Assessing and Managing Bleeding Disorders During Pregnancy: Faculty Selections
October 20, 2010
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**Introduction**

The presence of bleeding disorders presents unique clinical challenges during pregnancy and childbirth. Complications may include increased risk of miscarriage, placental abruption, postpartum hemorrhage (PPH), and bleeding complications for the fetus.

Recently, several publications have called attention to the clinical challenges of managing patients with rare bleeding disorders during pregnancy, as well as advances in point-of-care testing. A synopsis of these articles is provided below, along with commentary on their clinical relevance.

**Bleeding Disorders During Pregnancy: Clinical Manifestations and Management**

*Primary Author: R. Kadir*

*Co-authors: C. Chi and P. Bolton-Maggs*

*Article: Pregnancy and rare bleeding disorders*

*Reference: Haemophilia, 2009;15:990-1005, [Click here](#) to read the abstract of this article.*

**Synopsis**

Limited data exist on the management of pregnancy in women with rare inherited bleeding disorders. These include deficiencies of fibrinogen, factor V, factor VII, factor X, factor XI, and factor XIII, along with combined deficiencies of factors V and VIII and deficiency of the vitamin K-dependent factors, II, VII, IX, and X. Although these disorders account for only 3% to 5% of all inherited coagulation disorders, they are associated with high morbidity, including miscarriage, perinatal death, and PPH. Clinical manifestations vary, and treatment must be individualized based on the patient’s presentation, history, and factor deficiency. Obstetric risk factors and causes of PPH should not be overlooked in women with rare bleeding disorders ([Table 1](#)). A careful, multidisciplinary approach involving an obstetrician, hematologist, and anesthesiologist is paramount to minimize the potential for complications among such patients.
Key Facts

- The management of women with rare bleeding disorders may be complicated by a variable bleeding tendency
- Congenital bleeding disorders have been associated with recurrent miscarriages, placental abruption, PPH, and other complications
- The 3 principles for reducing the risk of PPH are prophylactic treatment to normalize hemostatic status, measures to avoid uterine atony, and delivery with minimal genital trauma

Key Recommendations

- A close and ongoing collaboration between obstetricians and hematologists is essential for the management of pregnancy in women with bleeding disorders
- Relevant coagulation factor levels should be routinely checked at initial visit, at 28 and 34 weeks of gestation, and prior to any invasive procedure
- A detailed written management plan for labor and delivery should be formulated during the third trimester and provided to the mother and all caregivers
- In cases involving hemorrhage, following initial assessment and restoration of circulatory volume, local causes should be excluded and replacement of the deficient clotting factor with concomitant monitoring of factor levels should be initiated in consultation with the hemophilia treatment center or the institution's hematologists
- Available therapeutic options for rare bleeding disorders are limited (Table 2) and may require clinicians to balance the risks of bleeding against the risk of thrombosis
Risks in Selecting Treatment for Pregnant Women With Rare Bleeding Disorders

It is critical for clinicians to consider the natural history of the bleeding disorder in question, including the inheritance pattern, as the fetal and neonatal concerns might influence the antepartum, intrapartum, peripartum, and early postnatal management. In addition, clinicians need to consider the thrombotic risks that can occur from a variety of factors, such as the nature of the bleeding disorder on occasion, the consequences of medications employed to treat the bleeding disorder, and pregnancy itself.

Case Report

This patient, first described by Funai and colleagues (1997), was a 31-year-old woman, gravida 5, para 0040, who manifested both a bleeding disorder and a thrombophilia. The patient had a medical history of deep vein thrombosis and pulmonary embolism while on oral contraceptives, and was ultimately diagnosed with a protein S deficiency and low titers of anticardiolipin antibodies. She experienced recurrent pregnancy loss with normal karyotypes, despite receiving heparin anticoagulation with each conception. Of interest, her fibrinogen levels were consistent, at 70 mg/dL. The patient's father was noted to have a fibrinogen level of 125 mg/dL. After a subsequent pregnancy, the patient was treated with fresh frozen plasma (FFP) transfusions, 1 to 2 U every 2 weeks, in addition to heparin, low-dose aspirin, and progesterone supplementation. Her fibrinogen level was maintained at greater than 150 mg/dL during this time. At 38 weeks' gestation, heparin was discontinued and induction of labor followed. Due to fetal heart rate tracing concerns, the patient delivered via cesarean section. She went on to have an uncomplicated postoperative course. Of note, the newborn's fibrinogen level was 66 mg/dL.

