Global Hemostasis in Pregnancy: Are We Using Thromboelastography to Its Full Potential?

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ABSTRACT

Pregnancy is a unique situation where significant physiological changes in all maternal organ systems take place. Most of these changes return to normal after delivery. During normal pregnancy the hemostatic balance changes in the direction of hypercoagulability, thus decreasing bleeding complications at time of delivery. The pregnancy-associated hypercoagulability sets a foundation for hemostatic abnormalities during pregnancy and may be associated with pregnancy complications. Assessment of the hemostatic status in pregnancy and its complications can be critical to diagnosis and management not only within the obstetric ward but in trauma, anesthesia, and other situations. Conventional global tests such as prothrombin time and activated partial thromboplastin time cannot define this status appropriately, and full assessment requires measurements of several parameters. Thromboelastography (TEG) is a global hemostatic test that can analyze both coagulation and fibrinolysis. The technique has been available since the 1940s, but only recently has it shown great impact within the clinical practice arena. TEG measures the interactive dynamic coagulation process from the initial fibrin formation to platelet interaction and clot strengthening to fibrinolysis, which makes it superior to other conventional tests. In addition, TEG can guide therapy by documenting changes in coagulation in vitro before a therapy is instituted and also by helping the clinician make critical decisions. Despite the clear value as a test for monitoring hemostatic status of pregnancy-related complications, TEG is still underused for reasons such as poor awareness regarding the technique and interpretations, lack of full standardization, and the unavailability of large clinical studies. However, the fact remains that TEG is undoubtedly attractive to both researchers and clinicians, particularly in a point-of-care setting. We hope that much more investment is directed to TEG studies in both experimental and clinical fields to improve applications and promote use, especially with respect to clinical decision making in pregnancy-related complications.

KEYWORDS: Pregnancy complications, thromboelastography, global hemostasis, placenta, amniotic fluid

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Normal human pregnancy is associated with extensive maternal hemostatic alterations and characterized by a state of hypercoagulability. Hemostasis is a complex network of interactions integrating blood vessels, platelets, coagulation factors, coagulation inhibitors, fibrinolytic factors, and natural anticoagulants, all of which contribute to maternal hemostatic alterations. Although most hemostatic measurements are reported in the peripheral circulation, evidence exists that more marked changes of coagulation and fibrinolytic activation take place within the utero–placental vasculature.2,3

The placenta is a unique organ that is highly vascularized, functioning as an interface between fetal and maternal blood; the latter flows in decidual arteries and washes the intervillous spaces in contact with syncytiotrophoblast (STB) cells. The special structure of the placenta requires efficient mechanisms for rapid activation and localized regulation of coagulation.4,5 STB cells acquire several vascular characteristics as pregnancy progresses including the expression of the adhesive protein von Willebrand factor (VWF), the CD31 marker, and other coagulation components. Both STB and trophoblast cells are a robust source of tissue factor (TF), the key initiator of hemostasis.6 The documented presence of placental fibrin depositions in normal pregnancies suggests that activation of coagulation may be a favored process for handling hemorrhages during pregnancy or at delivery. Increased levels of thrombin–antithrombin III complex, a marker of in vivo thrombin formation, has been reported in blood from the uterine vein of normotensive pregnancies compared with levels drawn from the antecubital vein.8 In addition, the placenta is a source of elevated levels of plasminogen activator inhibitor (PAI)-2 observed during pregnancy and at delivery.9

The placenta is not the only element involved in the maternal hemostatic alteration. Amniotic fluid (AF) has also been reported to have procoagulant activity.10 The addition of AF accelerates clot formation in vitro conventional coagulation tests,11 a property that has been attributed to TF.12 TF levels are higher in AF than that of the maternal plasma.13

The placenta and AF play a critical role in the hemostatic picture of pregnancy, and hemostatic alterations are also known to contribute to the observed hypercoagulable state in normal pregnancy.14,15 To maintain hemostatic balance, local inhibitory mechanisms including tissue factor pathway inhibitor (TFPI-1 and TFPI-2), thrombomodulin, annexin V, and the fibrinolytic system exist within the utero–placental vasculature to limit coagulation activation and fibrin deposition during pregnancy.8

This review discusses the hemostatic changes in normal pregnancy, explains the value of thromboelastography (TEG) in monitoring hemostatic status in normal pregnancy and pregnancy complications, analyzes different TEG studies available in the literature, and provides recommendations to support further investigations of TEG’s usefulness in this area.

