Clinical management of thrombophilia-related placental vascular complications

Benjamin Brenner

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, including pregnancy loss, preeclampsia, intrauterine growth restriction, and placental abruption. Preliminary data suggest that maternal antithrombotic prophylaxis may result in improved gestational outcome. Randomized trials are under way and hopefully will optimize maternal and neonatal outcome.

Introduction

Thrombophilic risk factors are common and can be found in 15% to 25% of white populations. Since pregnancy is an acquired hypercoagulable state, women harboring thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or at the postpartum period.

Data concerning treatment of venous thromboembolism (VTE) in pregnancy have been reviewed in a recent issue of Blood. This review will focus on the clinical evaluation and management of women with thrombophilia-related placental vascular complications including fetal loss, preeclampsia, intrauterine fetal growth restriction (IUGR), and placental abruption (Table 1). These complications are the leading cause of maternal and fetal adverse outcome and have a significant psychosocial impact and economical burden.

Hemostatic changes in pregnancy

In normal pregnancy, there is a marked increase in the procoagulant activity, characterized by an elevation—which is maximal around term—of factors VII, X, and VIII; fibrinogen; and von Willebrand factor. This is associated with an increase in prothrombin fragment 1+2 (PF12), and thrombin-antithrombin complexes. There is a decrease in physiologic anticoagulants manifest by significant reduction in protein S activity and by acquired activated protein C (APC) resistance. The overall fibrinolytic activity is impaired during pregnancy but returns rapidly to normal following delivery. This is largely due to placental-derived plasminogen activator inhibitor type 2 (PAI-2), which is present in substantial quantities during pregnancy. t-PA dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses. Overall, there is a 4- to 10-fold increased thrombotic risk throughout gestation and the postpartum period.

Thrombophilia and pregnancy loss

Case presentation

A 32-year-old woman presented with one child aged 6 years who was delivered after a normal pregnancy. Thereafter the woman suffered 3 consecutive pregnancy losses at 8 to 10 weeks of gestation. Thrombophilia workup revealed APC–sensitivity ratio (APC-SR) of 1.8 (normal range, > 2.0) and heterozygosity for factor V Leiden (FVL) mutation. Personal and family history of thrombosis was negative.

Analysis

Recurrent fetal loss (RFL) is a common problem. Of women at the reproductive age group, 1% to 2% experience 3 or more losses and 5% experience 2 or more losses. RFL has a well-established association with certain acquired thrombophilic disorders, such as the antiphospholipid syndrome.

A growing body of evidence suggests that hereditary thrombophilia is common in women with RFL (Table 2). A case-control study in women with inherited thrombophilia, protein C, protein S, and antithrombin deficiencies documented an increased risk for RFL. In 60 women with thrombophilia, 42 (22%) of 188 pregnancies resulted in pregnancy loss compared with 23 (11%) of 202 in controls (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.2-3.3). In addition, a high incidence of gestational abnormalities was reported in 15 women with dysfibrinogenemia associated with thrombosis. Of 64 pregnancies, 39% ended by miscarriage and 9% ended by intrauterine fetal death. In a recent study, at least one thrombophilic defect was found in 96 (66%) of 145 women with RFL compared with 41 (28%) of 145 in controls (OR, 5.0; 95% CI, 3.0-8.5; P < .0001). The association of factor V Leiden mutation with pregnancy loss has been recently analyzed by the College of American Pathologists Consensus Conference on Thrombophilia. At least 16 case-control studies found a high prevalence of FVL in women with unexplained recurrent fetal loss (up to
impaired fibrinolytic capacity resulted in normalization of impaired fibrinolysis, conception in 16 (80%) of 20, and successful live birth in 13 (81%) of 16.42

A recent collaborative study demonstrated the safety of using low-molecular-weight heparin during 486 gestations.43 A successful outcome was reported in 83 (89%) of 93 pregnancies in women with a history of recurrent pregnancy loss and in all 28 gestations in women who experienced preeclampsia during a previous pregnancy. A retrospective French study on use of enoxaparin during 624 pregnancies revealed a good safety profile.44

