MASTER CLASS

Thrombophilia and Adverse Outcomes

BY E. ALBERT REECE, M.D., PH.D., M.B.A.

Adverse pregnancy outcomes are among the most perplexing pregnancy-related problems because we still have little precise knowledge about the etiology—and often, the mechanisms—associated with them. Over time, a number of causes have been identified and suggested, and some potential therapeutic agents have been proposed.

The relationship between thrombophilia and adverse outcomes has been a long-term association. A number of experiential reports and uncontrolled trials have endorsed this relationship. In fact, experimental therapeutic trials with heparin and other agents have attempted to improve outcomes and have reported incremental benefits when these agents have been used.

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 Akiko 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

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 CHARLES LOCKWOOD, M.D., MHCM

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 through 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 fetal 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 study—the European Prospective Cohort on Thrombophilia (EPCOT)—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).

And an earlier meta-analysis of 31 studies looking at fetal loss and various thrombophilic disorders (most of them small case-control studies) concluded that FVL was associated with first-trimester pregnancy loss (OR 2.0) as well as later loss, although the association was much stronger (OR 3.3) with late, nonrecurrent fetal loss (Lancet 2003; 361:901-8).

Although these and other studies suggested a link between FVL and stillbirth (and perhaps other thrombophilias and stillbirth), the absolute magnitude of the association (i.e., the absolute risk) was still very small. Moreover, over the past decade, the number of negative reports, especially amongst prospective studies, has increased—a temporal dichotomy that strongly suggests an initial bias toward positive studies and a growing comfort in reporting negative studies.

The larger prospective cohort studies reported over the last 5 years or so enerally have not found an association between inherited thrombophilia and stillbirth—or other adverse pregnancy outcomes for that matter.

For example, a 2005 study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Maternal-Fetal Medicine Units Network identified 134 FVL mutation carriers among nearly 4,900 gravidas in their first trimester of pregnancy and found no increase in fetal loss, preeclampsia, abruption, or intrauterine growth retardation (IUGR). A secondary analysis of these data published earlier this year similarly found no association between the prothrombin gene G20210A mutation (PGM) and adverse pregnancy outcomes (Obstet. Gynecol. 2005;106:517-24 and Obstet. Gynecol. 2010;115:14-20).

Another prospective study of 4,250 unselected pregnancies also found no significant associations between FVL and preeclampsia, IUGR, and pregnancy loss (Br. J. Haematol. 2008;140:236-40).

Some of these findings are similar to previous reports from smaller prospective cohort studies. Investigators reported in 1999, for instance, no association between activated protein C resistance and fetal loss, preeclampsia, and IUGR. And in 2000, investigators had similarly reported a lack of association between FVL and methylenetetrahydrofolate reductase (MTHFR) polymorphism and preeclampsia or IUGR.

In general, the reported linkage between inherited thrombophilia and adverse outcomes other than stillbirth was always more tenuous. In the case of

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Suggested Thrombophilia Work-Up

Inherited thrombophilia	Thrombophilia test	Cut-off for diagnosis
Factor V Leiden	FVL polymerase chain reaction or second-generation activated protein C resistance assay	Positive
Prothrombin G20210A mutation (PGM)	PGM polymerase chain reaction	Positive
Protein C deficiency	Protein C functional assay	<50%
Antithrombin deficiency	Antithrombin activity (amidolytic [chromogenic]) assay	<60%
Protein S deficiency	Protein S free antigen	<55% (nonpregnant) ≤29% (first/second trimesters) ≤24% (third trimester)

Source: Dr. Lockwood

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preeclampsia, however, meta-analyses of studies done before 2000 showed a fairly strong association between thrombophilia and preeclampsia, while studies published in and after 2001 found no such association.

There are a few exceptions to the lack of association found in larger prospective cohort studies. Most notably, an Australian study published this year of nulliparous women was suggestive of a weak association between the PGM and a composite index of adverse pregnancy outcomes (Obstet. Gynecol. 2010;115:5-13).

However, when investigators analyzed individual outcomes, they found that the only statistically significant associations were between the PGM and placental abruption, and between FVL and stillbirth. These associations, moreover, were based on very small sample size (nine and six patients, respectively). The investigators concluded that "the majority of asymptomatic women who carry an inherited thrombophilia polymorphism have a successful pregnancy outcome."

There also is, at best, conflicting evidence in the literature of any benefit to heparin therapy for recurrent fetal loss.

A New Outlook on Screening

Given the evolving body of literature, it now seems wholly unjustified to screen low-risk populations. Knowing whether or not the patient has inherited thrombophilia, particularly in the nulliparous state, does not appear to be important for predicting outcomes.

There are questions that remain, however—most notably the question of whether women who have repetitive fetal losses or repetitive preeclampsia or abruptions should be screened and treated for inherited thrombophilia. Certainly, the failure of large prospective cohort studies to demonstrate any consistent association dampens our enthusiasm for the idea that inherited thrombophilia are to blame.

My opinion on this topic has evolved considerably over the last 10 years. I now believe that while screening for antiphospholipid syndrome is still warranted, screening for inherited thrombophilia in women having recurrent adverse pregnancy outcomes should occur only in the setting of an institutional review board–approved study in which ascertainment is done before a subsequent pregnancy and the patient's thrombophilia status is correlated with subsequent outcome (i.e., live birth, miscarriage, stillbirth, fetal growth restriction, preeclampsia, or abruption).

Furthermore, until we have established a definitive link between inherited thrombophilia and adverse pregnancy outcomes, we shouldn't even begin to think about clinical trials of thromboprophylaxis for affected women.

