); clotting time [CT] (ROTEM®)); the kinetics of fibrin formation and clot development (alpha angle (TEG® and ROTEM®)); and the maximal strength and stability of the fibrin clot (maximum amplitude [MA] (TEG®); maximum clot firmness [MCF] (ROTEM®)).[60] The FIBTEM test of ROTEM® provides data on the fibrinogen component to clot formation by using a platelet inhibitor (cytochalasin D). Furthermore, TEG® can provide information about thrombus generation which correlates with thrombin generation kinetics; these kinetic data cannot be evaluated with normal laboratory coagulation tests.[63] In obstetrics, these technologies have been used to verify the presence of hypercoagulability in pregnant and postpartum women[64–66] and, more recently, coagulation changes during the course of PPH.

In the setting of obstetric hemorrhage, these devices can be used as tools for the diagnosis and treatment of PPH-related coagulopathy. In particular, studies with TEG® and ROTEM® indicate that decreased fibrin-clot quality occurs during PPH and that specific TEG®/ROTEM® parameters correlate with fibrinogen concentration (Figures 2 and 3).[62, 67] Huissoud et al. performed a prospective study assessing coagulation profiles using ROTEM® for women with PPH vs. a control group.[68] In this study, the amplitude of formed clot was assessed at 5 min and 15 min with CA_5-FIBTEM and CA_{15}-FIBTEM respectively. During the early phase of PPH, decreases in plasma fibrinogen levels were consistent with decreases in CA_5-FIBTEM and CA_{15}-FIBTEM. In a prospective, observational study of women diagnosed with PPH (1000–1500 ml blood loss) after vaginal or cesarean delivery, Collins et al. assessed whether CA_5-FIBTEM could predict progression to severe PPH.[69] Based on area under the receiver operating characteristics curves (AUROC), fibrinogen and CA_5-FIBTEM had similar AUROCs (0.71 and 0.75 respectively) for progression to severe PPH (2500 ml blood loss).[69] Consistent with prior studies,[50–52] this study also provided evidence that the fibrinogen threshold for progression to morbidity (≥4 units RBCs) was 2.6 g/dl compare to 3.9 g/dl for those that did not develop

morbidity. This finding is extremely important as the threshold at which fibrinogen supplementation should be considered during obstetric hemorrhage is probably much higher than that recommended in current guidelines.[17] Karlsson et al. studied TEG® profiles in women with PPH (≥2000 ml blood loss) and without PPH.[67] TEG® showed faster clot initiation (shorter r times), reduced clot strength (a angle and MA) and depressed fibrinolysis (LY-30) compared to TEG® profiles for normal delivery. Furthermore, fibrinogen levels decreased during PPH with the strongest correlations found between MA and fibrinogen ($r = -0.7$).

Based on recent studies, TEG® and ROTEM® can provide early feedback to care providers about key changes in the maternal hemostatic profile during PPH. TEG® and ROTEM® can be considered for rapid hemostatic assessment during PPH and these technologies have been endorsed in guidelines from the Obstetric Anaesthetists Association (UK)[70], the European Society of Anaesthesiology[71] and the American Society of Anesthesiologists[72].

FUTURE AREAS OF INVESTIGATION

The ideal ratio of FFP: RBC or platelets: RBC for the management of PPH is uncertain. To date, only one retrospective study has assessed the need for interventional treatment (arterial embolization or hysterectomy) in patients receiving a “low” vs. “high” ratio of plasma:RBC.[73] A lower risk of intervention was reported for women who received a high plasma:RBC ratio (≤ 0.5), however this study involved only a small cohort (n=142) and did not account for the timing of blood product administration.