Our group has treated 61 pregnancies in 50 women with thrombophilia who presented with recurrent fetal loss with the LMWH enoxaparin throughout gestation and 4 to 6 weeks into the postpartum period. Enoxaparin dosage was 40 mg/d, except for patients with combined thrombophilia or in the case of abnormal Doppler velocimetry suggesting decreased placental perfusion, where the dosage was increased to 40 mg twice a day. Of the 61 pregnancies, 46 (75%) resulted in live birth compared with a success rate of only 20% in these 50 women in prior gestations without antithrombotic therapy.38

Carp et al41 reported a cohort study undertaken to assess the effect of enoxaparin on subsequent live birth rate in women with 3 or more consecutive pregnancy losses and hereditary thrombophilia. Live birth rate was higher in women treated with enoxaparin, 26 (70.2%) of 37 compared with 21 (43.8%) of 48 in untreated patients. The beneficial effect was mainly in primary aborters and in those with 5 or more miscarriages.

These preliminary results are encouraging. However, the optimal dosage of LMWH is yet unknown and should be determined by prospective randomized trials. Ideally large placebo-controlled trials should be advocated. However, there are logistic and ethical difficulties that limit enrollment in such studies.

LIVE-ENOX is a multicenter study recently conducted in Israel comparing 2 doses of enoxaparin, 40 mg/d and 40 mg/every 12 hours given throughout pregnancy, starting at 5 to 10 weeks of gestation and for 6 weeks at the postpartum period to women with thrombophilia and recurrent pregnancy loss.45 The results will be available soon.

In the mean time it is recommended that women with recurrent pregnancy loss and thrombophilia on subsequent gestation should be enrolled in clinical trials or treated on an individual basis. Accordingly, on subsequent pregnancy this patient should be offered LMWH at a prophylactic dose (0.5 mg/kg enoxaparin or 5000 U dalteparin) starting early after pregnancy is diagnosed and

Table 1. Pregnancy complications—definitions

<table>
<thead>
<tr>
<th>Pregnancy loss</th>
<th>Weeks of gestation</th>
</tr>
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<tbody>
<tr>
<td>Embryonic loss</td>
<td>Between 5 and 10</td>
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<tr>
<td>Fetal loss</td>
<td>After 10</td>
</tr>
<tr>
<td>Miscarriages (still birth)</td>
<td>Before 20</td>
</tr>
<tr>
<td>IUFD (still birth)</td>
<td>After 20</td>
</tr>
<tr>
<td>First-trimester loss</td>
<td>5–12</td>
</tr>
<tr>
<td>Second-trimester loss</td>
<td>13–24</td>
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<tr>
<td>Third-trimester loss</td>
<td>After 24</td>
</tr>
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Table 2. Association of thrombophilia with placental vascular complications

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>IUDF</th>
<th>Severe IUGR</th>
<th>Severe preeclampsia</th>
<th>Placental abruption</th>
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<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>III+</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>III+</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>III+</td>
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<tr>
<td>Dysfibrinogenemia</td>
<td>II+</td>
<td>I+</td>
<td>II+</td>
<td>III+</td>
</tr>
<tr>
<td>APC resistance</td>
<td>II+</td>
<td>I+</td>
<td>II+</td>
<td>III+</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>III+</td>
<td>I+</td>
<td>II+</td>
<td>II+ (18,26,32)</td>
</tr>
<tr>
<td>MTHFR 677TT</td>
<td>II+</td>
<td>I+</td>
<td>II+</td>
<td>II (14,34,35,35)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>II+</td>
<td>I+</td>
<td>II+</td>
<td>II+ (14,34,36)</td>
</tr>
<tr>
<td>Factor II 20210G&gt;A</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>II+ (25,29,31)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>II+ (26,32)</td>
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<tr>
<td>Combined defects</td>
<td>I+</td>
<td>I+</td>
<td>II+</td>
<td>II+ (26,32)</td>
</tr>
</tbody>
</table>

| Methodology                  |
|------------------------------|------|-------------|---------------------|---------------------|
| I                            | 1 or more well-designed prospective studies or 2 or more well-designed retrospective studies; level II (II), the recommendation is based on retrospective studies that reach consensus; level III (III), the recommendation is based on isolated anecdotal studies and/or the consensus of expert practitioners; +, association present; −, association not present; and ND, no data.