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**Plasma Fibrinogen to Reduce Postoperative Bleeding**

*Primary Author: N. Rahe-Meyer*

*Co-authors: M. Pichlmaier, A. Haverich, C. Solomon, M. Winterhalter, S. Piepenbrock, and K. A. Tanaka*
Synopsis

The traditional management of bleeding diathesis after complex surgery involves the administration of FFP and platelet concentrates. In this pilot study, a 2-step blood products transfusion algorithm (Figure 1) was developed using retrospective data from 42 elective cardiac surgery patients to compare the hemostatic effects of conventional transfusion management and FIBTEM (thromboelastometry test)-guided fibrinogen concentrate.

Select Study Facts

- Investigators examined whether postoperative hemostasis could be improved by increasing plasma fibrinogen concentrations
- 42 elective patients (group A) were transfused with 2 U of platelet concentrate after cardiopulmonary bypass, followed by 4 U of FFP if bleeding persisted
- Assignment to 2 prospective groups (neither randomized nor blinded)
  - Group B (n=5): treated according to algorithm
  - Group C (n=10): received fibrinogen concentrate prior to algorithm-based therapy
- Fibrinogen concentrate administration was guided by the bedside assay, FIBTEM (clot strength in the presence of platelet inhibition), with an empirical target maximum clot firmness (MCF) of 22 mm and an arbitrary limit for the maximal dose set at 6 g fibrinogen concentrate

Select Study Results

- A mean of 5.7 g fibrinogen concentrate decreased blood loss to below the transfusion trigger in all group C patients
- Prior to hemostatic therapy, coagulation disturbances seen in laboratory tests were comparable between the conventional therapy groups and prospective fibrinogen therapy group
Study Evaluation Summary

Study findings from Rahe-Meyer and colleagues suggest that fibrinogen replacement will decrease the amount of allogeneic blood product transfusion and improve surgical drainage in patients undergoing cardiac surgery. The FIBTEM (thromboelastometry) is a useful bedside test to guide fibrinogen concentrate administration. Since PPH is characterized by decreases in fibrinogen concentration, the FIBTEM represents an intriguing approach to the monitoring of patients with PPH due to uterine atony. This bedside test can monitor response to therapy, especially fibrinogen concentrate.

Measuring Global Hemostasis

Primary Author: S.C. Nair

Co-authors: Y. Dargaud, M. Chitlur, A. Srivastava

Article: Tests of global haemostasis and their applications in bleeding disorders

Reference: Haemophilia. 2010;16(suppl 5):85-92. Click here to read the abstract of this article.

Synopsis

Hemostasis and bleeding disorders have traditionally been assessed by plasma clotting times, including the prothrombin (PT), activated partial thromboplastin (APTT), and thrombin time. Although these times rely upon the thrombin-dependent conversion of fibrinogen to fibrin, they note only the beginning of this process and do not take into account its speed or extent. A more complete assessment with heightened sensitivity may be obtained by utilizing tests that measure global hemostasis, such as the thrombin generation tests/assay (TGT/TGA), activated partial thromboplastin time (APTT) wave-form analysis, and thromboelastography (TEG). Global hemostasis tests have the potential to revolutionize our understanding of hemostasis and related disorders. Research is ongoing to standardize methodology, applications, and clinical correlations with the measured hemostatic parameters.

“There is a potential for significant paradigm shift in the assessment of haemostasis from the conventional plasma recalcification times, such as prothrombin time (PT) and activated partial thromboplastin time (APTT), which correspond to artificially created compartments of haemostasis to tests that assess the entire process in a more physiological and holistic manner.”

Thrombin Generation Tests/Assay

Thrombin is both the final product and the key enzyme of the coagulation system. The rationale behind measurement of thrombin generation is that it has the capacity to reflect the overall coagulating capacity of an individual while considering all influential hemostatic parameters. A standard TGT measures the overall potential of plasma to form thrombin, while a second assay is available that gauges the amounts of thrombin that are formed in vivo. This includes D-dimers, which indicate that fibrin has been formed; F1 + 2, which indicate that prothrombin has been split; and thrombin-antithrombin complex, which indicates the presence of active thrombin. All of these are markers of ongoing coagulation activation.

APTT Waveform Analysis
Activated partial thromboplastin time analysis measures the time it takes for a fibrin clot to form. Many of the most advanced automated coagulometers, particularly those that have been enabled with a photo-optical mode of detection, evaluate the entire process of the rate of fibrin formation not only in seconds, but over an extended period of time as well. With this method, the change in the optical output of the incident light of photo-optical coagulation parameters during the formation of a fibrin clot is recorded as a clot curve. The clot curve can be displayed on the coagulometer monitor and provides information regarding the velocity and amount of fibrin formation, which is reflected in the height and shape of the curve. A novel method developed by Nair and colleagues, the APTT Clot Curve Analysis (CCA) for use with the ACL 10 0000, assesses thrombin generation and fibrin clot formation based on an analysis of photo-optical data and light scatter.