Compared to formula-driven strategies (such as fixed ratios of blood products), the use of goal-directed resuscitation has been advocated for managing coagulopathy following trauma. Goal-directed resuscitation can incorporate a point-of care strategy which can incorporate TEG® or ROTEM® for the diagnosis of altered hemostasis and treatment efficacy for correcting coagulopathy.[74, 75] Although formula-driven vs. goal-directed transfusion approaches for PPH have not been compared, several prospective studies in trauma have investigated fixed-ratio transfusion approaches. In a study assessing the feasibility of a fixed (1:1:1) ratio of RBC, plasma, and platelets, trauma patients who received a fixed ratio had a higher 28 day mortality compared to patients receiving blood components according to blood transfusion support based on standard, laboratory-derived information (29.7% vs. 9.4% mortality, respectively).[76] In a larger, multi-center, randomized trial comparing outcomes in major trauma patients receiving a 1:1:1 (plasma:platelets:RBC) ratio compared to a 1:1:2 ratio, no differences in 24 hr all-cause mortality (12.7% vs. 17%) or 30 day mortality (22.4% vs. 26.1%) were reported in the 1:1:1 group vs. the 1:1:2 group respectively.[77] There was a limited description of other administered hemostatic therapies. This is important as plasma has a lower fibrinogen concentration than cryoprecipitate and fibrinogen concentrate.[78] Data from mathematical models suggest that the ability to increase the plasma fibrinogen level is dependent on the baseline fibrinogen level and the fibrinogen concentration of specific hemostatic therapies.[79] As a consequence, further studies are needed to examine whether initial resuscitation during major PPH with an integrated approach comprising hemostatic agents (such as

fibrinogen concentrate) and transfusion therapy is more effective than a transfusion-only based approach.

CONCLUSION

If hypofibrinogenemia is identified during PPH, fibrinogen supplementation may be an important early intervention. However, the precise indications for fibrinogen supplementation still need to be properly investigated. With hypofibrinogenemia and PPH receiving attention in the literature, one should not overlook the fact that fibrinogen supplementation may not necessarily result in complete correction of coagulopathy because other coagulation factors are also essential for achieving a critical rate of thrombin generation.[80]

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in all groups (<8% respectively) and only 2% of patients who underwent predelivery type and screen testing subsequently required transfusion therapy for hemorrhage. These findings indicate that more research is needed to identify risk factors for obstetric hemorrhage to improve pretransfusion testing

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Key Points

i. A massive transfusion protocol is a key resource for ensuring sustained availability of blood products to the labor and delivery unit.

ii. During the early stages of postpartum bleeding, hypofibrinogenemia has been identified as an important predictor for severe postpartum hemorrhage.

iii. Point-of-care technologies, such as thromboelastography and rotational thromboelastometry, can provide important and timely information about altered clot formation and lysis that can develop during obstetric hemorrhage.