HEMOSTATIC CHANGES DURING NORMAL PREGNANCY

Most procoagulant factors increase during normal pregnancy. There is a progressive increase in the levels of factor (F) VII, FVIII, FX, FXII, VWF, and fibrinogen. The rise in these factors, in particular FVIII and VWF, is generally more marked in the third trimester.16,17 Levels of FV and FIX are slightly increased or unchanged during normal pregnancy.17,18 Studies of prothrombin (FII) have yielded inconclusive results, showing both increases17 and decreases18 and levels of FXI decrease during pregnancy.15,19 FXIII levels are reported to decrease during pregnancy.20 As a result of these changes, the international normalized ratio falls through pregnancy and is usually 0.9 by the third trimester, whereas the activated partial thromboplastin time (aPTT) usually remains unchanged.21 Several studies have reported an increase of global markers of coagulation activation such as a progressive increase in the thrombin–antithrombin complex,8 prothrombin fragment 1 + 2,21,22 and fibrinopeptide A.23,24

Platelet count, activation, and aggregability are also altered during normal pregnancy with most studies reporting thrombocytopenia. O’Brien and colleagues have demonstrated a significantly lower platelet count but an increase of circulating platelet aggregates in normal pregnancy compared with nonpregnant controls.25 Pregnancy is also associated with increased platelet activation as shown by elevated basal CD63 levels, a marker of activated platelets.26

Most studies report that natural inhibitors of coagulation, including antithrombin (AT) and protein C remain stable during pregnancy,17–21,27 with the exception of total and free levels of protein S reduction seen as early as 6 to 11 weeks of gestation.18,21,28 An activated protein C resistance has also reported in some normal pregnancies.29

TF is a key player and the primary initiator of coagulation. Soluble levels of TF remain constant during normal pregnancy.30,31 However, there is an increase in local expression of TF. STB and, to a lesser extent trophoblasts lining intervillous spaces, have been reported to express TF.4,30 Further, perivascular decidualized human endometrial stromal cells are ideally positioned to prevent hemorrhage during trophoblast invasion by expressing TF.31

Interestingly, monocyte TF activity and expression are lower in normal pregnancy when compared with nonpregnant women.32 TF expression on macrophages can be modulated by anti-inflammatory cytokine interleukin-10, which is increased in normal pregnancy.33 Lower TF expression and activity on
circulating monocytes may play an important role in protecting pregnant women from thromboembolism, despite increases in many of the clotting factors and the hypercoagulable state described earlier.

Although profound alterations of the fibrinolytic system are known to occur during normal pregnancy, reports on the status of fibrinolytic activity have been inconclusive. Some studies suggest that fibrinolytic activity is enhanced, perhaps as a compensatory response to increased fibrin levels. Others report fibrinolytic activity to be impaired. Further, some authors suggest that the observed alterations do not affect the overall fibrinolytic activity. Reported levels of tissue plasminogen activator (tPA) are also incongruent among authors. Cerneca et al reported an increase in tPA levels while still within the normal range. Conversely, Wright et al and Kjellberg et al reported significantly decreased tPA activity. It is well established, however, that there is an increase of the major cell- and placental-derived plasminogen activator inhibitors, PAI-1 and PAI-2, respectively. PAI-1 has been shown to be increased in late gestation, whereas PAI-2 is detectable in plasma during the first trimester and increases progressively. It is evident that fibrinolytic activity is not completely shut down because degradation products, namely levels of D-dimer and plasmin-α 2-antiplasmin complex are observable and actually increase as pregnancy progresses. Table 1 shows detailed changes in coagulation and fibrinolytic parameters during pregnancy.