Thromboelastography

Thromboelastography was first developed in 1948 by Dr. Hellmut Harter. Advances in technology over the years have improved its reliability and increased its usage and TEG is now gaining increasing attention for its potential to assess hemostatic parameters in a number of clinical settings. Thromboelastography allows for the assessment of the cumulative effects of plasma factors and platelets, leucocytes, and red cells on coagulation. Additionally, clot formation from initialization to formation and stability are measured by TEG. Currently, two instruments are available: the TEG® Hemostasis Analyzer and the ROTEM®. Minor mechanical differences between the two devices exist and results are not comparable between instruments. Initially, TEG was used to minimize transfusion requirements in patients undergoing complicated surgical procedures, but its use has now expanded to include bleeding and thrombotic disorders in a number of settings, including obstetrics.

Primary Author: A. Chen
Co-authors: J. Teruya
Article: Global hemostasis testing thromboelastography: old technology, new applications
Reference: Clin Lab Med. 2009;391-407. Click here to read the abstract of this article.

Synopsis

Thromboelastography has been in use for more than 60 years for the assessment of primary and secondary hemostasis. In recent decades, its utility in settings requiring rapid assessment of global hemostatic function during complex surgical procedures, such as liver transplants and cardiac bypass, has been well established. In addition, technical improvements including computerized equipment, real-time view from remote computers, and automatic calculation of all TEG parameters, have greatly improved its reliability. Its primary use has been to manage transfusion therapy during surgery; recently, however, its value in nonurgent patient care has garnered increasing attention.

TEG permits rapid, point-of-care calculation of many hemostatic parameters (Figure 2). These include:

- Reaction time (R): the time in minutes until levels of fibrin clot formation can be detected. This provides a general reflection of coagulation factor levels
- Angle (A): the size in degrees of the angle formed by the tangent line to TEG tracing measure at the reaction time. The angle reveals fibrinogen activity
- Maximum amplitude (MA): the width in millimeters of the widest gap in TEG tracing. This measurement indicates the greatest strength of the final hemostatic plug and evaluates the combination of platelet count and fibrinogen activity

The ability of TEG to provide rapid, point-of-care assessment of coagulation parameters with or without an FXII activator is a significant advantage. It is ideal for use in urgent settings where patients require blood component therapy. TEG is also gaining increasing use in central clinical laboratories for the assessment of hyperfibrinolysis, factor XII (FXII) deficiency, and hypercoagulable states. TEG platelet mapping can also monitor platelet function during antiplatelet therapy. TEG is also ideal for the assessment of hemostatic function in newborns because of the small specimen volume that is required. Despite the fact that the PT and PTT are prolonged in...
TEG may be useful for the early diagnosis and management of neonatal sepsis and to monitor the anticoagulant effect in neonates treated with extracorporeal membrane oxygenation (ECMO), in which bleeding complications are common due to the prematurity of the coagulation system together with the use of unfractionated heparin.

Other novel settings where the use of TEG can be valuable include:

- Factor VIII deficiency: TEG is faster and has a higher sensitivity than the standard 5 M urea solubility test or 1% monochloroacetic acid (Figure 4). TEG may also be used to monitor the effect of FXIII replacement therapy
- Hyperfibrinolysis: TEG may be a good substitute test where other tests are not available
- Glanzmann's thrombasthenia: TEG may be used when platelet dysfunction is suspected and to monitor the effects of recombinant activated factor VII (FVII) or platelet transfusion
- Hypofibrinogenemia and dysfibrinogenemia: TEG may be able to distinguish hypofibrinogenemia from dysfibrinogenemia
- Hypercoagulable states: Some data indicate TEG may reveal information relevant to thrombotic risk; more study is needed
- Disseminated intravascular coagulation: TEG may be used to monitor the effect of fibrin fragments on general hemostasis and on the inhibition of thrombin and platelets for appropriate management
- von Willebrand disease: TEG may be useful for monitoring the effect of replacement therapy in cases involving severe FVIII deficiency
- Monitoring recombinant activated FVII: Because TEG tracing demonstrates speed of clot formation and clot strength, it is considered a good test for predicting the efficacy and risk of thrombotic complications with rFVIIa therapy
- Monitoring antplatelet therapy: The advent of TEG platelet mapping enables TEG to be used for monitoring antplatelet therapy in patients using aspirin, dipyridamole, or clopidogrel

Primary Author: C. Huissoud
Co-authors: N. Carrabin, F. Audibert, A. Levrat, D. Massignon, M. Berland, and R.C. Rudigoz
Article: Bedside assessment of fibrinogen level in postpartum haemorrhage by thromboelastometry
Reference: BJOG. 2009;116:1097-1102. Click here to read the abstract of this article.

