Constitutional Hypofibrinogenemia
Associated with Third Trimester Hemorrhage*

D. K. McROYAN, M.D.,† C. J. McROYAN, MT(ASCP)SH,‡
D. Z. KITAY, M.D.,§ and P. I. LIU, M.D., Ph.D.†§

Departments of Pathology,†
Obstetrics and Gynecology,‡ and Medicine,§
University of South Alabama Medical Center,
Mobile, AL 36617

ABSTRACT

This case of a 31-year-old white woman presenting at 32 weeks gestation with vaginal bleeding supports a possible association between constitutional hypofibrinogenemia and third trimester hemorrhage. Clot based fibrinogen assays were persistently low for the third trimester (patient: 102 to 155 mg per dl; normal range: 400 to 650 mg per dl) and at follow-up, ten months post-partum (patient: 90 mg per dl; normal range 180 to 436 mg per dl); an immunologic fibrinogen level was comparable. The patient gave an unremarkable bleeding history. Of 11 previously reported pregnancies in five hypofibrinogenemic patients, six terminated in placental abruption during the third trimester, two others were complicated by significant post-partum hemorrhage, and one by spontaneous abortion. This case report emphasizes that low functional levels of fibrinogen are potentially disruptive to the integrity of the uteroplacental interface. The pregnant state unmasks and amplifies an otherwise silent to mild hemostatic disorder.

Introduction

This case and the few others previously described indicate an association between congenitally or constitutionally low functional fibrinogen levels and the development of a significant third trimester hemorrhage. Furthermore, these cases suggest that the pregnant state may often unmask and amplify an otherwise silent to mild hemostatic disorder.

Congenital quantitative and/or qualitative disorders of fibrinogen are uncommon and can be segregated into four categories: afibrinogenemia, hypofibrinogenemia, hypodysfibrinogenemia and dysfibrinogenemia. Individuals with congenital afibrinogenemia have no fibrinogen demonstrable by clot based or immunologic assays. These patients manifest a significant hemorrhagic diathesis...
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throughout life. Congenital hypofibrinogenemia, however, is usually a silent to mild hemostatic defect which may defy detection unless specifically sought; affected individuals have low fibrinogen levels, usually below 100 mg per dl, which are similar if measured by clot based or immunologic assays. Congenital hypofibrinogenemia may represent a distinct autosomal dominant entity or the heterozygous state of congenital afibrinogenemia, a variably penetrant autosomal recessive disorder. Individuals with congenital hypodysfibrinogenemia or dysfibrinogenemia may manifest hemorrhage, thrombosis, or paradoxically both; the diagnosis is suggested by incongruence between clot based and immunologic fibrinogen assays and confirmed by more sophisticated and specific techniques.

The unmasking of hypofibrinogenemia during pregnancy and its contribution to the genesis of gestational hemorrhaging may be related to the hemostatic milieu present at the uteroplacental interface. This hypothesis was proposed by Prichard in 1961 as a possible cause of chronic abruption in his hypofibrinogenemic patient. Since then, studies utilizing laboratory techniques unavailable to Prichard have lent support to his speculation that hemostatic measurements on peripheral blood may not accurately reflect the environment at the uteroplacental interface. This case report assimilates some of the pertinent observations in this vein.

Case Report

A 31-year-old white gravida II, ab I at 32 weeks gestation was admitted for evaluation of third-trimester bleeding. The bleeding was initially associated with mild abdominal pain. Subsequently, irregular uterine contractions were maintained and a diagnosis of threatened premature labor and possible abruptio placenta was made. The cervix was closed, 70 percent effaced with the fetus in vertex presentation and floating. Ultrasound showed a fundal placenta with no evidence of abruption. Vaginal bleeding and uterine contractions ceased without hemotherapy within 24 hours. Liver function studies were normal. Coagulation studies revealed hypofibrinogenemia and are detailed in table I. Diagnosis of marginal sinus separation was made by exclusion.

A urinary tract infection was treated with ampicillin, and the patient was discharged on the fourth hospital day. She had an uneventful vaginal delivery at term. Ten month post-partum her fibrinogen was 90 mg per dl.

