Thromboelastometry, a Possible Tool to Identify Women at Risk of Pregnancy Loss

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Abstract: *Background*: Laboratory methods to study women at risk of fetal loss are essential. Global hemostasis assays are the best methods to detect hypercoagulable states. Thromboelastometry (TEM), may provide extensive information for hypercoagulable states. TEM, performed by the ROTEM (the modified rotation thromboelastogram analyzer), provides a velocity curve of clot formation with new parameters: MaxVel, t-MaxVel, AUC.

Methods: TEM was performed on 87 non-pregnant women (average age 33 years, range 20-45) with a history of recurrent early/or late pregnancy loss and on 76 healthy women (average age 34 years, range 25-42) with no history of pregnancy loss. TEM standard CT, CFT, MCF and ROTEM velocity parameters were assayed. Prothrombin fragment 1+2 (F1+2), Thrombin Activatable Fibrinolysis Inhibitor (TAFI) were also determined. Continuous variables were analyzed using the Mann- Whitney U test. P values less than 0.05 were taken as statistically significant. The correlation between AUC with F1+2 and TAFI values was calculated by the Bland and Altman plot and the Mountain plot methods of comparison.

Results: The CT (51 sec; 49- 59; *vs* 51sec; 47- 54; p= 0.1113), the CFT (87 sec; 79-95; *vs* 77 sec; 69- 81; p ‹ 0.0001), the MCF (62 mm; 58- 65; *vs* 65; 61- 70; p= 0.0020) were not different in women with recurrent fetal loss (RFL) as compared with controls. The MaxVel (14 mm*100 sec; 8-30; *vs* 15 mm*100 sec; 11-23, p = 0.0989) the t-MaxVel (101sec; 54-146; *vs* 115 sec; 57-158; p= 0.0649) were not significantly different in women with RFL compared with controls. The AUC (6122 mm; 5074- 6932) was significantly higher amongst patients compared with controls (AUC 5778 mm; range 4683- 6784; p‹ 0.0001). Positive correlation of AUC values was found with higher F1+2 and TAFI levels.

Conclusions: The women with previous fetal loss, tested in our study, showed high AUC values, indicating a hypercoagulable pattern. Therefore, the authors believe that further studies are necessary to clarify whether ROTEM velocity parameters could be utilized to identify women at risk of fatal loss and to suggest a suitable prophylactic regimen to prevent pregnancy loss.

INTRODUCTION

Approximately 1 in every 10 pregnancies ends in early death of the embryo or the fetus and 1 in every 200 pregnancies ends in late fetal loss [1, 2]. A successful pregnancy requires the development of physiological placental circulation. The pregnancy loss (embryonic and fetal loss) may have an impaired placental circulation as the determinant. The inadequate placental circulation (in part due to uteroplacental thrombosis) and/ or abnormal placentation is likely to be influenced by coagulation activation and fibrinolysis at the maternal- fetal interface [1]. Acquired and genetic thrombophilia has been associated with such a condition [3] Pregnancy is a hypercoagulable state with an increased thrombotic risk throughout gestation and the postpartum period. Women with thrombophilia may have a further increased risk of placental vascular complications [4]; thrombophilia indeed may increase the risk of placental insufficiency due to thrombosis and also increase the risk of abnormal placentation due to coagulation activation at the maternal-fetal interface [5]. In view of the potential association of thrombophilia and pregnancy loss, and of the high prevalence of thrombophilia in white people, demand for screening has increased [6]. Moreover, as the performance of a comprehensive laboratory screening for thrombophilia is complicated and expensive, new tests for thrombotic risk are eagerly expected. Conventional laboratory clotting techniques can not fully identify subjects with an increased thromboembolic risk. The performance in plasma and the addition of buffered solutions limit their relevance to overall dynamic clot formation in whole blood; in contrast, thromboelastography (TEG), a test on whole-blood hemostasis, specifically assessing overall coagulation, may provide a global evaluation of haemostatic function also in subjects at thrombotic risk [7]. Studies using TEG have previously shown a hypercoagulable state in healty full term parturients compared to non-pregnant women [8, 9]. Rai *et al*., have reported that pre-pregnancy MA of TEG was

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history of pregnancy loss are examined for known thrombophilias but the relative risk associated with a single factor is small and the prognostic significance for an individual is unclear. Thromboelastography is a valuable method which monitors hemostasis under low shear environment, as a whole dynamic process, instead of revealing information on isolated parts of different, linked pathways. Indeed TEG provides information about the inter process of clot formation which results from interdependent steps: coagulation activation, thrombin production, fibrin formation and polymerization, platelet activation, platelet-fibrin interaction. However, TEG may detect hemostatic alterations that lead to a prothrombotic state not revealed on conventional tests. Rai *et al*. have shown TEG to be useful in investigating non-pregnant women with previously unexplained recurrent fetal losses (RFL). The RFL group had significantly greater (MA) compared with control group [9]. Thromboelastometry (TEM), is the latest modification of classical thromboelastography where the activation of the samples accelerates the measurement process and enhances reproducibility. Until now TEM has been utilized mainly to detect hypocoagulative states [21] and to drive therapeutic interventions in patients who undergo major surgery and organ transplantation [22]. To date, it has been rarely utilized in hypercoagulability setting [7, 23]. Therefore, we decided to see whether TEM would be a tool to identify women at risk of RFL. In our study, standard ROTEM parameters, CT, CFT, MCF were not different between patients and controls. Among ROTEM derivate parameters, AUC values, which are expected to better correlate with hypercoagulable state [24], were significantly higher in patients than in controls. An increased level of prothrombin fragment (F1+2), a marker of thrombin generation, amongst non-pregnant women with RFL, complements our study. Increased level of thrombin-antithrombin complexes, in non-pregnant women with previous RFL, compared with controls, was found in the work of Vincent *et al*. [25]. TAFI levels were not increased in women with RFL; nevertheless a positive correlation has been found between high AUC values and higher F1+2 and TAFI levels. The role of TAFI system (proCPU/CPU) is important in the balance between fibrin deposition and removal; the proCPU provides a regulatory link between the coagulation and fibrinolysis. When the system is altered, such as in the case of exacerbated thrombin generation, then, this can lead to an enhanced thrombotic tendency [26]. Therefore TEM, being relatively fast and reproducible, would be a possible tool to study women at risk of fetal loss with or without thrombophilia.

In conclusion, the authors believe that high AUC may indicate a hypercoagulable pattern and further studies should be performed to clarify whether these new ROTEM parameters could be used to identify women at risk of fetal loss. Moreover, to identify as soon as possible a trend towards the hypercoagulable state in women with RFL, without other etiological factors, may be particularly interesting. The antithrombotic treatment in thrombophilic pregnant women with previous RFL has improved prognosis of the pregnancy; the possibility of starting early antithrombotic prophylaxis before the beginning of pregnancy, after a positive TEM analysis, should be considered

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