Placental abruption indicates premature separation of a normally located placenta prior to delivery of the fetus; preeclampsia, pregnancy-induced or aggrandized hypertension that may be associated with proteinuria and/or other manifestations; and intrauterine growth restriction (IUGR), a fetus small for gestational age (<10th percentile, or <3rd percentile [severe IUGR]).

30% compared with 1% to 10% of control subjects (odds ratios ranging from 2 to 5).

Despite differences in study populations and selection criteria, the results were consistent. No association between FVL and fetal loss was found by 6 other case-control studies. These latter studies were smaller and mostly included women with early first-trimester fetal losses (which often are due to non–thrombophilia-related factors). There are 3 retrospective cohort studies that also found that FVL carriers have a significantly increased risk of recurrent fetal loss. The risk for fetal loss is greater in homozygotes than in heterozygotes with FVL21 and in female siblings of thrombophilic women with FVL.22 Women with thrombophilia have an increased percentage of losses at later stages of gestation. Activated protein C resistance in the absence of FVL has also been associated with pregnancy loss.13,16

A recent meta-analysis demonstrated that FVL is associated with early (OR, 2.01; 95% CI, 1.13-3.58) and late (OR, 7.83; 95% CI, 2.83-21.67) recurrent fetal loss.23 Exclusion of women with other pathologies associated with fetal loss strengthens the association with FVL. In this meta-analysis APC resistance (APCR) was also associated with early recurrent fetal loss (OR, 3.48; 95% CI, 1.58-7.69).

Fetal loss has also been associated with factor II 20210G>A but not with the methylenetetrahydrofolate reductase (MTHFR) TT polymorphisms.13,17

Data on treatment of women with inherited thrombophilia and pregnancy loss are predominantly uncontrolled and include small series of patients treated mostly with low-molecular-weight heparin (LMWH; Table 3). Administration of the LMWH, 20 mg/d enoxaparin, to women with primary early recurrent fetal loss and

Reference numbers are listed in parentheses.
Table 3. Observational studies on prevention of poor gestational outcome in carriers of thrombophilia

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Type of thrombophilia</th>
<th>Obstetric history</th>
<th>Treatment</th>
<th>Live birth with normal outcome</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Inherited and acquired</td>
<td>RFL</td>
<td>Enoxaparin (+ LDA for APS)</td>
<td>46/61 (75%)</td>
<td>Brenner et al 26</td>
</tr>
<tr>
<td>25</td>
<td>Factor V Leiden or Factor II 20210G→A</td>
<td>RFL, preeclampsia IUGR</td>
<td>UFH or LMWH or LDA</td>
<td>29/31 (93%)</td>
<td>Grandone et al 23</td>
</tr>
<tr>
<td>33</td>
<td>Not specified</td>
<td>Pregnancy complications</td>
<td>40 mg enoxaparin + LDA</td>
<td>30/33 (91%)</td>
<td>Kupferminc et al 25</td>
</tr>
<tr>
<td>26 patients vs 19 controls</td>
<td>Inherited and acquired</td>
<td>Pregnancy complications</td>
<td>40 mg enoxaparin + LDA</td>
<td>Higher birth weight in LMWH group</td>
<td>Riyazi et al 40</td>
</tr>
<tr>
<td>37 patients vs 48 controls</td>
<td>Inherited</td>
<td>RFL</td>
<td>40 mg enoxaparin</td>
<td>70% vs 44% in controls</td>
<td>Carp et al 41</td>
</tr>
</tbody>
</table>

APS indicates antiphospholipid syndrome; LDA, low-dose aspirin; RFL, recurrent fetal loss; and IUGR, intrauterine growth restriction.

Thrombophilia and IUGR

Case presentation

A 25-year-old woman presented after delivering a 1500-g newborn at 36 weeks of gestation in her first pregnancy. Thrombophilia workup 3 months after delivery was normal except for activated protein C resistance (APC-SR, 1.7; normal range, > 2.0), with factor V R506Q genotype. Family history was negative for thrombosis.

