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New Paradigms for Anticoagulation in Pregnant Women With Inherited Thrombophilia

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H&O How common is inherited thrombophilia among women of childbearing age, and how often does it lead to venous thromboembolism?

DA The term *thrombophilia* is used to describe conditions associated with an increased predisposition to the development of venous thromboembolism (VTE). Acquired forms of thrombophilia include antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and myeloproliferative disease, whereas inherited forms include factor V Leiden (FVL) variant (G1691A), prothrombin gene (PGA) variant (G20210A), protein C deficiency, protein S deficiency, and antithrombin (AT) deficiency.[1] Inherited thrombophilia is more common among people with European ancestry than among other ethnic groups, with a prevalence of up to 15%.[2]

Pregnancy itself is a hypercoagulable state, caused at least in part by physiologic changes in the coagulation and fibrinolytic systems. The combination of pregnancy and an acquired or inherited thrombophilia will further increase the risk for thrombosis. VTE occurs in 10 per 100,000 women of childbearing age and affects 100 in 100,000 pregnancies.[3] A history of previous VTE and inherited thrombophilia are the 2 most common risk factors for VTE during pregnancy. Inherited thrombophilia is present in approximately 30% to 50% of women with pregnancy-associated VTE.[4]

H&O Which complications of pregnancy can be attributed to inherited thrombophilia?

DA Although the link between inherited thrombophilia and VTE is clear, the evidence is conflicting regarding the association between inherited thrombophilia and early pregnancy complications—specifically recurrent miscarriages—and late pregnancy complications—specifically pre-eclampsia/eclampsia, intrauterine growth retardation, and fetal death.[1] Although some studies have demonstrated a link between inherited thrombophilia and pregnancy complications, this finding has been refuted by other studies. Furthermore, the underlying mechanisms of such potential associations remain unclear. Although it is possible that thrombophilia plays a role in the development of placental microvascular thrombosis, which leads to recurrent miscarriages, placental microvascular thrombosis cannot play a role in miscarriages that occur early in the first trimester, before the placenta is fully formed. Late pregnancy complications may affect more than 5% of pregnancies and can have multiple causes.[5] Although evidence exists to link these complications to a common pathophysiology of inappropriate activation of coagulation pathways,[6] studies have so far failed to produce convincing evidence to prove that inherited thrombophilia is a cause of these complications.

H&O Are some types of inherited thrombophilia more likely than others to produce thrombotic complications during pregnancy?

DA Some types of inherited thrombophilic defects will place women at a higher risk for VTE, as will the presence of a family history of VTE. The absolute risk seems to be low (<1%) in those with no family history of VTE who are heterozygous for FVL G1691A or PGA

G20210A, and in those who have an AT, protein C, or protein S deficiency.[7,8] Women who have a family history of VTE and an inherited thrombophilic defect other than AT deficiency still have a low pooled risk for antepartum VTE, at less than 2%. The risk for VTE is considerably higher in women who have an AT deficiency and a family history of VTE (2.70%; 95% CI, 0%-8.53%). The risk ranges from 1.0% to 7.0% in women who are homozygous for the FVL mutation, depending on study design,[9] and is 1.6% for individuals who are homozygous for the PGA mutation.[9]

H&O Which women with inherited thrombophilia require thromboprophylaxis to prevent pregnancy associated VTE?

DA If a woman has a personal history of VTE—even if it was provoked, especially in relation to the use of estrogen-containing contraceptive pills, and regardless of whether she has inherited thrombophilia—she should receive thromboprophylaxis with low-molecular-weight heparin (LMWH) throughout the pregnancy and for 6 weeks in the postpartum period. If a woman has no personal history of VTE but has a family history of VTE along with inherited thrombophilic defects, the question of thromboprophylaxis depends on the specific thrombophilic defect.

The guidelines are inconsistent for women who are heterozygous for FVL G1691A or PGA G20210A or who have a protein C or protein S deficiency, with or without a family history of VTE. The American Society of Hematology (ASH) guidelines[9] recommend against the use of thromboprophylaxis in these women, whereas the Royal College of Obstetricians and Gynecologists (RCOG) guidelines do recommend its use in these women, especially if additional risk factors for VTE are present, such as high body mass index.[10]

