Approach to Thrombophilias in the Female Patient

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Objectives

- Review the background of thrombophilias
- Identify the various thrombophilias that are associated with thrombosis
- Understand the medical risks associated with thrombophilias
- Recognize when treatment is indicated
- Emphasize the importance of preconceptional counseling
Background

- Thrombophilias a/w ↑ risk of VTE during pregnancy
- Thrombophilic disorders: acquired (e.g. APLS) or inherited (e.g. Factor V Leiden)
- Acquired disorders also ↑ risk of arterial events
- Controversy as to whether they may adversely affect other pregnancy outcomes (e.g. pregnancy loss, placental abruption, severe preeclampsia, & stillbirth)
Epidemiology

- Risk of thromboembolic event
  - during pregnancy = 200/100,000
  - postpartum = 500/100,000
- Risk Factors:
  - AMA
  - SLE
  - sickle cell dz
  - Obesity
  - postpartum complications
  - Thrombophilias
- PE = leading cause of death in developed countries; accounts for 20% of pregnancy-related deaths
**During Normal Pregnancy**

**Table 1. Changes in the Normal Functioning of the Coagulation System During Pregnancy**

<table>
<thead>
<tr>
<th>Coagulant Factors</th>
<th>Change in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor X</td>
<td>Increased</td>
</tr>
<tr>
<td>Von Willebrand factor</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-2</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor II</td>
<td>No change</td>
</tr>
<tr>
<td>Factor V</td>
<td>No change</td>
</tr>
<tr>
<td>Factor IX</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Free Protein S</td>
<td>Decreased</td>
</tr>
<tr>
<td>Protein C</td>
<td>No change</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>No change</td>
</tr>
</tbody>
</table>

The hemostatic system

- Venous stasis in lower extremities
  - Compression of IVC & pelvic veins by gravid uterus
  - Increased deep vein capacitance due to estrogen, prostacyclin, and nitric oxide

- Net effect in pregnancy
  - Increased clotting potential
  - Decreased anticoagulant activity
  - Decreased fibrinolysis
Contact activation (intrinsic) pathway

Damaged surface

XII \rightarrow XIIa

XI \rightarrow XIIa

IX \rightarrow IXa \rightarrow VIIIa

Prothrombin (II) \rightarrow Xa \rightarrow Thrombin (IIa)

V \rightarrow VIIIa

Fibrinogen (I) \rightarrow Fibrin (Ia) \rightarrow XIIIa \rightarrow XIII

Active Protein C

Protein S

Protein C + thrombomodulin

Tissue factor (extrinsic) pathway

Trauma

TFPI

VIIa \rightarrow VII

Tissue factor \rightarrow Trauma

VIII \rightarrow Xa

X \rightarrow Va

Fibrinogen (I) \rightarrow Fibrin (Ia) \rightarrow Cross-linked fibrin clot

Antithrombin
Antiphospholipid antibody syndrome (APS)

- Acquired thrombophilia

- Increased maternal complications
  - Venous thrombotic events include DVT, PE
  - Arterial thrombotic events include CVA, TIA
  - Recurrence risks up to 30%, may require long-term prophylaxis

- Increased obstetric complications
  - Pregnancy loss after 10wks (OR with +LA 3–4.8)
  - IUGR (15–33%), PIH (OR 5.5–8.1), PET (50%)
Lupus anticoagulant
- OR for arterial thrombosis 8.6–10.8
- OR for venous thrombosis 4.1–16.2

Anticardiolipin antibody
- OR for arterial thrombosis 1–18
- OR for venous thrombosis 1–2.5

Anti-β₂-glycoprotein I

Maternal & obstetrics complications may still occur despite therapy
- VTE 5%
- Pregnancy loss 27%
- PIH 17%
- IUGR 15%
APS: Who to screen?

- Hx of $\geq$ 1 vascular thrombosis (arterial or venous)
- Hx of $\geq$ 1 fetal death (>10wks) normal morphology
- Hx of $\geq$ 1 preterm births (<34wks) normal morphology, due to eclampsia, severe PET, or placental insufficiency
- Hx of $\geq$ 3 unexplained consecutive pregnancy loss (<10wks)
  - No maternal anatomic or hormonal abnormalities
  - Normal maternal & paternal chromosomes

**APS: Lab Criteria**

- Lupus anticoagulant present on 2 or more occasions, 12 weeks apart or
- Anticardiolipin antibody IgG &/or IgM, medium or high titer (>99th %ile), on 2 or more occasions, 12 weeks apart, by standardized ELISA, or
- Anti-β₂-glycoprotein I antibody IgG and/or IgM, medium or high titer (>99th %ile), on 2 or more occasions, 12 weeks apart, by standardized ELISA