Analysis

This patient had an early delivery of a small (for gestational age) neonate.

Risk factors for IUGR can be of maternal, fetal, or placental origin. Among maternal causes are chronic vascular disease, and inherited and acquired thrombophilia. Chronic abortion and extensive infarction are among the placental abnormalities.

The association of IUGR and thrombophilia is controversial. An association was demonstrated in women with severe IUGR (Table 2) but not in milder cases. Martineilli et al 46 studied 63 women with history of IUGR, defined as birth weight under the 10th percentile, and 93 parous women with uneventful pregnancies. Among women with IUGR, 13% had FVL compared with 2.2% in controls (OR, 6.9; 95% CI, 1.4-33.5), and 12% had prothrombin mutation compared with 2.2% in controls (OR, 5.9; 95% CI, 1.2-29.4). In a regression analysis model these thrombophilias were independently associated with IUGR. A later report from the same group 24 tested these mutations in neonates weighing less than 2500 g. Neonates delivered by mothers with FVL or prothrombin mutations accounted for 30% of newborns weighing less than 1000 g, 18.7% ranging from 1001 to 2499 g, and only 9.5% weighing 2500 g or more. Overall, 27.6% of neonates of mothers with the mutations weighed less than 2500 g compared with 13.9% in neonates of mothers without mutations (OR, 2.4; 95% CI, 1.5-3.7).

Recently, Infante-Rivard et al 25 did not find an association between thrombophilic mutations and intrauterine growth restriction less than 10th percentile. In this study the prevalence of thrombophilia in mothers of 493 newborns with IUGR and 472 controls did not differ significantly. However, one third of the studied population was not white and the degree of IUGR was mild, with mean birth weight of 2393 ± 606 g and 83% of newborns delivered at 36 to 40 weeks’ gestation. In contrast, in the study by Kupferminc et al 26 the mean birth weight was 1387 ± 616 g and mean gestational week was 33 ± 4.0. Similarly, Martineilli et al 46 reported a mean gestational week at delivery of 35 ± 3 and a mean birth weight of 1584 ± 586 g. It is therefore suggested that these studies are dealing with noncomparable fetal and neonatal populations with different clinical relevance.

Data on antithrombotic prophylaxis for IUGR at index pregnancy and on subsequent gestations are limited. However, in view of the risk for recurrences of other gestational complications, including IUGR, prophylaxis can be considered. This case can be managed with LMWH at a prophylactic dose (0.5 mg/kg enoxaparin or 5000 U dalteparin) once daily throughout gestation, and for 6 weeks in the postpartum period. This regimen may also be useful for prevention of other vascular complications.

Thrombophilia and preeclampsia

Case presentation

A 36-year-old woman presented on her second gestation at 25 weeks with preeclampsia that progressed rapidly into hemolysis-elevated liver enzymes–low-platelet syndrome (HELLP) and necessitated cesarean delivery at 26 weeks of a 700-g neonate. The newborn had a complicated course including necrotizing enterocolitis at the neonatal intensive care unit. Thrombophilia workup revealed heterozygosity for factor II 20210G→A mutation. Her first gestation ended by miscarriage at 10 weeks. Family history was negative for thrombosis.

Analysis

This patient had complications on gestations, a miscarriage, and severe early-onset preeclampsia with HELLP syndrome.

Preeclampsia can be found in 3% to 7% of pregnancies and is a leading cause of maternal and fetal life-threatening complications. In preeclampsia the placental vasculature fails to become a high-volume, low-pressure system, which is the earliest difference that can be detected between preeclamptic and normal pregnancies. Widespread deposition of fibrin and vascular damage normally occur in hypertensive disorders of pregnancy, suggesting an activation of the coagulation cascade in this condition. 47 Recent reports suggesting that vascular endothelial growth factor is decreased in preeclampsia 48,49 may be relevant for development of novel therapeutic modalities for this disorder.
The association of preeclampsia and thrombophilia is controversial. A number of case-control studies have demonstrated an association, while other studies have refuted this occurrence (Table 2). An association between the presence of FVL and a history of severe forms of preeclampsia was reported.27