For women who are homozygous for FVL G1691A or who have compound heterozygosity for thrombophilic defects, all guidelines recommend the use of thromboprophylaxis to prevent VTE during pregnancy, irrespective of a family history of VTE. For women who are homozygous for PGA G20210A but have no family history of VTE, however, the ASH guidelines suggest that antepartum antithrombotic prophylaxis not be used to prevent a first VTE, whereas other guidelines recommend the use of antithrombotic prophylaxis. For women who have an AT deficiency, we recommend the use of antithrombotic prophylaxis during pregnancy regardless of a family history of VTE, although the ASH guidelines suggest that this approach be used only in women who have a family history of VTE. Although the risk for VTE is spread across all 3 trimesters, the risk seems to be highest in the third trimester. In addition, because the postpartum period is much shorter than the antepartum period, the daily risk for VTE is higher after birth than before birth.[11] Therefore, some guidelines still recommend postpartum prophylaxis even when this is not recommended throughout gestation. Furthermore, the risk for VTE generally is highest in the first 6 weeks of the postpartum period and may persist for 12 weeks post-partum.[11,12] Therefore, it is important to assess each woman we see in the clinic individually and evaluate her risk factors for VTE and bleeding, taking all the above points into consideration, and then make a personalized recommendation regarding the use of thromboprophylaxis, along with the dose and duration. This evaluation process is particularly important in situations for which the guidelines provide conflicting recommendations.

H&O Should women with inherited thrombophilia ever be advised not to become pregnant?

DA In general, there is no situation in which we would advise a woman not to become pregnant because of an inherited thrombophilic defect. If a pregnant woman is at elevated risk for VTE owing to combined risk factors, such as family history, personal history, and severe AT deficiency, she should be managed in a high-risk obstetric/hematology clinic, with regular follow-up to assess fetal and maternal health and prevent complications.

H&O How should VTE be managed during pregnancy?

DA If VTE is suspected during pregnancy, this should be confirmed objectively with a suitable imaging technique. Although superficial vein thrombosis is often diagnosed clinically, it should also be confirmed by compression ultrasound whenever possible because the benefits of treatment with LMWH are thought to outweigh the potential harms of bleeding and the burden of injections.[9,10] Furthermore, superficial vein thrombosis carries a risk for extension into the deep venous system. Pregnant women with suspected deep vein thrombosis (DVT) should receive serial compression ultrasound or magnetic resonance venography with imaging of the iliac veins, even if the initial ultrasound result is negative.[9] In pregnant women with suspected pulmonary embolism (PE), ventilation/perfusion (V/Q) lung scanning should be performed rather than computed tomography (CT) pulmonary angiography to confirm the event. Unless it is strongly contraindicated,[9,10] LMWH should be commenced immediately in cases of clinically suspected DVT or PE until the diagnosis is excluded by imaging. LMWH

can be give either once or twice per day; twice-per-day regimens are more appropriate for women with a high body weight (>90 kg). Confirmed VTE during pregnancy should be treated with therapeutic doses of LMWH for the remainder of the pregnancy and for at least 6 weeks postnatally, with at least 3 months of treatment in total.[10] Women with VTE during pregnancy should be managed in a joint obstetric/hematology clinic. A plan for delivery should be clearly documented, and the patient should be given clear instructions on what to do when she goes into labor, which is to stop the LMWH injections and report to the maternity unit.

H&O Do DOACs have a role in VTE prophylaxis or therapy during pregnancy?

DA Direct-acting oral anticoagulants (DOACs), which include direct factor Xa inhibitors such as rivaroxaban (Xarelto, Janssen), apixaban (Eliquis, Bristol-Myers Squibb), and edoxaban (Savaysa, Daiichi Sankyo), along with the direct thrombin inhibitor dabigatran (Pradaxa, Boehringer Ingelheim), are not recommended for VTE prophylaxis or treatment during pregnancy owing to the risk for teratogenic effects.[13] No systematic clinical data exist on pregnancy outcome after DOAC exposure. In one study, researchers collected data on a total of 233 women who were exposed to a DOAC during pregnancy. Information on pregnancy outcome was available in only 137 of 233 cases (58.8%), with 67 live births (48.9%), 31 miscarriages (22.6%), and 39 elective pregnancy terminations (28.5%). In 93 cases (39.9%), no outcome data were available, including 3 cases of ongoing pregnancy. Of the 137 pregnancies with reported outcomes, 7 showed abnormalities (5.1%), of which 3 (2.2%) could possibly be interpreted as embryopathy: live birth with facial dysmorphism, miscarriage in week 10 with limb abnormality, and elective pregnancy termination because of a fetal cardiac defect in a woman who had a history of previous pregnancy termination owing to tetralogy of Fallot.[14]

H&O What special precautions should be taken during the use of warfarin and DOACs in pregnancy?