### APS Treatment

- **Women without previous thrombotic event**
  - Clinical surveillance or prophylactic anticoagulation antepartum
  - Prophylactic anticoagulation 6 wks postpartum

- **Women with previous thrombotic event**
  - Prophylactic anticoagulation antepartum & 6 wks postpartum
  - +/- low-dose ASA

- **Women with pregnancy loss or recurrent SABs, without previous thrombotic event**
  - Prophylactic anticoagulation + low-dose ASA antepartum & for 6 wks postpartum

Inherited Thrombophilias

- Factor V Leiden mutation
- Prothrombin gene mutation
- Antithrombin III deficiency
- MTHFR / hyperhomocysteinemia
- Protein C deficiency
- Protein S deficiency
## Risk of VTE with Thrombophilias

**Table 1. Risk of Venous Thromboembolism With Different Thrombophilias**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence in General Population (%)</th>
<th>VTE Risk per Pregnancy (No History) (%)</th>
<th>VTE Risk per Pregnancy (Previous VTE) (%)</th>
<th>Percentage of All VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden heterozygote</td>
<td>1-15</td>
<td>&lt;0.3</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Factor V Leiden homozygote</td>
<td>&lt;1</td>
<td>1.5</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombin gene heterozygote</td>
<td>2-5</td>
<td>&lt;0.5</td>
<td>&gt;10</td>
<td>17</td>
</tr>
<tr>
<td>Prothrombin gene homozygote</td>
<td>&lt;1</td>
<td>2.8</td>
<td>&gt;17</td>
<td>0.5</td>
</tr>
<tr>
<td>Factor V Leiden/prothrombin double heterozygote</td>
<td>0.01</td>
<td>4.7</td>
<td>&gt;20</td>
<td>1-3</td>
</tr>
<tr>
<td>Antithrombin III activity (&lt;60%)</td>
<td>0.02</td>
<td>3-7</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Protein C activity (&lt;50%)</td>
<td>0.2-0.4</td>
<td>0.1-0.8</td>
<td>4-17</td>
<td>14</td>
</tr>
<tr>
<td>Protein S free antigen (&lt;55%)</td>
<td>0.03-0.13</td>
<td>0.1</td>
<td>0-22</td>
<td>3</td>
</tr>
</tbody>
</table>
# How to Test for Thrombophilias

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td>Activated protein C resistance assay (second generation)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>If abnormal: DNA analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prothrombin gene mutation G20210A</td>
<td>DNA analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Protein C activity (&lt;60%)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Functional assay (&lt;55%)</td>
<td>No*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Antithrombin activity (&lt;60%)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.
Who to screen?

- Hx of VTE associated with a nonrecurrent risk factor (ie fracture, surgery, prolonged immobilization)

- 1st degree relative (ie parent, sibling) with high-risk thrombophilia or VTE prior to age 50

- Not recommended for women with recurrent fetal loss, placental abruption, early onset PET, or IUGR
  - Insufficient evidence that anticoagulation prevents recurrence

Inherited Thrombophilias

- Factor V Leiden mutation
  - Most common of the serious inherited thrombophilias
  - Mutation makes Factor V refractory to proteolysis by activated Protein C

- Prothrombin gene mutation
  - Mutation results in elevated prothrombin levels

- Combination of heterozygous Factor V Leiden & prothrombin gene mutation results in synergistic hypercoagulable effects
Inherited Thrombophilias

- Antithrombin III deficiency
  - Highly thrombogenic
  - Mutations can result in decreased production, decreased activity, or both

- MTHFR gene mutation / hyperhomocysteinemia
  - Homozygosity for MTHFR gene mutation is the most common cause for hyperhomocysteinemia
  - MTHFR mutations themselves do not increase risk of VTEs
  - Elevated homocysteine levels are a weak risk factor for VTEs
  - It is **not** recommended to check for MTHFR mutations or fasting homocysteine levels in the w/u for VTE

Inherited Thrombophilias

- Protein C deficiency
  - Mutations can result in decreased production, decreased activity, or both
- Protein S deficiency
  - Mutations result in decreased production

