THROMBOPHILIAS AND PREGNANCY

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Key Points
Pregnant women are known to be hypercoagulable during pregnancy primarily due to 1,2

- increased resistance to the effects of activated protein C
- decrease in protein S activity because of reductions in total/free protein C antigenicity
- increases in serum fibrinogen plus factors II, VII, VIII and X
- increases in the levels and activities of fibrinolytic inhibitors, especially plasminogen activator
- inhibitor types 1 & 2 (PAI-1 & PAI 2)
- increased pressure on the pelvic veins and decreased flow in the lower extremities secondary to a gravid uterus3

Of Note 3,7
The thrombogenic potential of women with underlying thrombophilias is increased/enhanced by their hypercoagulable state related to pregnancy (an overall VTE rate of 200/100,000 deliveries). Co-existent morbidities/conditions such as lupus, sickle cell disease, smoking, impaired mobility, advanced maternal age, a C-section delivery, and obesity also add to the risk of VTE (venous thromboembolism) and pregnancy related problems in addition to thrombophilias. Women with multiple underlying thrombophilias are at even greater risk for these complications (an odds ratio of 14.3). Women who have suffered a prior spontaneous cloting event are also at risk for a recurrence during pregnancy (estimated rate of 10.9%). The thrombogenic potential typically remains elevated until about 6 weeks postpartum and is actually most significant during the postpartum period (an overall VTE rate of 500/100,000 deliveries).

Two main types of thrombophilias are inherited and acquired.

Thrombophilias can lead to a variety of complications during pregnancy that may include: 4,7,15,16

- deep venous thrombosis/pulmonary embolism
- miscarriage/stillbirth
- placental abruption
- fetal growth restriction (IUGR)
- pre-eclampsia

Inherited Thrombophilias: 5,6

- factor V Leiden mutation
- antithrombin III deficiency
- protein C deficiency
- protein S deficiency
- prothrombin 20210 gene mutation (also known as factor II mutation)
- MTHFR polymorphisms (C677T & 1298C): pregnancy association is controversial
- PAI-1 gene mutation
These thrombophilias are associated with over 50% of the VTE cases related to pregnancy. The greatest risk is for pregnant women who are homozygous for the factor V Leiden mutation (an odds ratio of 43.4) and the prothrombin gene mutation (an odds ratio of 24.4). These thrombophilias, however, have a relevance in fetal loss that remains controversial. Studies linking the use of anticoagulants to pregnancy success for these thrombophilias have produced conflicting results and remain inconclusive.

**Acquired Thrombophilias:**
- antiphospholipid antibody syndrome (APS)
- anticardiolipin antibodies (aCL): IgG and IgM
- antiphospholipid antibodies (serine, ethanolamine, and inositol): IgG and IgM
- lupus anticoagulant (LAC)
- anti-beta-2 glycoprotein-I antibodies: IgG and IgM

These thrombophilias are associated with pregnancy related VTE and pregnancy/fetal loss with an estimated odds ratio of 15.8 for a clotting event during pregnancy. The aCL and LAC pose the greatest thrombotic risks to pregnant women. Anticoagulation therapy is associated with markedly improved pregnancy outcomes when combined with baby ASA (81 mg PO daily): live birth rate increased by 50% in one study. UHF is typically used by itself without any accompanying baby ASA therapy.

**Diagnostic Criteria for Antiphospholipid Antibody Syndrome**
- one or more documented cases of thrombosis (pregnancy related)
- recurrent (3 or more) miscarriages in the first 10 weeks of pregnancy
- one or more fetal losses after 10 weeks of pregnancy
- preterm delivery at 34 weeks gestation or less due to pre-eclampsia/placental insufficiency
- accompanied by:
  - LAC being present in plasma on two separate occasions at least 12 weeks apart
  - aCL (IgG, IgM, or both) at titre > 40
  - anti-b2GPI (IgG or IgM) present on two or more occasions at least 12 weeks apart

**Anticoagulant Therapy**
- The preferred choice is low molecular weight heparin (LMWH): Lovenox (enoxaparin) because of
  - an extended half-life
  - better bioavailability
  - decreased incidence of bone loss when compared to UHF (unfractionated heparin)

**Ease of Use**
- Lovenox has no known reversal agent, anti-Xa levels can be used for dosing purposes
  - prophylactic dosage target: anti-Xa level = 0.1-0.3 four hours s/p administration of Rx, most common dosages are 40 mg SQ daily or BID
  - therapeutic dosage target: anti-Xa level = 0.6-1.0 four hours s/p administration of Rx, most common dosage is 1 mg/kg given subcutaneously every 12 hours (IV use is only appropriate and used for patients with an acute MI)
- UHF can be reversed with protamine, PTT levels can be used for dosing purposes
  - most common prophylactic doses are 5,000 units SQ daily or BID
○ therapeutic dosage target is a PTT of 1.5-2.5 x higher than control
○ patients are often changed from LMWH to UHF at 36 weeks gestation or when hospitalized (if delivery is likely in the next few days) in order to minimize potential epidural/delivery related bleeding complications