Table 1 Parameters of Hemostasis and Their Changes during Normal Pregnancies

<table>
<thead>
<tr>
<th>Hemostatic Parameter</th>
<th>Change during Normal Pregnancy</th>
<th>Authors Cited</th>
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<tbody>
<tr>
<td>FXI</td>
<td>Decrease</td>
<td>Bonnar, Bern, Brenner, Letsky</td>
</tr>
<tr>
<td>TAT III complex</td>
<td>Increased levels especially in mid to late gestation (28–32 weeks) Significantly elevated levels in uterine vein versus antecubital vein</td>
<td>Higgins et al, Bremme et al</td>
</tr>
<tr>
<td>Soluble fibrin (end product of coagulation)</td>
<td>Significantly elevated during third trimester as compared with postpartum levels, although no change during pregnancy Significantly elevated in uterine vein versus antecubital vein of normotensive women</td>
<td>McKillop et al, Higgins et al, Bremme et al</td>
</tr>
<tr>
<td>PT</td>
<td>Decreased throughout gestation up to 20th week, after which it remained stable</td>
<td>Cerneca et al, Uchikova and Ledjev</td>
</tr>
<tr>
<td>TT</td>
<td>Significantly increased</td>
<td>Uchikova and Ledjev</td>
</tr>
<tr>
<td>APC-R</td>
<td>Progressive resistance</td>
<td>Schlit et al, Walker et al</td>
</tr>
<tr>
<td>TAT III complex</td>
<td>Increased levels especially in mid to late gestation (28–32 weeks) Significantly elevated levels in uterine vein versus antecubital vein</td>
<td>Higgins et al, Bremme et al</td>
</tr>
<tr>
<td>Prothrombin fragment 1,2</td>
<td>Increase progressively, peaking in the third trimester</td>
<td>Schlit et al, Rosenkranz et al, Cerneca et al</td>
</tr>
<tr>
<td>FPA</td>
<td>Significantly increased during mid and late gestation in comparison with first trimester</td>
<td>Woodhams et al, Bellart et al</td>
</tr>
<tr>
<td>Plasmin-α 2-antiplasmin complex</td>
<td>Increase</td>
<td>Uchikova and Ledjev, Hellgren</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Significantly elevated during late gestation (33 weeks +) as compared with early gestation and postpartum</td>
<td>Francalanci et al</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Increased</td>
<td>Bellart et al, Bremme et al, Halligan et al</td>
</tr>
<tr>
<td>PAI-2</td>
<td>Increased</td>
<td>Rosenkranz et al, Cerneca et al</td>
</tr>
<tr>
<td>tPA</td>
<td>Decreased</td>
<td>Ishii et al</td>
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VWF, von Willebrand factor; TAT, thrombin-antithrombin; PT, prothrombin time; TT, thrombin time; APC-R, activated protein C resistance; FPA, fibrinopeptide A; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator.
can still be mounted.23 Generally, it appears there is an equilibrium between fibrinolysis and coagulation maintaining a hemostatic balance in normal pregnancy (Table 1).

ENHANCED COAGULATION IN RELATION TO THE GESTATIONAL AGE

Although numerous studies have focused on hemostatic changes during a restricted period of pregnancy, sequential longitudinal studies carried throughout gestation have elucidated gradual changes in several hemostatic parameters. These studies have helped the definition of timing of certain hemostatic changes. Fibrinogen starts to increase as early as the 10th week of gestation up to the 20th week of gestation, after which levels do not change significantly.21 There is a gradual increase in thrombin generation over the course of pregnancy from week 7 through 42.40

AF studies have shown that its procoagulant effect is related to gestational age,41 and it was also shown that the second and third trimesters are periods of enhanced coagulability throughout normal pregnancy42 and persist through the first 24 hours after delivery. It is also known that hemostatic parameters are normalized on average by 43 to 64 weeks postpartum.

It must be noted that the discrepancy seen in the literature regarding changes in hemostatic parameters during pregnancy is likely to be due to variation in methodology and also timing of testing in relation to gestational age.

GLOBAL HEMOSTASIS IN PREGNANCY

Thromboelastography: Principle and Technique

TEG is a global hemostatic assay that measures the kinetics of clot formation. When coagulation begins, fibrin strands form between a thermostatically controlled warmed cuvette that oscillates through an angle of 4° to 45° degrees to mimic venous flow. A torsion wire is inserted and subjected to a change in tension as the clot begins to form. Through electromagnetic measurements, the changes in tension are transmitted to a computer to produce a real-time tracing that includes several parameters by which the coagulation status of the blood can be analyzed. The trace represents a continuous development of the clot, initiated within a fluid blood, through its formation and increased clot strength and stability, to fibrinolysis or clot dissolution.45 Further, TEG provides information on the rate and strength of the clot. TEG is sensitive to detection of both hyper- and hypocoagulation abnormalities. Whereas TEG illustrates a real-time continuum of coagulation and fibrinolysis, conventional coagulation tests such as prothrombin time (PT) and aPTT measure specific points of the process in isolation. For further details about the assay, interpretations, and standardization, refer to other reviews within this issue of Seminars in Thrombosis and Hemostasis.46–48

