

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Hypercoagulability and Recurrent Miscarriages

Benjamin Brenner, MD
 Professor of Hematology
 Caster Chair of Leukemia Research
 Director, Thrombosis and Hemostasis Unit
 Rambam Health Care Campus
 Technion-Israel Institute of Technology
 Haifa, Israel

H&O What is the association between thrombophilia and pregnancy complications?

BB Recurrent miscarriage is a common disorder that affects 1–3% of women of reproductive age; the prevalence can be up to 5% for women with 2 pregnancy losses. In a majority of these women, however, especially in those with early pregnancy losses, the causative factors for pregnancy loss can include chromosomal aberration of the fetus; anatomic abnormalities of the uterus; endocrine disorders, such as hypothyroidism; infections; and hypercoagulable states, such as antiphospholipid syndrome and hereditary thrombophilia.

The association between antiphospholipid syndrome and pregnancy complications in general, and in recurrent miscarriage in particular, is known. This syndrome is defined by the presence of antiphospholipid, anti-lupus coagulant, anti-cardiolipin, and/or anti-beta-2-glycoprotein I antibodies, and by the presence of either pregnancy complications or thrombotic events in the venous or arterial system. For inherited thrombophilia, the association is relatively new because the more common thrombophilic disorders such as factor V Leiden mutation or prothrombin mutation were reported approximately 15 years ago.

Epidemiologic studies have largely demonstrated the association between hereditary thrombophilia and pregnancy complications, especially recurrent pregnancy loss after 10 weeks of gestation. However, it must be noted that not all studies demonstrated these associa-

tions; several other factors, such as ethnicity or geography, also affected results. For example, factor V Leiden and prothrombin mutation are more commonly found in the white population, but even in this population, there are differences. In the middle east, factor V Leiden is very common (approximately 10–15%), whereas in western Europe, the prevalence could be as low as approximately 2%.

As expected, in areas where inherited thrombophilia (factor V Leiden or prothrombin mutation) is more prevalent, there were more reported cases in which it was associated with pregnancy complications. In areas where thrombophilia is less common, its association with pregnancy complications was reported less often, which could also mean that the study was too small (ie, prevalence is low) to demonstrate or refute an association. It could also indicate that other mechanisms could be involved. However, it is generally understood that there is an association—not a strong one—but a valid one. Additionally, the association is stronger when the patient experiences miscarriages that are recurrent, frequent, and in the later stages of pregnancy.

H&O What do we know of the pathogenetic mechanism responsible for these associations?

BB The first thinking was that pregnancy at hypercoagulable states may fail, and if a woman could be hypercoagulable because she has thrombophilia (eg, factor V Leiden heterozygosity), she would have a 5- or 6-fold increase of thrombotic risk in the venous system, where the circulatory flow is slow, unlike the arterial system. As this phenomenon can be observed in the placental villi, it is possible that thrombotic events such as local thrombosis in the placenta could explain, in part, this association.

Later on, some other mechanisms have been suggested. Microparticles—cellular elements that are smaller than 1 micron, which bleb from cells—are thought to be involved with coagulation and inflammatory processes. This is a relatively new area of investigation, and there are several studies under way looking into it in various areas of medicine, including thrombosis and hemostasis. Our lab has also studied this in women with pregnancy complications.¹

H&O What are the guidelines for screening pregnant women for thrombophilia?

BB In Israel, thrombophilic risk factors are very common. Factor V Leiden is found in approximately 5% of the Jewish population and up to 15% of the Arab population. Prothrombin mutation is also very common—5% in both these populations. Between these 2 thrombophilias, we are talking about 10–20% of women in the general population. Following our study that showed high prevalence of thrombophilia in women with recurrent pregnancy loss (of which the first was published in the late 1990s), we have demonstrated a 3-fold increase in the rate of thrombophilic risk factors in women with recurrent pregnancy loss compared to women with normal pregnancy. Therefore, because it is quite common, we look for thrombophilia in women who present with recurrent pregnancy loss. It is important to note that recurrent pregnancy loss is defined as follows: 3 or more losses in the third trimester, 2 or more losses in the second trimester, or at least 1 fetal death in the third trimester, which is after 26 weeks of gestation. Obviously, there is no consensus on this definition. Some people will say that 1 intrauterine fetal death after 20 weeks of gestation is a sufficient indication. Several investigators have started to look for thrombophilic risk factors after 2 losses before 20 weeks; I think that this is fine if the 2 losses are between 10 and 20 weeks. If the 2 losses are before 10 weeks, I would not advocate screening for thrombophilia because, as mentioned, many of the early losses are associated with chromosomal aberrations and other mechanisms.