DA The risk for teratogenicity is highest during weeks 6 to 12 of gestation. The literature supports that the risk for teratogenicity before 6 weeks of gestation is extremely low with warfarin or other vitamin K antagonists (VKAs).[13] Pregnant women who are taking VKAs should be switched to LMWH as soon as possible before 6 weeks of gestation, and this agent should be continued throughout the pregnancy.[13]

DOACs should not be used in any stage of pregnancy because the risk for embryopathy related to DOACs is not well established.[9,13] Controversy exists regarding the management of women who are receiving long-term therapy with DOACs and are attempting to conceive. Guidelines from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH SSC) recommend conversion from a DOAC to warfarin or LMWH before conception is attempted; as soon as pregnancy is confirmed, those taking warfarin should be switched to LMWH.[10] However, some experts have suggested that there is no difference between switching to warfarin and remaining on DOACs while trying to conceive, given that both treatments are associated with embryopathy.[15] If a woman unintentionally becomes pregnant while on a DOAC, the DOAC should be discontinued immediately and LMWH should be commenced.[10] These women should undergo an early obstetric review and early ultrasound examination to assess fetal viability and detect evidence of any subchorionic/retroplacental bleeding. Following that, regular assessment with fetal ultrasound and other relevant monitoring, such as fetal echocardiography, should be done in a high-risk joint obstetric/hematology clinic.

H&O If a woman with hypercoagulability is on LMWH, is there any need to switch the patient to unfractionated heparin at term?

DA LMWH is preferred to unfractionated heparin (UFH) for the treatment or prevention of VTE during pregnancy. For women who are on a prophylactic or treatment dose of LMWH, the time since the last LMWH dose should be at least 12 hours before a cesarean delivery and 24 hours before spinal or epidural analgesia. For women who are planning to have a vaginal delivery, the advice is to halt LMWH injections if they are going into labor.[10] However, the time between the start of labor and delivery can vary significantly. It is possible that some women will remain without anticoagulation for a prolonged period, exposing them to a high risk for thrombotic events. Conversion to intravenous UFH with cessation at 4 to 6 hours before delivery or the anticipated need for epidural insertion, with a repeat heparin anti–factor Xa level drawn after 4 hours to confirm normalization, is appropriate in patients considered to be at high risk for recurrent VTE during prolonged anticoagulant interruption (eg, those with proximal DVT or pulmonary embolism diagnosed 2 to 4 weeks before delivery) or in patients with a mechanical heart valve. Although this recommendation is the most appropriate choice for women with a mechanical heart valve, it is not based on any randomized controlled studies. Further research is required to assess the transition from LMWH to intravenous UFH close to delivery in

all women at high risk for VTE. Women with a high risk for both thrombosis and bleeding also may benefit from a switch to UFH from LMWH at term, in addition to a planned delivery.

H&O Should compression stockings be used in the peripartum period?

DA Either intermittent pneumatic compression stockings or anti-embolic stockings are acceptable for peripartum management. Women at high risk for hemorrhage, with risk factors including major antepartum hemorrhage, coagulopathy, progressive wound hematoma, suspected intra-abdominal bleeding, and postpartum hemorrhage, may be managed with anti-embolic stockings, foot impulse devices, or intermittent pneumatic compression devices without chemical thromboprophylaxis with LMWH. UFH also may be considered.[10] Those who are at even higher risk for thrombosis despite prophylactic or treatment doses of LMWH should have additional protection with anti-embolic stockings or intermittent pneumatic compression stockings. Pneumatic stockings may be preferred if the patient has diabetes and is obese because anti-embolic stockings are more likely to cause ulcers.

H&O What recent changes have occurred that relate to anticoagulation in pregnancy?

DA The 2 recent changes are the recommendations regarding the use of LMWH either once or twice daily (compared with previous recommendations regarding the use of LMWH twice daily) and the avoidance of DOACs during pregnancy and lactation. An ongoing clinical trial called Highlow is comparing 2 different doses of LMWH in pregnant patients with a history of previous VTE and will provide information on which dose is more efficacious at preventing recurrent VTE in pregnancy (NCT01828697).

H&O Is there anything you would like to add?

DA The evidence is conflicting with respect to the presence and strength of the associations between inherited thrombophilia and pregnancy complications other than VTE. Therefore, inherited thrombophilia testing is not required outside a clinical trial for women who have recurrent pregnancy losses or late pregnancy complications. The only reasons for testing a woman of childbearing age for inherited thrombophilia are (1) to offer her long-term rather than short-term anticoagulation, considering the VTE event is provoked or unprovided and (2) to identify asymptomatic relatives who are at increased risk for VTE.

Even if a heritable thrombophilic defect is found in a woman with recurrent miscarriages or late pregnancy complications, no evidence exists to suggest that LMWH or other interventions, such as antiplatelet treatment, will provide benefit, apart from some studies showing a beneficial effect of low-dose aspirin to prevent preeclampsia in women with a history of preeclampsia, regardless of the presence of thrombophilia.

Disclosures

Dr Arachchillage has received sponsorships to attend international scientific meetings and has received funding from Bayer for an investigator-initiated multicenter observational study on COVID-19.

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