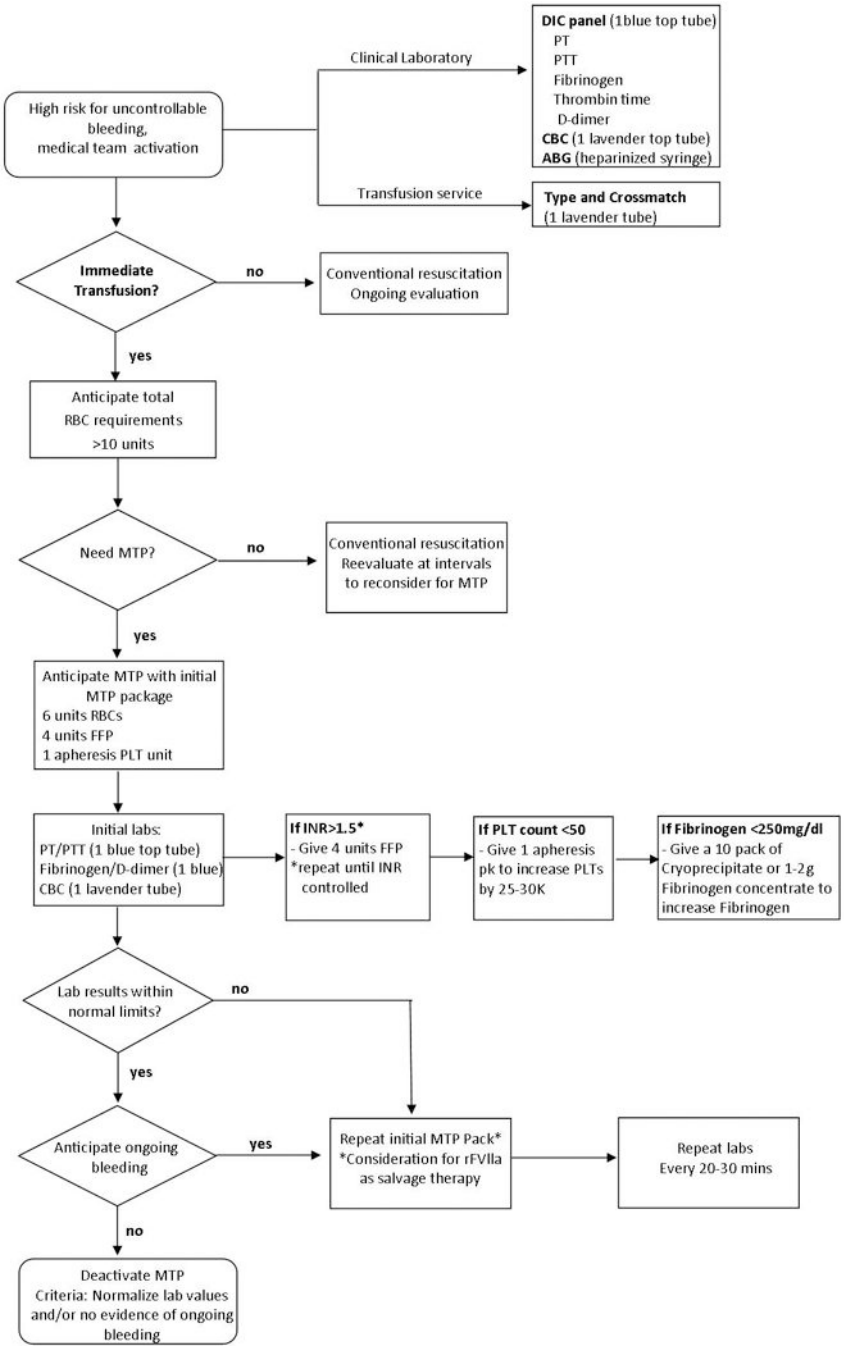

Figure 1.

Massive transfusion protocol; modified from Burtelow et al.[29] ABG = arterial blood gas; CBC= complete blood count; DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; INR = international normalized ratio; MT = massive transfusion protocol; PLT = platelets; PT = prothrombin time; PTT = activated partial thromboplastin time; RBC = red blood cells; rFVIIa = recombinant factor VIIa.