- warfarin (Coumadin) can be used postpartum (OK for lactating mothers) but NOT in pregnancy due to known embryopathy associated with its use
- new, oral anticoagulant agents are not recommended for pregnant/postpartum women by ACOG or ACCP (American College of Chest Physicians) as their use has never been studied in pregnancy to date

ACOG Screening Recommendations for Inherited Thrombophilias

(see Appendix A): Level B (based on limited or inconsistent scientific evidence) and C (based primarily on consensus and expert opinion) recommendations only!

ACOG Treatment Recommendations for Inherited Thrombophilias

(see Appendix B): Level C (based primarily on consensus and expert opinion) recommendations only!

As a performance measure, ACOG proposes documentation of an individual risk assessment for women with known inherited thrombophilias (therefore, please be aware that variations in the management of these patients may vary among providers, especially MFM consultants)

APPENDIX A

Women who breast-feed may receive postpartum warfarin, low-molecular-weight heparin (LMWH), and unfractionated heparin anticoagulation (level B recommendation, based on limited or inconsistent scientific evidence).

For women who have had recurrent fetal loss or placental abruption, inherited thrombophilia testing is not recommended, because it is unclear whether anticoagulation reduces recurrence (level B recommendation).

In women with previous intrauterine growth retardation or preeclampsia, evidence is insufficient to recommend screening for or treatment of thrombophilias (level B recommendation).

Screening with fasting homocysteine levels or methylenetetrahydrofolate reductase (MTHFR) mutation analyses is not recommended, because the MTHFR mutation has not been associated with negative pregnancy outcomes (level B recommendation).

Screening for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies (level C recommendation, based primarily on consensus and expert opinion).

Individualized risk assessment, which may modify management decisions, is recommended for all patients with inherited thrombophilias (level C recommendation).

APPENDIX B

For low-risk thrombophilia without previous VTE, surveillance without anticoagulation, or prophylactic LMWH or unfractionated heparin, is recommended antepartum. Low-risk
thrombophilia includes factor V Leiden heterozygous, prothrombin G20210A heterozygous, and protein C or protein S deficiency. Postpartum management should include surveillance without anticoagulation, or postpartum anticoagulation therapy if there are additional risk factors.

For low-risk thrombophilia with a single previous episode of VTE in women not receiving long-term anticoagulation therapy, antepartum management should include prophylactic or intermediate-dose LMWH or unfractionated heparin, or surveillance without anticoagulation. Postpartum management should include anticoagulation therapy or intermediate-dose LMWH or unfractionated heparin.

Women with high-risk thrombophilia without previous VTE should receive prophylactic LMWH or unfractionated heparin antepartum, and postpartum anticoagulation therapy. High-risk thrombophilia includes antithrombin deficiency, double heterozygous for prothrombin G20210A mutation and factor V Leiden, factor V Leiden homozygous, or prothrombin G20210A mutation homozygous.

High-risk thrombophilia with a single previous episode of VTE in women not receiving long-term anticoagulation therapy should be managed antepartum with prophylactic, intermediate-dose, or adjusted-dose LMWH or unfractionated heparin. Postpartum, these women should receive anticoagulation therapy or intermediate- or adjusted-dose LMWH or unfractionated heparin for 6 weeks, with the therapy level at least as high as the antepartum treatment.

Women without thrombophilia but with a previous episode of VTE associated with a single transient risk factor that is no longer present (excluding pregnancy or another estrogen-related risk factor) should have surveillance without anticoagulation antepartum, and anticoagulation therapy postpartum.

Women without thrombophilia with a previous single episode of VTE associated with a pregnancy- or estrogen-related transient risk factor should receive prophylactic-dose LMWH or unfractionated heparin antepartum, and anticoagulation therapy postpartum.

For women without thrombophilia who have had a previous single episode of idiopathic VTE without an associated risk factor, and who are not receiving long-term anticoagulation therapy, prophylactic-dose LMWH or unfractionated heparin is recommended antepartum, and anticoagulation therapy postpartum.

Regardless of whether they have thrombophilia, women who have had 2 or more episodes of VTE and are not receiving long-term anticoagulation therapy should receive prophylactic or therapeutic-dose LMWH antepartum, and anticoagulation therapy postpartum. If they are already receiving long-term anticoagulation therapy, they should receive therapeutic-dose LMWH or unfractionated heparin antepartum and resume their long-term anticoagulation after delivery.

REFERENCES