Kupferminc et al found that the prevalence of thrombophilia in 110 women with severe obstetric complications was 65% compared with 18% in 110 controls.26 Women with obstetric complications also had a significantly higher incidence of combined thrombophilias. The results showed a higher prevalence of the thrombophilic polymorphisms, FVL, factor II 20210G>A, and MTHFR 677TT in women presenting with preeclampsia.26 In a sample of 140 Italian women with a history of gestational hypertension, with or without significant proteinuria, a significantly higher prevalence of thrombophilic risk factors was documented regardless of the presence of proteinuria.28 Logistic regression showed that FVL and factor II 20210G>A mutations were independently associated with occurrence of gestational hypertension.

Other studies failed to find an association between a common genetic risk factor for thrombosis and the occurrence of preeclampsia.29 However, these studies seem to differ in selection of controls and in ethnic backgrounds.

A recent meta-analysis has demonstrated an association with FVL and factor II 20210G>A only in women with severe early onset of preeclampsia.30 HELLP syndrome is a severe form of preeclampsia manifesting disseminated platelet aggregation and liver dysfunction, necessitating emergent termination of pregnancy. This syndrome has been associated with thrombophilia particularly with the factor V Leiden mutation.31

In the 1980s, the potential benefit of aspirin in prevention of preeclampsia was raised and refuted. To date there are no placebo-controlled trials on prevention of preeclampsia at subsequent gestation with LMWH. Small, uncontrolled studies have suggested a benefit in outcome of subsequent gestations after antithrombotic prophylaxis (Table 3).39,40,50

However, the result in this woman is high and therefore counseling should take into account her age, the severe obstetric history, and risks of recurrence on subsequent gestation. Prophylaxis during pregnancy should probably include LMWH at a moderate to high prophylactic dose throughout gestation and the postpartum period, aiming for anti-Xa levels of 0.4 to 0.6 U/mL 3 hours after injection. Whether aspirin should be added is currently unknown.

**Hyperhomocysteinemia and MTHFR 677**

Homocysteine levels decrease in pregnancy by 50%. Gestational vascular complications can be associated with hyperhomocysteinemia documented in 26% of women with placental abruption, in 11% of cases with intrauterine fetal death, and in 38% of women delivering babies whose birth weight was below the fifth percentile compared with an estimated 2% to 3% in controls.14 Likewise, hyperhomocysteinemia was documented in 26 (31%) of 84 women with previous placental infarcts or abruption compared with 4 (9%) of 46 in controls.34 In the Hordaland Homocysteine Study, which is the largest performed to date, plasma homocysteine levels were evaluated in 5883 women with 14 492 pregnancies.35 The study demonstrated that when comparing the upper with lower quartile of plasma homocysteine, the adjusted risk for preeclampsia was 1.32 (95% CI, 0.98-1.77); for prematurity, 1.38 (95% CI, 1.09-1.75); for very low birth weight, 2.01 (95% CI, 1.23-3.27); and for stillbirth, 2.03 (95% CI, 0.98-4.21).

In a recent meta-analysis, Nelen et al33 reviewed 10 case-control studies that examined the association of RFL (Table 2) and hyperhomocysteinemia and reported a 3- to 4-fold increased risk, while in 6 other studies the odds ratios for homozygosity for MTHFR were not significant. These data suggest that while hyperhomocysteinemia is a risk factor for RFL, homozygosity for MTHFR as a solitary thrombophilic defect is not. However, testing for hyperhomocysteinemia and MTHFR 677TT may be of value in women with relative proteinuria, a sign of proteinuria documented in 26% of women with placental abruption compared with 4 (9%) of 46 in controls.34 In the Hordaland Homocysteine Study, which is the largest performed to date, plasma homocysteine levels were evaluated in 5883 women with 14 492 pregnancies.35 The study demonstrated that when comparing the upper with lower quartile of plasma homocysteine, the adjusted risk for preeclampsia was 1.32 (95% CI, 0.98-1.77); for prematurity, 1.38 (95% CI, 1.09-1.75); for very low birth weight, 2.01 (95% CI, 1.23-3.27); and for stillbirth, 2.03 (95% CI, 0.98-4.21).