A particularly thorny question that has been raised concerns the issue of early fetal loss. Some have argued that the latest prospective cohort studies involved blood collection at or after 10 weeks' gestation and, therefore, are not relevant to conclusions drawn about the association (or lack thereof) between inherited thrombophilia and embryonic fetal loss.

However, I believe there are several reasons why we can conclude that thrombophilia and embryonic fetal losses are not linked. For one, there are enough data available from negative retrospective studies in which blood was obtained right after the pregnancy was completed. Secondly, there is no correlation between inherited thrombophilia and subsequent in vitro fertilization (IVF) failures in almost a dozen published studies. In fact, there is actually some evidence that FVL is associated with IVF success.

Lastly, we now know there is very little blood flow to the placenta before 10 weeks' gestation. There is some evidence, in fact, that hypoxia is the normal state of the embryo and may even be the preferred condition for culturing embryos in IVF.

Again, this issue requires prospective studies amongst patients with recurrent loss in which ascertainment occurs before the pregnancy commences.

Maternal Thrombotic Risk

While it's fair to say that, in general, inherited thrombophilia modestly increases the risk of maternal venous thrombotic events (VTE), it is critical to appreciate the role that a personal or strong family history of thrombosis (i.e., an affected first-degree relative) plays in determining a mother's risk.

Most women (greater than 93%) without a personal or strong family history of VTE will have uneventful pregnancies even when highly thrombogenic mutations are present. Once a personal or family history is factored in, however, the risk of VTE increases dramatically.

In the absence of a personal history of VTE or such an episode in a first-degree relative, heterozygosity for FVL or PGM is associated with a risk of thrombosis in pregnancy of well under 1% (0.2% and 0.5%, respectively). Similarly, protein C and protein S deficiencies are associated with a VTE risk under 1% in the absence of a personal or close family history.

In contrast, with a positive personal or family history, the risk of VTE in pregnancy increases to 10% in women who have heterozygosity for FVL, greater than 10% for women who have heterozygosity for PGM, 4%-17% in cases of protein C deficiency, and potentially up to 22% in cases of protein S deficiency.

Without a personal or family history, therefore, women with these lower-risk thrombophilia do not require anticoagulation during pregnancy unless they have other risk factors for thrombosis, such as significant obesity or orders for bed rest.

Patients with known inherited thrombophilia and a positive history, on the other hand, should receive antepartum thromboprophylaxis followed by postpartum anticoagulation. (Women who have a cesarean delivery should receive postpartum anticoagulation whether they have a personal or family history or not.)

Anticoagulation during pregnancy is also warranted—regardless of personal or family history—in the rare cases in which a patient is known to have homozygosity for FVL or homozygosity for PGM, or if a patient is known to have "double heterozygosity" for both FVL and PGM. Antithrombin deficiency, the most thrombogenic of all the inherited thrombophilias, also warrants antepartum anticoagulation as well as antithrombin infusions during labor and delivery.

To date, two studies have attempted to determine the value of screening for inherited thrombophilia based on a family history of prior VTE, and neither has shown that widespread screening would be particularly useful or cost effective in this setting. One certainly can argue, on the other hand, in favor of screening for thrombophilia in women who have a strong family history of VTE coupled with other risk factors.

Individualized risk assessment is always valuable. A woman with multiple risk factors—one who is obese, smokes, and is being put on bed rest, for instance—is a candidate for low-molecular-weight heparin (LMWH) therapy, for instance, even without a history of thrombosis and regardless of her thrombophilia status. If such a patient also has hypertension or preeclampsia, however, I'd be reluctant to give her either heparin or LMWH, for fear of abruption or even intracranial hemorrhage.

In what other circumstances is screening for thrombophilia warranted?

It can be justified when there is a personal history of VTE associated with a risk factor that is not recurrent. In this case, the absence of a thrombophilia reduces the risk of occurrence/recurrence of VTE during pregnancy to a very low level, while the presence of a thrombophilia would mandate antepartum anticoagulation. In any case, she should receive postpartum prophylaxis since 75%-80% of fatal pulmonary emboli in pregnancy occur after cesarean delivery.

For instance, screening is valuable in a woman who had a VTE earlier in her life when she was on oral contraception and was put in a cast after a skiing accident. If she does not have a documented thrombophilia, you will not need to give her anticoagulation during the pregnancy—only post partum.

The Work-Up

When screening for inherited thrombophilia is warranted, I recommend limiting it to FVL, PGM, protein C deficiency, antithrombin deficiency, and protein S deficiency. (See table, p. 20.)

Screening for FVL, even during pregnancy, can be done with a second-generation screening test for active protein C resistance, or by polymerase chain reaction (PCR).

Screening for the PGM should be done by PCR, and I recommend getting an antithrombin activity level and a protein C activity level to screen for antithrombin deficiency and protein C deficiency, respectively.

Screening for protein S deficiency is trickier, since circulating protein S activity levels can vary dramatically in pregnancy (i.e., various conditions from infections to surgery to hormonal status can affect activity levels of protein S).

I recommend first assessing the protein S free antigen level. In nonpregnant patients, a free antigen level less than 55% indicates risk for deficiency. Free antigen levels drop significantly in pregnancy, however, making a level at or below 29% in the first and second trimesters, and a level at or below 24% in the third trimester, indicative of risk. Such levels can be accepted as indicating protein S deficiency, or deficiency can be confirmed by then measuring the protein S activity level.

I do not recommend screening for MTHFR mutations or hyperhomocysteinemia. There does not appear to be any association between MTHFR mutations and adverse pregnancy outcomes, and the probable association between hyperhomocysteinemia and maternal venous thrombotic events that exists in general is of far less concern in the United States since grains are fortified with folate. If there is any concern, extra folic acid supplementation should be protective. ■

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

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.

Source: Dr. Lockwood