The patient’s past medical history was negative except for a single spontaneous abortion. Her menstrual history was unremarkable; there was no personal or family history of a bleeding diathesis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>12/18-22/82</th>
<th>10/13/83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet counts</td>
<td>140 - 440 x 10^9/L</td>
<td>380</td>
<td></td>
</tr>
<tr>
<td>Bleeding time</td>
<td>4 - 7 minutes</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>9.4 - 12.2 seconds</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin</td>
<td>24.0 - 35.0 seconds</td>
<td>30.5</td>
<td></td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Control, 5 seconds</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Quantitative-functional fibrinogen</td>
<td>400 - 650 mg/dl*</td>
<td>138</td>
<td>90 (ml 180 - 463)</td>
</tr>
<tr>
<td>Quantitative-immunologic plasma fibrinogen</td>
<td>400 - 650 mg/dl*</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>&lt; 10 ug/ml</td>
<td>&lt;10</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>78 - 122% Activity/ml</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen lysis time</td>
<td>&gt; 60 minutes</td>
<td>&gt;60</td>
<td></td>
</tr>
<tr>
<td>Plasminogen</td>
<td>2.1 - 4.5 CTA U/ml</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Plasmin</td>
<td>0 CTA U/ml</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alpha-2 antiplasmin</td>
<td>75 - 119% Activity/ml</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Urea solubility test</td>
<td>&gt; 24 hours</td>
<td>&gt;24</td>
<td></td>
</tr>
</tbody>
</table>

*Normal non-pregnant ranges, normal ranges in pregnancy not definitively established, reference 8; + normal range for third trimester, reference 9; CTA U: Committee on Thrombolytic Activity Units, reference 15.
Materials and Methods

All laboratory testing was performed in the University of South Alabama Clinical Laboratory utilizing standard published methodologies. Blood for coagulation testing was collected into vacutainer tubes containing 3.2 percent sodium citrate in a ratio of 9:1; blood for hematological evaluation was collected similarly into disodium ethylenediamine tetraacetic acid (EDTA) at a concentration of one mg per ml of blood. Platelet poor plasma for coagulation studies was obtained by centrifugation at 1,500 × g for 10 minutes. Complete blood counts (CBC) and platelet counts (PLT) were generated on a Coulter Model S-plus II.* The bleeding time (TBT)18 was measured using a Simplate II device.† Prothrombin time (PT) and activated partial thromboplastin time (APTT) were performed on a Coagamate X-2.† The thrombin time (TT) was generated by visual inspection of end-point using human thrombin.‡ The urea solubility test (UST), a qualitative test for factor XIII, was performed using 5M urea.

Quantitative-functional fibrinogen (FIB-CB) determinations were performed on a fibrometer§ using a Data-Fi Fibrinogen Determination Kit¶ by the method of Okuno et al.23 Quantitative-immunologic plasma fibrinogen (FIB-I) was determined¶ using a radial immunodiffusion technique with a M-Partigen Fibrinogen Kit.¶ Fibrinogen/Fibrin degradation products (FDP) were enumerated by the Thrombo-Wellco-test,** a semi-quantitative latex agglutination test using anti-FDP globulin.

The euglobulin lysis time (ELT) was determined17 using the Data-Fi Euglobulin Lysis Test Kit.¶ Plasma levels of plasminogen (PGEN), plasmin, alpha-2 antiplasmin (A2AP), and antithrombin III (AT-III) were measured13 on a Protopath Fluorometer†† using fluorogen tagged synthetic substrates in a proteolytic enzyme detection system.††

Results

Review of the coagulation studies reveals that the patient manifested a markedly decreased plasma level of clottable fibrinogen for the third trimester despite normal levels of fibrin(ogen) degradation products.10 Additionally, the level of antithrombin III was normal further discounting the possibility of disseminated intravascular coagulopathy.7 The normal platelet count and bleeding time discount quantitative or qualitative platelet dysfunction. The normal euglobulin lysis time, plasminogen, plasmin, and alpha-2-antiplasmin levels for pregnancy discount a disorder of systemic fibrinolysis.7 The normal urea solubility test, a screen for Factor XIII deficiency, discounts this defect and dysfibrinogenemias with a stabilization defect.19 The normal thrombin time discounts dysfibrinogenemias with a proteolytic phase defect. The comparability of the clot-based and immunologic fibrinogen assays is compatible with hypofibrinogenemia, but it does not totally exclude the possibility of a hypodysfibrinogenemia.11,19,21,25