Hyperhomocysteinemia and MTHFR 677 are significant risk factors for RFL. Whether aspirin should be added is currently unknown. LMWH should be administered twice daily starting at a high prophylactic dose (0.5 mg/kg enoxaparin or 5000 U dalteparin every 12 hours) aiming for an anti-Xa level of 0.4 to 0.6 U/mL 3 hours after injection. Close monitoring of fetal growth and estimation of placental perfusion by Doppler velocimetry are advocated. Prophylaxis should be given throughout gestation and the postpartum period.

**Combined thrombophilic risk factors**

**Case presentation**

A 22-year-old woman presented with one previous pregnancy loss at 10 weeks. She is currently on her sixth week of gestation. Family history includes deep vein thrombosis (DVT) in her father at 35 years and pulmonary embolism in his brother at 40 years. In the first pregnancy, the patient had preterm birth at 21 weeks. The patient had a history of recurrent miscarriages. She had a positive family history for deep vein thrombosis (DVT) in her father at 35 years and pulmonary embolism in her brother at 40 years. She started treatment with low molecular weight heparin (LMWH) at 10 weeks of gestation.

**Antithrombin deficiency**

Antithrombin deficiency is an uncommon severe thrombophilia often manifest clinically by gestational vascular complications with significant increased maternal and fetal risks. The risk is estimated to be increased by 100- to 150-fold, which translates to clinically overt DVT in 7% of antithrombin-deficient pregnant women and up to 40% in cases of severe familial DVT.51-53

Furthermore, antithrombin deficiency has been associated with other pregnancy complications including pregnancy loss and late gestational complications.11

**Combined thrombophilic defects**

Combined thrombophilic defects were documented in 31 (21%) of 145 women with pregnancy loss compared with 8 (5.5%) of 145 in controls (OR, 5.0; 95% CI, 2.4-86) in patients with combined thrombophilic defects.12

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In the Nimes Obstetricians and Haematologists Study 5 (NOHA5), placental pathologic vascular findings were documented in 88% of women with combined thrombophilia and in 100% of those with a combination of any thrombophilia and MTHFR 677TT.37

Therefore, in this patient with severe combined thrombophilia, the presence of moderate to severe thrombophilia and MTHFR 677TT should be confirmed. LMWH should be administered twice daily starting at a high prophylactic dose (0.5 mg/kg enoxaparin or 5000 U dalteparin every 12 hours) aiming for an anti-Xa level of 0.4 to 0.6 U/mL 3 hours after injection.
Inherited thrombophilias and abruptio placentae

Case presentation

A 30-year-old woman presented with placental abruption at 27 weeks' gestation with delivery by emergent cesarean section of an 800-g neonate. Thrombophilia workup revealed heterozygosity for factor II 20210G>A.

Analysis

Placental abruption is an uncommon devastating clinical presentation occurring in 0.5% of gestations but carrying a high fetal mortality and significant maternal risk. Risk factors for placental abruption include preeclampsia, prior abruption, sudden uterine decompensation, chemical teratogens, external trauma, and uterine malformations. A potential association with thrombophilia is suggested by a number of studies (Table 2).

Van der Molen et al found that the prothrombotic risk factors for placental vasculopathy are decreased levels of APCR and protein C, elevated homocysteine, MTHFR TT, and, particularly, combinations of these factors.

Wiener-Megnagi et al studied 27 women who had abruptio placentae and 29 control subjects matched for age, parity, and ethnic origin. Of case patients, 63% had an activated protein C ratio of 2.5 or less, compared with 17% of control subjects with an OR of 8.16 (P = .001). Of 15 patients, 8 were found to have the factor V Leiden, compared with 1 heterozygote in the controls (3.4%). In another study thrombophilia was found in 70% of 20 women with abruptio placentae, and the OR for factor II 20210G>A mutation was 8.9 (95% CI, 1.8-43.6), whereas the OR for factor V Leiden was 4.9 (95% CI, 1.0-17.4). An increased prevalence in first-degree relatives for venous thrombosis in women with placental abruption indicates a higher prevalence of thrombophilia. Based upon these data and in the absence of prospective clinical trials on subsequent gestation these women may be offered prophylaxis with LMWH (0.5 mg/kg enoxaparin or 5000 U dalteparin) throughout gestation and the postpartum period.