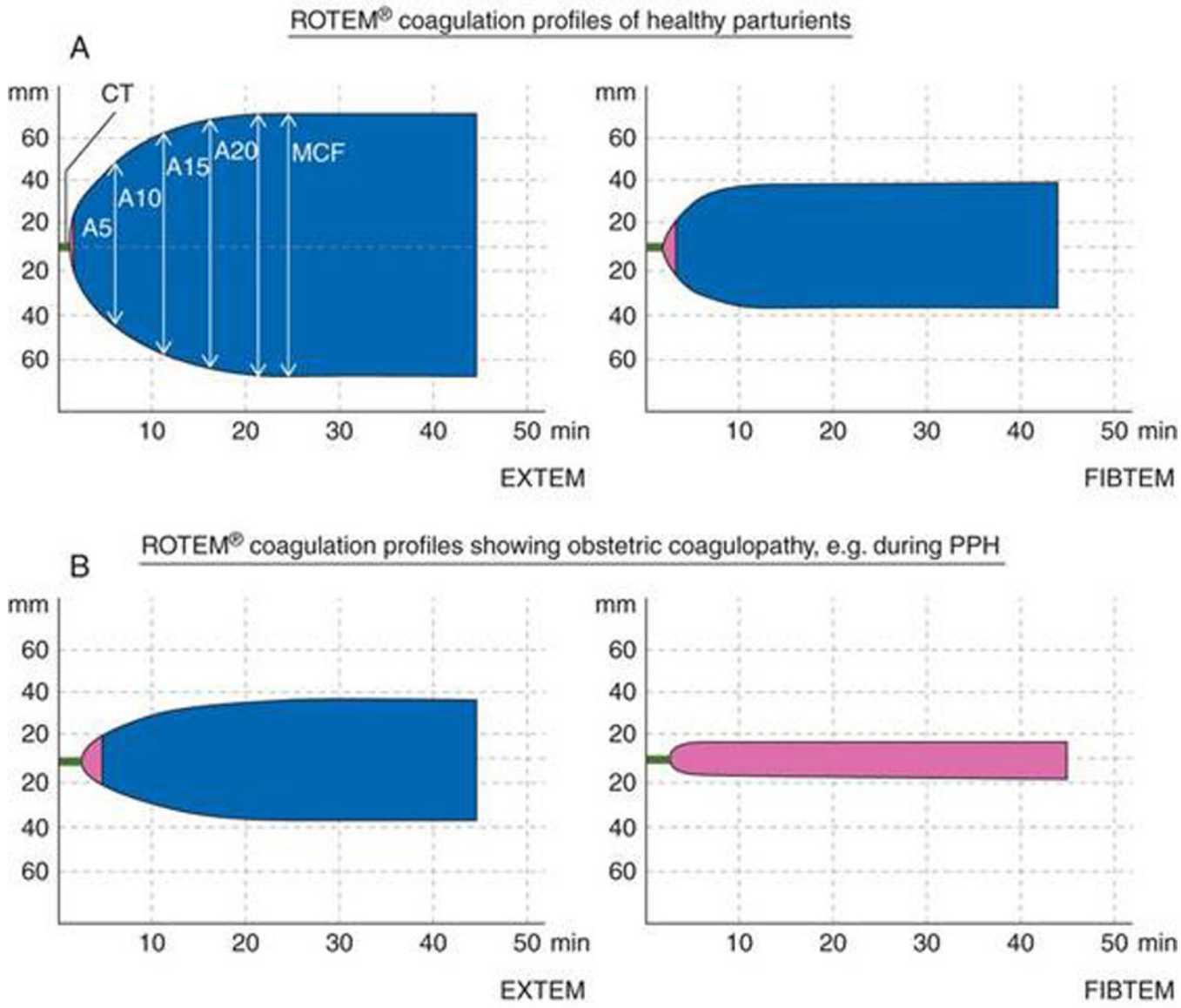

Figure 2.

ROTEM coagulation profiles in health parturients and in parturients with obstetric coagulopathy due to severe postpartum hemorrhage.[62] Schematic representations of healthy (A) and coagulopathic (B) ROTEM coagulation profiles for EXTEM and FIBTEM tests. Tissue factor is used in EXTEM assays for assessment of the extrinsic pathway. A platelet inhibitor, cytochalasin, is added to the blood sample for the FIBTEM assay to differentiate between platelet dysfunction and the alterations in fibrin polymerization. CT = Clotting time; A5/A10/A15/A20 = Clot amplitude at 5, 10, 15 and 20 min after clotting time has passed; MCF = maximum clot firmness.

Source =

Title = Haemostatic monitoring during postpartum haemorrhage and implications for management