Discussion

This patient’s persistently low circulating level of fibrinogen for the third trimester and a decreased level at follow-up, ten months post-partum, confirm a

* Coulter Electronics, Inc., Hialeah, FL.
† General Diagnostics, Morris Plains, NJ.
‡ Fibrindex-Ortho, Ortho Diagnostics, Inc., Raritan, NJ.
§ Becton, Dickinson and Co., Rutherford, NJ.
¶ Dade Diagnostics, Inc., Agunda, PR.
§§ Calbiochem-Behring, La Jolla, CA.
** Welcome Reagents Ltd., Beckenham, England.
†† American Dade, Inc., Miami, FL.
Hypofibrinogenemic state. The absence of a remarkable family history and the unavailability of family members for testing do not allow diagnosis of a congenital deficiency although it is believed this is likely. The normality of other laboratory testing and clinical observations suggest a constitutional deficiency and not an acquired or transient lesion, e.g., disseminated intravascular coagulation (DIC), liver disease, etc. The similarity of a clot based and immunologic fibrinogen assay suggest hypofibrinogenemia rather than hypodysfibrinogenemia. However, because of the lack of more sophisticated investigatory techniques in our laboratory, our data do not allow us to exclude totally the possibility of hypodysfibrinogenemia. In any event, it is the fibrinopenic state that is the focus of this report. Furthermore, the patient's mild bleeding history, previous spontaneous abortion, normal menstrual history, and third trimester hemorrhage are compatible with previous reports of congenital hypofibrinogenemia and hypodysfibrinogenemia in pregnancy.

On the basis of studies of peripheral blood, pregnancy has been characterized as a "hypercoagulable" state. The levels of most coagulation factors increase: fibrinogen, plasminogen, and factors II, VII, VIII, IX, and X increase, while factors XI, XIII, plasminogen activators, and antithrombin III decrease. However, there is a mounting body of evidence that these peripherally based measurements may not accurately reflect the hemostatic milieu at the uteroplacental interface.

The plasma fibrinogen level begins to rise in the first month and by late in the third trimester normally reaches a level of 400 to 650 mg per dl. This increase in fibrinogen is accompanied by a parallel increase in plasminogen, but a decreased level of plasma fibrinolytic activity as measured by the euglobulin lysis time. This effect becomes most pronounced during the third trimester. These findings have been interpreted as demonstrative of impaired fibrinolysis during pregnancy. The explanation for this apparent paradox has been the finding of decreased circulating plasminogen activators and an increased level of inhibitors. However, the euglobulin lysis time is not specific and reflects primarily activator activity as the euglobulin fraction lacks plasmin inhibitors. Further, there is evidence of sequestration of activator activity as parturition is accompanied by sharp increases in plasminogen activator levels which Bonnar attributed to loss of inhibition mediated by the placenta. The euglobulin lysis time returns to normal non-pregnant levels shortly after parturition.

Fletcher et al assaying soluble fibrin monomer complexes, a measurement of fibrin formation, fibrin(ogen)olysis and, therefore, fibrinogen turnover, have shown that (1) fibrin formation rates steadily increase fivefold by late pregnancy over control values, and (2) this correlates significantly with the progressive increase in fibrinogen throughout pregnancy. This progressive increase in soluble fibrin monomer complex formation has been confirmed. Further, the level of factor XIII, fibrin stabilizing factor, falls steadily during late pregnancy, supporting these observations. Fletcher presumed that this progressive fibrinogen requirement involves the uteroplacental circulation and noted that the histologic paucity of fibrin deposition in the term placenta supports the concept of local fibrinogen consumption and turnover.