Synopsis

It has been established that early diagnosis and management of PPH is associated with improved maternal outcomes. In most cases, PPH develops as a result of uterine atony, with the subsequent presentation of coagulation disorders. PPH can also occur secondary to surgical bleeding, placenta previa, placenta accreta, abruptio placentae, uterine rupture, amniotic fluid embolism, or vaginal tearing. When bleeding occurs, a decrease in fibrinogen levels is the first indication of impairment among the coagulation biomarkers.

“When bleeding occurs, a decrease in fibrinogen levels is the first indication of impairment among the coagulation biomarkers.”

A rotation thromboelastometry system, ROTEM®, can be used in the laboratory or at patient bedside for the diagnosis of coagulation disorders in hemorrhaging patients. Huissoud and colleagues recently demonstrated that the ROTEM system can be used to detect hypercoagulation related to pregnancy. Moreover, the investigators demonstrated that ROTEM provides a fast, reliable assessment of coagulation during normal pregnancy parameters. In this paper, they analyzed the use of ROTEM to detect early decrease in fibrinogen levels in obstetric patients with PPH.

Select Study Facts
Select Study Results

- As shown in Table 3, median fibrinogen level was significantly lower in the PPH group than in the control group (3.4 and 5.1 g/L, respectively, \( P < .0001 \))
- Median clotting time (CT) was higher in the PPH group than in the control group \( (P = .05) \)
- Clot amplitude at 5 and 15 minutes was significantly lower in the PPH group than in the control group and strongly correlated with fibrinogen levels in both groups \( (r = .84-.87, \ P < .0001) \)
- Lower clot amplitudes in cases of PPH, in association with lower fibrinogen values, translated into substantial differences observed in real time on FIBTEM TEMograms (Figure 5)
- These findings suggest that the use of ROTEM in PPH could allow early and objective screening of coagulation disorders as well as rapid identification of patients at high risk for negative outcomes
- Further evaluation of real-time coagulability monitoring in PPH is recommended

Decreases in fibrinogen represent the earliest coagulation changes associated with PPH. Huissoud and colleagues have demonstrated in this elegant study that the thromboelastometry system ROTEM, with FIBTEM, detects hypofibrinogenemia and provides a real-time assessment of the evolving coagulation changes associated with PPH. The ROTEM therefore enables the physician to monitor response, literally at the patient’s bedside, to specific therapies such as fibrinogen replacement. This type of coagulation assessment, coupled with targeted therapies aimed at reversing the hemostatic derangements, represents a rational approach to the contemporary management of PPH. Confirmatory studies are required to determine if this strategy should be adopted as the norm in managing patients with PPH, particularly those with uterine atony.
**Figure 3. Normal newborn on day 0 with a low-normal reaction time.**


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**Figure 4. (A) Mild factor XIII deficiency (13%). (B) Severe factor XIII deficiency (less than 3%) before and after transfusion of cryoprecipitate.**

Table 3. Results of Standard Laboratory Tests and FIBTEM Results

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<thead>
<tr>
<th></th>
<th>Control group (n=54)</th>
<th>PPH group (n=51)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>120</td>
<td>91</td>
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<tr>
<td>Platelets (G/L)</td>
<td>193</td>
<td>145</td>
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<td>Fibrinogen (g/L)</td>
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<td>CT (s)</td>
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<tr>
<td>CAo (mm)</td>
<td>16</td>
<td>12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CAV (mm)</td>
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<td>14</td>
<td>&lt;.0001</td>
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<tr>
<td>MCF (mm)</td>
<td>19</td>
<td>15</td>
<td>&lt;.0001</td>
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Values are median.
*Comparison between controls and hemorrhages using Mann-Whitney U-test
due to tailed probability.
CAo or CAV=amplitude of the clot at 5 and 15 minutes; CT=clotting time; Hb=hemoglobin;
MCF=maximum clot firmness; PPH=postpartum hemorrhage.

Figure 5

FIBTEM traces in severe PPH.

To learn about acquired factor VIII inhibitors as a precipitating cause of postpartum hemorrhage, click here.
References


Obstetric risk factors and causes of to therapy, especially fibrinogen

Disseminated intravascular coagulation: TEG may be used to monitor the effect of fibrin

Table 3

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and low titers of anticardiolipin antibodies. She

As shown in

Reference: Clin Lab Med.

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With and without gynecologic malignancies using the thromboelastograph coagulation analyzer.


Weinkove R, Rangarajan S. Fibrinogen concentrate for acquired hypofibrinogenaemic states.