H&O How does antithrombotic therapy affect those women with recurrent miscarriages?

BB If one looks at the general population, it is quite common to find thrombophilia. However, the majority of women with thrombophilia will not have pregnancy complications. These complications often recur in those who originally have this tendency. Therefore, the aim of studies was to intervene, with antithrombotic therapy, in women with a history of pregnancy complications.

To further investigate the association of thrombophilia and pregnancy complications, especially recurrent miscarriages, we studied the use of antithrombotic therapy in women to further prevent losses in their next pregnancy. In particular, we have done some studies using low-molecular-weight heparin in the intervention of pregnancy complications with women who have had recurrent miscarriages (3 or more losses in the first trimester, 2 or more losses in the second trimester, or at least 1 fetal death in the third trimester) and were found to have thrombophilia.

The LIVE-ENOX trial was a multicenter study in 12 institutions in Israel.² In this study, we used enoxaparin (Lovenox, Sanofi-Aventis) in women with recurrent pregnancy loss with thrombophilia, and found that prophylaxis with enoxaparin 40 mg/day or 80 mg/day resulted in favorable gestational and neonatal outcomes. First, we compared 2 doses of enoxaparin: 40 mg and 40 mg twice daily (ie, 80 mg/day). We started with treatment after pregnancy, between 5–10 weeks of gestation, and continued throughout pregnancy and 6 weeks postpartum because these women, who also had thrombophilia, needed to prevent thrombosis in the postpartum period. The patients' obstetric history showed that the live birth rate before the study was approximately 28%. During the study, there was no statistical difference in the live birth rate between the 2 arms: the 40 mg-dose-arm had a 84% live birth rate, and the 80 mg-dose-arm had a 78% live birth rate. Also, with this therapy, we observed a reduction in late pregnancy complications, such as preeclampsia, intrauterine growth restriction, and placental abruption, which are associated with the impaired perfusion of the placenta, compared to the obstetric history of these women.

Another study was published around the same time by Dr. Jean-Christophe Gris from France, in which he compared enoxaparin 40 mg to low-dose aspirin in women who had at least 1 fetal loss after 10 weeks of gestation and who also had thrombophilia (ie, factor V Leiden, prothrombin mutation, or protein S deficiency).³ This study demonstrated a significant difference between the 2 arms: the live birth rate in the enoxaparin arm was 86%, and that in the low-dose aspirin arm was only 29%.

Aspirin and low-molecular-weight heparin are prescribed for women with unexplained recurrent miscarriage, and there are some trials that looked into the effectiveness of these therapies. First, a study done in Israel a couple of years ago by Dr. Mordechai Dolitzky compared the effect of aspirin and enoxaparin on live births in women with unexplained recurrent miscarriages.⁴ Most of the patients were women with early and recurrent pregnancy losses, who screened negative for thrombophilia. Therefore, all the women in this study were without thrombophilia.

This study compared enoxaparin 40 mg to low-dose aspirin. Results showed that both groups had similar live birth rates, both over 80%.

Recently, in a paper published in the *New England Journal of Medicine*, Kaandorp and associates compared the efficacy of aspirin alone versus aspirin plus low-molecular-weight heparin in women with unexplained recurrent miscarriage.⁵ In this randomized trial (ALIFE [Anticoagulants for Living Fetuses]), 364 women who had a history of unexplained recurrent miscarriage and were attempting to conceive or those who were less than 6 weeks' pregnant were randomly assigned to receive daily 80 mg of aspirin plus subcutaneous nadroparin, 80 mg of aspirin alone, or placebo.

Unlike the Dolitzky study, in which the unexplained pregnancy loss was defined after ruling out thrombophilia, the investigators of the ALIFE trial did not screen for thrombophilia before patient selection. The women studied were those who had recurrent miscarriages according to the definition; of those women, a relatively small portion (16% of all women in the study) had thrombophilia. Results showed that live-birth rates did not differ among the 3 study groups. The live-birth rate was 54.5% in those receiving aspirin plus nadroparin, 50.8% in the aspirin-only group; and 57.0% in the placebo group. The study was underpowered to demonstrate any effect of these 3 therapies in terms of thrombophilia.

At the same time, there was another study published in *Blood*, by Dr. Peter Clark, called the SPIN (Scottish Pregnancy Intervention) study.⁶ Similar to the Kaandorp study, researchers compared enoxaparin plus aspirin versus no intervention (ie, intensive pregnancy surveillance) in women with unexplained pregnancy loss. This study also found that there was no difference in live birth rate between the treatment arms. Only 3.5% of women had thrombophilia, and thus this study was also underpowered for this condition. Future studies should focus on women with thrombophilia and recurrent pregnancy loss.

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