The data available on the uteroplacental unit support the concept of normal pregnancy as a progressive state of increasingly compensated consumptive coagulopathy. The concentration of fibrinogen is lower in placental and uterine venular bloods compared to periph-
eral blood during pregnancy.\textsuperscript{4,7} Furthermore, the euglobulin lysis time in pregnant patients has been found to be shorter in ovarian blood than in peripheral blood.\textsuperscript{4} This may be attributable to elevated plasminogen activator levels in the myometrium which increase in toto by a factor of ten in late pregnancy over the non-pregnant state.\textsuperscript{3,28} However, the plasminogen activator content of the term uterus is very low and, perhaps, is related to consumption by attachment to fibrin at the time of parturition.\textsuperscript{14,28}

Trophoblastic tissue contains a larger concentration of tissue thromboplastin than any other tissue in the mammalian organism.\textsuperscript{10,26} Also, the placenta lacks plasminogen activators and is rich in plasminogen activator inhibitors.\textsuperscript{2,7,26,29} The observations that plasma plasminogen activator levels increase sharply after delivery of the placenta and that systemic fibrinolytic activity returns to normal suggest that inhibition of fibrinolysis is mediated directly or indirectly through the placenta. Taken together, the observations suggest a formidable antagonism between the plasminogen activator rich uterus and the tissue thromboplastin, plasminogen activator inhibitor rich placenta.

Of 11 documented pregnancies in five hypofibrinogenemic patients, six pregnancies have been complicated by abruptio in the third trimester, two others by significant post-partum hemorrhage, and one by a spontaneous abortion (table II). This rate is far in excess of the rate of complications in the general obstetric population. Furthermore, the present patient experienced a less serious but analogous lesion, a marginal sinus hemorrhage, at 32 weeks gestation, and a spontaneous abortion in her previous pregnancy. It is believed these bleeding complications reflect an inability to compensate for increased fibrinogen requirements with adequate production at times of increasing fibrin turnover. The plasminogen activator rich myometrium may unmask a fibrinogen deficit that was silent in the non-pregnant state.

\begin{table}[h]
\centering
\caption{Reported Complications During Pregnancy}
\begin{tabular}{lll}
\hline
\textbf{Study} & \textbf{Patient/Pregnancy} & \textbf{Complication} \\
\hline
Prichard,\textsuperscript{24} 1961 & 1/1 & 3rd trimester, abruptio \\
& 1/2 & 32nd week, abruptio \\
& 1/3 & 31st week, abruptio \\
& 1/4 & 34th week, spontaneous abortion \\
Hasselback et al,\textsuperscript{15} 1963 & 2/1 & Post-partum hemorrhage \\
Ness et al,\textsuperscript{22} 1983 & 3/1 & 32nd week, abruptio \\
& 4/1 & 28th week, abruptio \\
Strickland et al,\textsuperscript{27} 1982 & 5/1 & Post-partum hemorrhage \\
McRoyan et al, 1982 & 6/1 & 1st trimester, spontaneous abortion \\
& 2/2 & 32nd week, marginal sinus hemorrhage \\
\hline
\end{tabular}
\end{table}

Fibrinogen concentration normally increases from a mean of approximately 300 mg per dl in the non-pregnancy state to approximately 500 mg per dl in the third trimester or an approximate 60 to 70 percent increase. Our patient's non-pregnant baseline was 90 mg per dl and, during the third trimester, varied from 102 to 155 mg per dl. Although this reflects an approximately proportionate normal increase in fibrinogen, it is far below the normal mean for pregnancy and probably below the level required for uteroplacental hemostasis.

Bleeding in these hypofibrinogenemic patients may be attributable to a critical dysequilibrium at the uteroplacental interface favoring placental fibrinolysis. It is contended by us that it is this critical dysequilibrium that has precipitated the abruptions reported in these patients and the marginal sinus hemorrhage noted in our patient. This effect may be responsible for unmasking this otherwise silent to mild hemostatic defect during pregnancy. Furthermore, Prichard's original speculation that the chronic abruptions in his hypofibrinogenemic patient might be related to hemostatic requirements not reflected in peripheral blood measurements now seems quite reasonable.
References


11. **Carlbochem-Behring: M-Partigen Fibrinogen Kit, Document Number 1B2208, La Jolla, CA, 1983.**


