Thrombophilia and Adverse Outcomes

Inherited thrombophilia and its association with both maternal thrombosis and adverse pregnancy outcomes is an issue that has come to the forefront over the past few years.

The association between inherited thrombophilia and maternal thrombosis appears to be fairly robust. Collectively, these thrombophilias account for 50%-70% of all maternal venous thrombotic events in pregnancy. Knowledge of the thrombophilic status of a patient can, therefore, have a significant impact on her clinical care. We understand better today, however, that personal and family history plays a critical role in assessing maternal thrombotic risk.

By contrast, the precise nature of the link between inherited thrombophilia and adverse pregnancy outcomes is still unclear. Over the past decade, the number of negative reports—those showing a lack of association—has increased significantly, and multiple prospective cohort studies have failed to consistently demonstrate the associations suggested by prior case-control studies that were smaller and mainly retrospective.

Collectively, this new landscape of research findings suggests that we should stop screening for inherited thrombophilia in patients with adverse pregnancy outcomes except in the setting of institutional review board–approved studies, and that we should better focus our approach to preventing maternal thrombosis toward more careful, individualized risk assessment and through targeted use of antithrombotic therapy.

A New Evidence Base

Initial reports of associations between inherited thrombophilia and adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and abruptio placentae made some biological sense, but were based largely on small retrospective case-control studies with often inconsistent or contradictory findings. In the case of fatal loss, numerous studies published in the 1990s and into the next decade showed a moderate association between inherited thrombophilia and stillbirth in particular.

A European retrospective cohort study published in 1996, for instance, found that the increased risk of loss among women with thrombophilia was greater after 28 weeks (odds ratio 3.6) than at or before 28 weeks (OR 1.4), and that the highest risk for stillbirth was associated with combined thrombophilic defects and antithrombin and protein C deficiencies (Lancet 1996;348:913-6).

This confusingly named retrospective case-control study—"the European Prospective Cohort on Thrombophilia (EPICOT)—involved 571 women with thrombophilia having 1,524 pregnancies, and 395 controls having 1,019 pregnancies.

In 2005, investigators of a larger case-control study nested within the 32,683-patient Nimes Obstetricians and Haematologist cohort reported an association between the factor V Leiden (FVL) mutation and pregnancy loss after 10 weeks (OR 3.5) but not between 3 and 9 weeks (J. Thromb. Haemost. 2005;3:2178-84).

A retrospective cohort study published in 2004 of 491 patients with a history of adverse pregnancy outcomes suggested, moreover, that one or more thrombophilia were actually protective of recurrent fetal losses at less than 10 weeks (Thromb. Haemost. 2004;91:290-5). However, the association of any one thrombophilia with later fetal losses was less significant in this study than in other studies (OR 1.76).

This has further galvanized the belief that thrombophilia may in fact be strongly etiologic in the pathophysiology of some adverse pregnancy outcomes. Thus, interventions based on a presumed mechanistic basis have been supported. However, newer data have seemed not to bear out this long-held association between thrombophilia and adverse outcomes, and the implied treatment.

It is in light of this controversy and the conflicting positions that we have decided to do a Master Class to thoroughly review the subject, to look at what data exist that can help unravel this relationship, and to examine whether screening patients for thrombophilia and treating it as a basis for improving pregnancy outcomes is warranted.

We have invited Dr. Charles J. Lockwood to address the topic. Dr. Lockwood is the Anita O’Keeffe Young Professor of Women’s Health and chair of the department of obstetrics, gynecology, and reproductive sciences at Yale University, New Haven, Conn., and chief of obstetrics and gynecology at Yale–New Haven Hospital.

Dr. Lockwood has studied and thought a great deal about the association between inherited thrombophilia and adverse pregnancy outcomes, as well as the association between thrombophilia and maternal thrombosis. He urges us to step back and, in light of a “new landscape of research findings,” take a more careful approach to assessment and screening.

Dr. REECE, who specializes in maternal-fetal medicine, is vice president for medical affairs at the University of Maryland, Baltimore, as well as the John Z. and Aleko K. Bowers Distinguished Professor and dean of its school of medicine. He said he had no conflicts of interest relevant to this column. He is a member of the Ob.Gyn. News editorial advisory board and medical editor of this column.

Maternal Thrombosis and Link to Thrombophilia

Thrombophilia and Adverse Outcomes

Suggested Thrombophilia Work-Up

<table>
<thead>
<tr>
<th>Inherited thrombophilia</th>
<th>Thrombophilia test</th>
<th>Cut-off for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>FVL polymerease chain reaction</td>
<td>Positive</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation (PGM)</td>
<td>PGM polymerease chain reaction</td>
<td>Positive</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Protein C functional assay</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Antithrombin activity (amidolytic [chromogenic]) assay</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Protein S free antigen</td>
<td>&lt;55% (nonpregnant) ≤29% (first/second trimesters) ≤24% (third trimester)</td>
</tr>
</tbody>
</table>

Source: Dr. Lockwood
Key Points

- Most positive associations between inherited thrombophilia and adverse pregnancy outcomes were derived from small case-control studies.
- Many studies are contradictory.
- Large prospective cohort studies have failed to demonstrate any consistent association between inherited thrombophilia and adverse pregnancy outcomes.
- There appears to be a modest association between thrombophilia and fetal loss after 10 weeks in retrospective, but not most prospective, studies.
- There is no current support for screening for inherited thrombophilia in women experiencing recurrent unexplained fetal loss or other adverse pregnancy outcomes. Diagnosis and treatment regimens should occur only in the context of an institutional review board–approved research protocol.
- Patients with known inherited thrombophilia and a personal or family history of prior VTE should receive antepartum thromboprophylaxis followed by postpartum anticoagulation.
- Unless they have additional, significant risk factors, women with lower-risk thrombophilias (i.e., heterozygotes for FVL, PGM, protein C deficiency, or protein S deficiency) and no history of prior VTE or an affected first-degree relative do not require antepartum thromboprophylaxis.
- Women who have a personal history of VTE associated with a nonrecurrent risk factor should be screened.

Dr. Lockwood indicated that he has no conflicts of interest to disclose.