Asymptomatic factor V Leiden carrier

Case presentation

A 27-year-old asymptomatic woman was found to be heterozygote for factor V Leiden (FVL) mutation as a result of familial workup performed after her father had deep vein thrombosis. She is now planning her first pregnancy. How would you consult her?

Analysis

A recent Canadian survey suggests that 54% of obstetricians in Canada would treat this patient with some form of antepartum prophylaxis. However, this is not supported by solid data. In fact, the risk for VTE during pregnancy in an asymptomatic woman heterozygote for factor V Leiden is around 0.2% to 0.5%. The risk may increase somewhat in the presence of significant familial history of thrombosis but is still too low to confer the need for antepartum prophylaxis. The risk for placental vascular complications on first pregnancy in women heterozygote for factor V Leiden is not significantly increased compared with controls. Therefore, thromboprophylaxis is not recommended and this woman should be managed by clinical surveillance. In women with severe or combined thrombophilia the risk is increased, and therefore antepartum thromboprophylaxis should be considered.

Unresolved issues

Fetal genotype

While there have been reports that fetal thrombophilia is important for the outcome of pregnancy, there are a number of reasons to suggest that this may not be the case. First, most thrombophilic polymorphisms are mild risk factors for gestational vascular complications (GVCs) and gestational VTE. Second, thrombotic changes are noted mainly on the maternal side of the uteroplacental unit. Third, LMWH that does not cross the placenta is beneficial. Thus, unless there is a severe thrombophilic defect (ie, homozygous protein C deficiency), fetal thrombophilic state is probably not a major contributor to GVC or VTE.

Does aspirin have a role?

The role of aspirin, if any, in the setting of thrombophilia and vascular gestational abnormalities remains to be confirmed. Currently, as an extrapolation to studies with unfractionated heparin (UFH) in patients with antiphospholipid syndrome, aspirin is given along with LMWH. However, whether aspirin has an added value to UFH or LMWH alone has not been evaluated.

Women with unexplained pregnancy loss

When evaluation for current known thrombophilia is negative, the idea is that yet-undiscovered thrombophilia may be implicated in the placental thrombotic changes that can be found in women with GVC without thrombophilia. Following preliminary experience with antithrombotic therapy in these women, prospective randomized multicenter trials are currently under way.

Future perspectives

There are a number of issues in this field that probably need to be addressed.

First, as of now 30% to 50% of vascular gestational pathologies cannot be accounted for by currently available tests for thrombophilia. Whether other genetic or acquired thrombophilia will be found to play a role remains to be determined. Preliminary observations claim that the PAI-1 gene 4G/4G polymorphism and polymorphisms at the thrombomodulin and endothelial protein C receptor genes may be associated with RFL. Circulating microparticles identified by flow cytometry have recently been suggested to play a role in women with RFL. While the involved mechanism has not been established it is intriguing to speculate whether antithrombotic strategies will be of value in this setting.

Second, in view of the potential association of thrombophilia and RFL, and the high prevalence of thrombophilia in white populations, issues of screening are raised. As complete thrombophilia workup is currently elaborate and costly, screening tests are highly warranted. One such potential assay is the protein C global test, which in a preliminary study was found to be abnormal in most women with RFL and could also identify women with RFL who did not have any other thrombophilic defect.
Third, the pathogenic mechanisms responsible for placental vascular pathologies in women with thrombophilia have not been elucidated, and it is yet unknown why certain women with thrombophilia express vascular gestational pathologies while others do not. It is possible that this may relate to local factors affecting coagulation, fibrinolysis, and vascular tone at the level of placental vessels.

Finally, the role of antithrombotic modalities deserves prospective clinical trials in order to improve results in a large population of women who currently experience poor gestational outcome. Future trials should focus on efficacy and safety of tailored therapy for specific thrombophilic polymorphisms in a particular gestational complications setup.

References


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Benjamin Brenner