TEG at the end of a normal pregnancy shows decreased clotting time (R), decreased clot formation (K), increased rate of clot formation (α), and increased maximum amplitude (MA), which in conjunction represent a hypercoagulable state (Fig. 1).49,50 However, it is not clear at which gestational age these TEG changes actually become apparent. Sharma et al showed that between 12 and 18 weeks of gestation, R values are normal, but K, α, and MA already show evidence of hypercoagulability.49 Further work is needed to establish a precise point during which hypercoagulation can be demonstrated in pregnancy and also how long it persists postpartum.

It must be noted that typical laboratory tests such as PT and aPTT do not give separate reference intervals for normal pregnant women, and different reference ranges/intervals must be established for each laboratory when employing TEG.51

Little is reported of sequential TEG changes in normotensive pregnancies. Grogan and Gorton52b reported a single case of normotensive pregnancy using serial TEG analysis performed throughout pregnancy. Samples were taken once in the first trimester, then at 2 to 3 weekly intervals. MA plotted against gestational age indicated an increase in clot strength starting in early in the second trimester and becoming more stable later in
Why Do We Need a Test for Global Hemostasis in Pregnancy?
As outlined earlier, normal human pregnancy is associated with a state of hypercoagulation. A sixfold higher incidence of venous thromboembolism has also been reported in pregnancy, with the increased risk beginning as early as the first trimester. Conventional global tests, such as PT and aPTT cannot detect this hypercoagulable condition, and therefore there is a need for a global and more sensitive test to help unravel the causes of this increased risk.

Pregnancy can also be associated with a considerable number of clinical complications in which hemostatic diatheses can be a major manifestation, including preeclampsia, amniotic fluid embolism, disseminated intravascular coagulation (DIC), miscarriages, placental abruption, and intrauterine fetal death.

Evidence exists that global hemostatic tests are more sensitive than conventional tests in detecting abnormal hemostasis compared with individual measurements of coagulation components. Thrombin generation tests, for example, have shown that endogenous thrombin potential is increased with duration of normal uncomplicated pregnancy. Preterm labor (PTL) has been associated with an increased thrombin generation in the maternal circulation and in amniotic fluid. Women in PTL have a higher TF activity and a lower TFPI concentration compared with those in labor at term. This is not associated with a significant change in the maternal plasma TF concentration, suggesting that the increased thrombin generation reported in these patients may be the result of activation of the extrinsic pathway of the coagulation cascade or insufficient anti-coagulation.

Difference was shown between the levels of intra-amniotic thrombin generation between term and preterm parturition. Preterm delivery is associated with an increased intra-amniotic thrombin generation regardless of the presence of intra-amniotic infection/inflammation (IAI). In contrast, term delivery is associated with an increased intra-amniotic thrombin generation only in patients with IAI. These reports indicate the value of using a global assay to predict, diagnose, or monitor hemostasis in pregnancy and its complications.

It is well established that some cases of recurrent miscarriage have a thrombotic basis. TEG has identified women with recurrent miscarriage to be in a prothrombotic state outside of pregnancy and has helped stratify the risk of miscarriage in future untreated pregnancies. Furthermore, increased thrombin generation in the maternal circulation has been reported in several other obstetric syndromes including preeclampsia, fetal growth restriction, and preterm rupture of membranes.

The Value of Thromboelastography in the Diagnosis and Management of Pregnancy Complications
TEG was used for the management of the hemostatic problems in obstetric disorders until the early 1990s. TEG is capable of making a distinction between dilutional coagulopathy and DIC and was also found to represent a rapid diagnostic tool of coagulopathy, allowing a timely therapeutic administration of blood products. A TEG-guided management of a case of essential thrombocythemia was also reported.

