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CLINICAL ARTICLE

Changes in thromboelastography parameters in pregnancy, labor, and the immediate postpartum period

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ABSTRACT

Objective: To demonstrate changes in clot mechanics during pregnancy, and to determine the effect that delivery has on immediate postpartum thromboelastography parameters. *Methods:* In an observational cross-sectional/longitudinal study, thromboelastography was performed on whole blood aliquots obtained from women carrying singleton pregnancies attending a center in London, UK, between December 2013 and March 2014. Thromboelastography was repeated 6 hours after delivery among patients recruited in the third trimester or labor. Bleeding questionnaires were completed and routine clinical/demographic data obtained. *Results:* Overall, 112 women were included. The thromboelastography parameters were significantly correlated with length of pregnancy. From the third trimester to the postpartum period, there was a significant decrease in time until fibrin formation (R value; 5.8 vs 5.0 minutes, $P = 0.036$) and in time to reach a certain clot strength (amplitude of 20 mm; K value; 1.3 vs 1.1 minutes, $P = 0.007$). From established labor to after delivery, there was a significant increase in clot lysis at 60 minutes after the maximum amplitude of clot formation (LY60; 1.8% vs 3.1%, $P = 0.001$). *Conclusion:* The present study describes a novel finding regarding changes in clot mechanics in late pregnancy/puerperium and supports the concept of using thromboelastography as part of the routine assessments at delivery.
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1. Introduction

Thromboelastography and rotational thromboelastometry are point-of-care tests used to measure whole blood coagulation, including fibrinolysis. Thromboelastography is useful because it encompasses, and is sensitive to, all the cellular and plasma factors in whole blood involved in clot formation and degradation. It is widely used within a number of hospital settings including intensive care [1] and among patients undergoing liver and cardiac surgery [2]. Although attempts at establishing peripartum reference ranges for rotational thromboelastometry have been made [3,4], these ranges have not yet been widely accepted or validated. There are little longitudinal data demonstrating how the normal hemostatic changes that occur throughout pregnancy and the puerperium affect thromboelastography parameters.

It has long been postulated that women become hypercoaguable as pregnancy progresses, but how these changes directly affect clot mechanics is poorly understood. A previous study [5] looking at one sample timepoint has confirmed the hypercoaguable status of women at term through thromboelastography analysis. Similarly, a shift toward hypercoagulability as measured by thromboelastography [6] and rotational thromboelastometry [7] has been reported in uncomplicated pregnancies as pregnancy advances.

Globally, postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and mortality. In the UK, PPH with blood loss of more than 500 mL occurs in approximately 18% of births, with approximately 4% of births being associated with significant PPH, defined as blood loss of more than 1000 mL [8,9]. Although a previous review [10] called for a focus on thromboelastography/rotational thromboelastometry in guiding PPH management, uptake of this technology for clinical use in obstetric units has been slow, with few reported observational studies [11,12].

Current PPH management guidelines do not account for the altered baseline coagulation status seen in pregnancy. Previous authors [12] have developed thromboelastography-guided transfusion algorithms for the management of established PPH. However, although thromboelastography could potentially be used for the guidance of early interventions in PPH, data are limited and more research is required in this area [13].

The present study aimed to demonstrate how the hypercoagulable state that develops as pregnancy progresses can be measured by thromboelastography, and to determine the effect of delivery on thromboelastography parameters within the first 24 hours after delivery.

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2. Materials and methods

The present study was a single-center, observational, cross-sectional/longitudinal study. Women carrying singleton pregnancies with no substantial medical or psychiatric history were included. Women with a history of PPH and those currently taking antiplatelet or anticoagulant medications were excluded. Women with a known disorder of coagulation and those who scored positively on the self-rated bleeding score questionnaire (scores range from –3 to 41; >4 considered positive because usually warrants further hematological investigation) were excluded from the study. All women were recruited from the Royal Free London National Health Service Foundation Trust, London, UK, between December 1, 2013, and March 31, 2014. All women were approached in outpatient or inpatient departments. Ethics approval for the study was obtained from the Royal Free Hospital NHS Research Ethics Committee, London, UK. All patients gave written informed consent.

Basic demographic data were obtained and women were interviewed for completion of a bleeding score questionnaire. The questionnaire was initially validated in patients with von Willebrand disease [14], but has also been tested in patients with other mucocutaneous bleeding disorders [15].

The patients were separated into four subgroups: A1 (pregnancy duration <14 weeks), A2 (pregnancy duration 14–28 weeks), A3 (pregnancy duration 28^{+1}–42 weeks), and L (women in established labor at term [pregnancy duration 37–42 weeks]). Analyses involving groups A1 and A2 were cross-sectional analyses with one sample timepoint per patient, whereas analyses involving only groups A3 and L were longitudinal studies with two sample timepoints per patient (one during the third trimester or labor and one approximately 6 hours after delivery).

All women in group L underwent vaginal examination by trained clinical staff and were at least 3 cm dilated with regular uterine contractions. The estimated blood loss was retrieved from the labor notes, as measured and recorded by midwifery/medical staff. Blood loss was estimated "by eye" and/or by weighing swabs, as per accepted routine clinical practice.