Reference = C. Solomon et al.; Brit J Anesth 2012; 109: 851–63

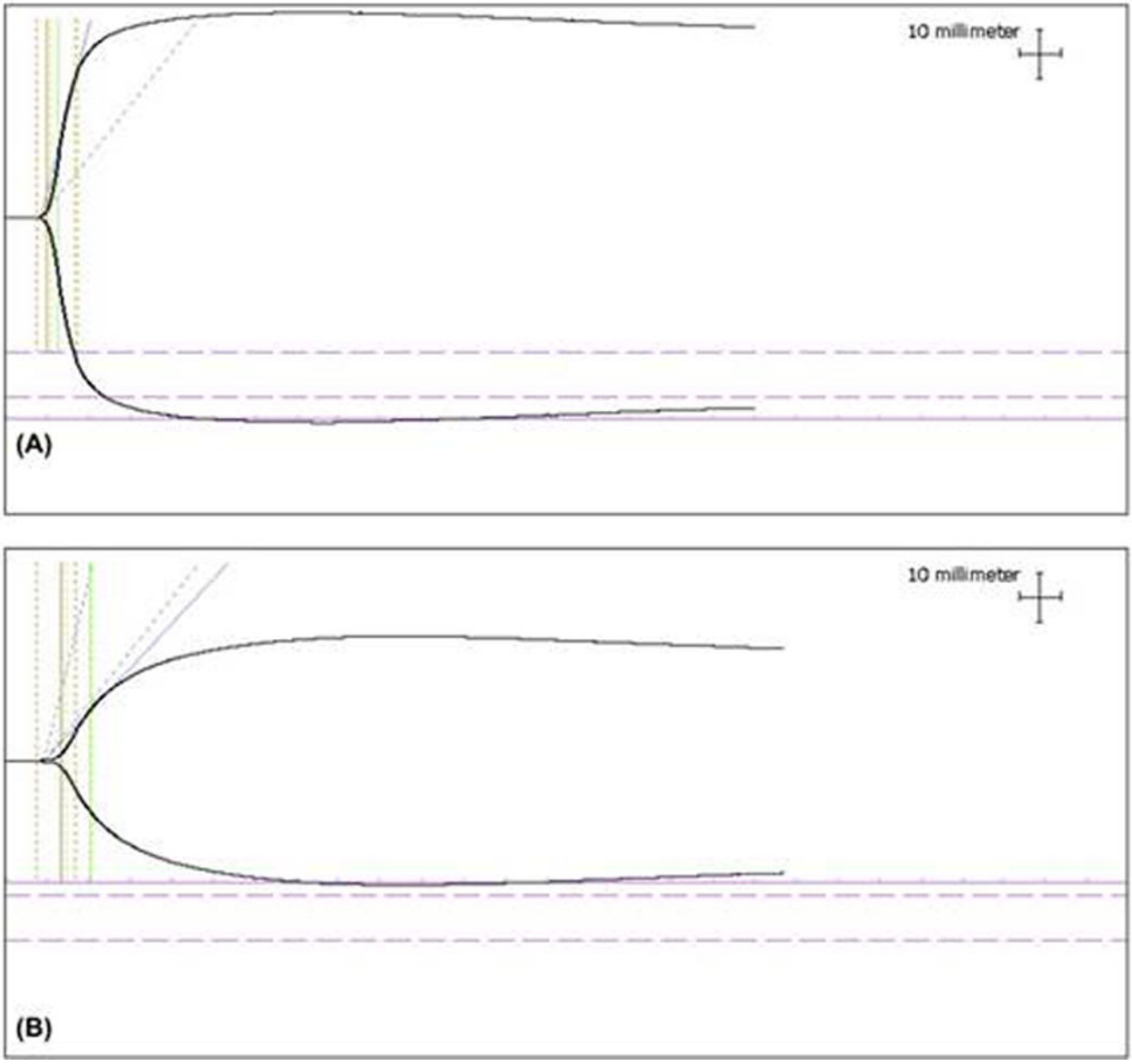

Figure 3.

TEG profiles from a healthy parturient who experienced normal bleeding postpartum and a parturient who experienced major obstetric hemorrhage.[67] Two thromboelastographic profiles represent: (A) TEG profile in a woman with normal bleeding postpartum with an estimated blood loss 250 mL, TEG-R 4.9 min, TEG-MA 81.4 mm, platelets 239 × 10^9/L, fibrinogen 6.0 g/L and antithrombin 0.98 kIU/L; and (B) TEG profile in a woman with major obstetric hemorrhage with an estimated blood loss 2500 mL, TEG-R 6.6 min, TEG-MA 48.9 mm, platelets 55 × 10^9/L, fibrinogen 1.7 g/L, antithrombin 0.37 kIU/L.

Source =

Title: Major obstetric haemorrhage: monitoring with thromboelastography, laboratory analyses or both?

Reference: Karlsson O et al.; Int J Obstet Anesth 2014; 23: 10–17.

Table 1

Estimated Turn Around Time for Issuing Blood

Emergency Release Products	Time (minutes)
O negative uncrossmatched red blood cells:	
2 units	2
6 units	5
Type specific red blood cells:	
Electronic crossmatched	15
Type & Cross, new specimen (Antibody Screen Negative)	60
Coomb's crossmatched (antibody screen positive, requiring antibody identification)	≥ 90

Table 2

Data on fibrinogen levels in non-pregnant women and in pregnant women during the first, second and third trimester.

	Non-pregnant controls	1st trimester	2nd trimester	3rd trimester
	Fibrinogen concentration (g/l)			
Huissoud et al.[41]	3.3 [3.1–4.6]	4.0 [3.7–4.3]	4.6 [4.3–4.8]	5 [4.4–5.8]
Adler et al.[42]	2.2 (0.4)	NA	NA	3.79 (0.78)
Uchikova et al.[43]	2.6 (0.6)	NA	NA	4.7 (0.7)
Cerneca et al.[44][a]	3.7 (0.8)	4.1 (0.7)	4.6 (0.8)	5.6 (1.1)
Oliver et al.[45][a]	NA	2.6 (0.3)	3.0 (0.2)	3.5 (0.2)
Manten et al.[46][b]	NA	3.5 (NA)	3.79 (NA)	5.1 (NA)
Choi et al.[47]	3.3 (0.5)	3.3 (0.5)	3.8 (0.5)	4.4 (0.5)

Data are mean (SD) or median [IQR]. NA, not available.

[a] Units converted from mg/dL to g/L for comparison.

[b] 1st Trimester values correspond to 9–16 weeks of gestation.