Various studies have used TEG to assess aspirin treatment in both normotensive and high-risk pregnancies, but results were sometimes of limited value. Among pregnancy complications, preeclampsia appears to be the highest focus in most TEG reports, where pronounced TEG changes were reported. Although patients with mild preeclampsia are known to be hypercoagulable, those with severe preeclampsia and platelet count <100 x 10^9/L are usually hypocoagulable. Significant associations were found between TEG changes and proteinuria, an essential feature in the preeclampsia syndrome. There is a strong correlation between low platelet count and MA, and it has been shown that the MA does not decrease until the platelet count decreases below 70 x 10^9/L. A study by Orlikowski and colleagues of 49 women suggested that TEG could be used as an alternative or in conjunction with platelet count as an index of coagulopathy.

TEG has been employed to rapidly evaluate the coagulation status and monitor patient response to goal-directed therapeutic interventions during pregnancy and the postpartum period. In a case of severe vaginal bleeding following delivery of twins at 40 weeks of gestation, TEG facilitated the management of the hemostatic defects and appropriate transfusion products. TEG parameters (MA, R, K, and a) were also found to be useful in the evaluation of coagulation in the hemolysis, elevated liver enzyme, and low platelets syndrome.

TEG has been reported to be useful in assessing hemostasis in a variety of other obstetric conditions. It was used to assess coagulation during regional anesthesia with low platelets, guide the treatment of DIC, monitor the anticoagulant effect of low molecular weight heparin in the peripartum period, assess coagulation in preeclampsia, and study the effect of magnesium on coagulation in preeclamptic parturients receiving intravenous magnesium.
ARE WE INVESTING ENOUGH IN THROMBOELASTOGRAPHY IN OBSTETRICS?

Historically, TEG was used frequently in liver transplantation and cardiac surgery to monitor coagulopathy and anticoagulant therapy and guide the administration of transfusion products. Between the 1980s and early 1990s, several studies focused on exploring other values of TEG. During the mid to late 1990s, there was an intensive use of TEG in trauma and obstetrics, monitoring coagulopathy in preeclampsia and other pregnancy complications. Most studies that showed the benefit of TEG measurements compared with standard coagulation tests were in anesthesia and trauma patients.

TEG is not a conventional hemostasis test. TEG uses whole blood samples, whereas coagulation tests (PT, aPTT, fibrinogen) are performed with platelet-poor plasma. This makes the test more physiological and therefore likely to provide a closer to “real” hemostatic picture, taking into consideration the interactions between different components of hemostasis within the whole blood sample. TEG is a point-of-care test and is relatively easy to perform compared with other conventional tests of coagulation. In addition, TEG requires only small blood volumes.

Up until the early millennium years, criticism has been that the relationship between the hypercoagulable nature of pregnancy and TEG is not fully explored, the correlation between coagulation factors, fibrinogen, and TEG tracings is not fully investigated, and appropriate reference intervals are sometimes lacking or not always used. Variation among laboratories has existed in methodology that has led to some inconsistencies and inability to compare data from various studies. TEG has not been typically included by hemostasis laboratories in quality assurance procedures, and there is lack of large randomized, highly powered comparative biological studies, and thus TEG has remained a research tool in the view of some authors.

In the past 5 years, however, this picture has improved dramatically. Interpretation of the TEG trace and the factors that affect the kinetics of the clot are now better understood. The technique has now gained international scientific support form investigators worldwide and also from international thrombosis and hemostasis organizations. An international working group, supported by the International Society of Thrombosis and Haemostasis, has been established and is currently active in addressing the need for standardization of this assay. The group has undertaken several exercises in this respect to date. In addition, TEG is currently subject to careful assessment and quality control measures and studies.

CONCLUDING REMARKS

Pregnancy is a state of hypercoagulability, which is clearly demonstrated by conventional tests as well as TEG. Normalization of parameters occurs around 6 weeks postpartum. Pregnancy-related complications can result in hemostatic diathesis, which is critical to the fetal and maternal outcome. The availability of a single, sensitive, and global test such as TEG to monitor hemostasis is undoubtedly attractive to both clinicians and researchers, particularly as it can be used in the point-of-care setting. We hope that an investment in further experimental and clinical studies will continue to enrich our understanding and promote the use of TEG with respect to clinical decision making in pregnancy-related complications. We believe collaborative worldwide efforts as well as standardization studies will gradually improve the confidence in the use of TEG in obstetrics and other clinical fields.

REFERENCES


52b. Grogan H, Gorton H. Thromboelastography (TEG) changes during pregnancy: a personal view. Presented at: The Obstetric Anaesthetists' Association annual meeting; May 9–10, 2002; Nottingham, United Kingdom