Whole blood samples were collected in blood bottles containing sodium citrate (a reversible anticoagulant) and left to stand for 30–120 minutes before being placed in a TEG 5000 Thrombelastograph Hemostasis Analyzer system (Haemonetics, Braintree, MA, USA). A 340 μL aliquot of citrated blood was pipetted into a warmed cuvette and recalcified with 20 μL of 0.2 M calcium chloride before undergoing analysis [16]. The computerized thromboelastography analyzer recorded parameters of clot formation/lysis for each sample. Fig. 1 displays the basic relationship between thromboelastography measures and clot mechanics.

The distributions of the outcomes were tested for normality using Kolmogorov–Smirnov tests, and all were proven to be suitable for parametric statistical tests. Multiple linear regression was used to assess the relationships between pregnancy and thromboelastography outcomes. The thromboelastography outcomes in prenatal and postpartum samples were compared using paired-sample *t* tests. Group differences were explored using one-way analysis of variance. Two-tailed significance values were used, and $P < 0.05$ was considered statistically significant. The statistical analysis was performed with SPSS version 21.0 (IBM, Armonk, NY, USA).

3. Results

Of the 115 recruited women, two were excluded from the analysis because their samples were not fully analyzed by the thromboelastography analyzer, and one was excluded because of psychiatric illness. The remaining 112 women were allocated to the four subgroups: 32 to A1, 24 to A2, 33 to A3, and 23 to L. Eight women from group A3 were not followed up after delivery because of logistic difficulties. There were no significant differences in age, body mass index, platelet count, and bleeding score between the groups (Table 1). There was a significant decrease in the hemoglobin concentration as pregnancy advanced ($P = 0.030$).

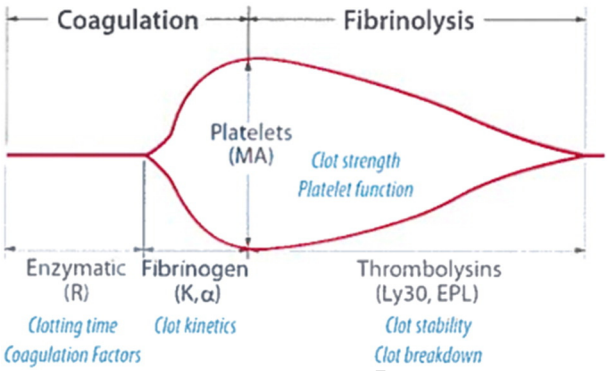

Fig. 1. A simple representation of a thromboelastography. The single line on the left of the figure represents the time taken for clotting to occur. After a short period, this line splits into two, indicating that a clot has started to form, and the shape thereon represents the size, strength, and stability of the clot. Abbreviations: α, angle between R and K (reflects the rapidity of fibrin build-up and cross-linking); EPL, estimated percent lysis; K, time to reach a certain level of clot strength (amplitude of 20 mm; reflects the fibrinogen level); LY30, rate of amplitude reduction 30 minutes after MA (reflects clot stability); MA, maximum amplitude (reflects the dynamic properties of fibrin and platelet bonding via glycoprotein IIb/IIIa); R, time from placement of blood in the analyzer until initial fibrin formation (reflects the reaction time). Reproduced from *TEG 5000 Haemostasis analyzer system* brochure [17], with permission from Haemonetics (Braintree, MA, USA).

The main thromboelastography values during pregnancy and the postpartum period are displayed in Table 2. There were significant differences between the groups for all thromboelastography variables except for the latency from placement of the blood in the analyzer until initial fibrin formation (R value). Multivariate linear regression was used to correlate pregnancy with thromboelastography parameters across all four groups. When taking age, body mass index, hemoglobin concentration, and platelet count into consideration, there was a significant positive correlation between pregnancy and the rapidity of fibrin build-up and cross-linking (α parameter; $\beta = 0.253$, $P = 0.012$) and between pregnancy and the dynamic properties of fibrin and platelet bonding via glycoprotein IIb/IIIa (maximum amplitude [MA]; $\beta = 0.358$, $P < 0.001$). Moreover, there was a significant negative correlation between pregnancy and the time taken to reach a certain level of clot strength (K value; $\beta = -0.240$, $P = 0.011$) and between pregnancy and the rate of amplitude reduction 30 minutes after the maximum amplitude had been reached (LY30 value; $\beta = -0.264$, $P = 0.012$).

The thromboelastography parameters for paired prenatal/intrapartum and postpartum samples were compared in groups A3 and L (Table 3). In group A3, both the R time and the K time were significantly shorter in the postnatal samples. In group L, the values for LY30 and LY60 were significantly higher in the postnatal samples (Table 3, Fig. 2).

All women in the study underwent full blood count testing at the time of each thromboelastography analysis, unless they had already undergone full blood count testing within the previous 30 days. Every patient in the study had a platelet count of more than 100×10^9/L and a hemoglobin concentration greater than 80 g/L at all sample points while in the study.

4. Discussion

The present study has provided further evidence to indicate that women become hypercoaguable as pregnancy increases and provides data for the establishment of thromboelastography reference ranges throughout pregnancy, labor, and the immediate postpartum period. It has also demonstrated novel findings regarding the mechanics of clot breakdown within the first 24 hours after delivery. The present data indicate that, as pregnancy continues toward term, thromboelastography

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