- Homozygous deficiency can result in rare neonatal purpura fulminans & require life-long anticoagulation
Table 4. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Antepartum Management</th>
<th>Postpartum Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk thrombophilia without previous VTE</td>
<td>Surveillance without anticoagulation therapy or prophylactic LMWH or UFH</td>
<td>Surveillance without anticoagulation therapy or postpartum anticoagulation therapy if the patient has additional risks factors†</td>
</tr>
<tr>
<td>Low-risk thrombophilia with a single previous episode of VTE—Not receiving long-term anticoagulation therapy</td>
<td>Prophylactic or intermediate-dose LMWH/UFH or surveillance without anticoagulation therapy</td>
<td>Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH</td>
</tr>
<tr>
<td>High-risk thrombophilia without previous VTE</td>
<td>Prophylactic LMWH or UFH</td>
<td>Postpartum anticoagulation therapy</td>
</tr>
<tr>
<td>High-risk thrombophilia with a single previous episode of VTE—Not receiving long-term anticoagulation therapy</td>
<td>Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen</td>
<td>Postpartum anticoagulation therapy or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.
*Postpartum treatment levels should be greater or equal to antepartum treatment. Treatment of acute VTE and management of antiphospholipid syndrome are addressed in other Practice Bulletins.
†Low-risk thrombophilia: factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency.
‡First-degree relative with a history of a thrombotic episode before age 50 years, or other major thrombotic risk factors (eg, obesity, prolonged immobility).
§High-risk thrombophilia: antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous.
¶Surveillance without anticoagulation is supported as an alternative approach by some experts.

| No thrombophilia with previous single episode of VTE associated with transient risk factor that is no longer present—Excludes pregnancy- or estrogen-related risk factor | Surveillance without anticoagulation therapy | Postpartum anticoagulation therapy

| No thrombophilia with previous single episode of VTE associated with transient risk factor that was pregnancy- or estrogen-related | Prophylactic-dose LMWH or UFH | Postpartum anticoagulation therapy

| No thrombophilia with previous single episode of VTE without an associated risk factor (idiopathic)—Not receiving long-term anticoagulation therapy | Prophylactic-dose LMWH or UFH | Postpartum anticoagulation therapy

| Thrombophilia or no thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy | Prophylactic or therapeutic-dose LMWH or Prophylactic or therapeutic-dose UFH | Postpartum anticoagulation therapy or Therapeutic-dose LMWH/UFH for 6 weeks

| Thrombophilia or no thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy | Therapeutic-dose LMWH or UFH | Resumption of long-term anticoagulation therapy

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

*Postpartum treatment levels should be greater or equal to antepartum treatment. Treatment of acute VTE and management of antiphospholipid syndrome are addressed in other Practice Bulletins.

Low-risk thrombophilia: factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency.

First-degree relative with a history of a thrombotic episode before age 50 years, or other major thrombotic risk factors (eg, obesity, prolonged immobility).

High-risk thrombophilia: antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous.

Surveillance without anticoagulation is supported as an alternative approach by some experts.
<table>
<thead>
<tr>
<th>Anticoagulation Regimen</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic LMWH*</td>
<td>Enoxaparin, 40 mg SC once daily</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 5,000 units SC once daily</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin, 4,500 units SC once daily</td>
</tr>
<tr>
<td>Therapeutic† LMWH</td>
<td>Enoxaparin, 1 mg/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 200 units/kg once daily</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin, 175 units/kg once daily</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 100 units/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>May target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.</td>
</tr>
<tr>
<td>Minidose prophylactic UFH</td>
<td>UFH, 5,000 units SC every 12 hours</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>UFH, 5,000–10,000 units SC every 12 hours</td>
</tr>
<tr>
<td></td>
<td>UFH, 5,000–7,500 units SC every 12 hours in first trimester</td>
</tr>
<tr>
<td></td>
<td>UFH, 7,500–10,000 units SC every 12 hours in the second trimester</td>
</tr>
<tr>
<td></td>
<td>UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated</td>
</tr>
<tr>
<td>Therapeutic UFH†</td>
<td>UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5) 6 hours after injection</td>
</tr>
<tr>
<td>Postpartum anticoagulation</td>
<td>Prophylactic LMWH/UFH for 4–6 weeks or vitamin K antagonists for 4–6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism</td>
</tr>
</tbody>
</table>
Anticoagulation

- Monitoring
  - Obtain baseline CBC, coags prior to start of therapy
  - Check PLT on day 4, day 7, day 14 of therapy
  - Supplement with Vit D & calcium
  - Check aPTT or anti-factor Xa levels 1wk after dose adjustments or every trimester if within therapeutic range

- Restart anticoagulation
  - 4–6h after SVD
  - 6–12h after C/S
Anticoagulation

- **LMWH**
  - Check anti-factor Xa levels 4–6h after last injection
  - Therapeutic anti-factor Xa level 0.6–1 u/mL

- **UFH**
  - Check aPTT 6h after last injection
  - Therapeutic aPTT 1.5–2.5x normal

- **Fondaparinux (Arixtra)**
  - Use in patients with heparin allergy (ie HIT)
  - Factor Xa inhibitor
  - 2.5–10 mg SC qd
Contraception

- VTE risk with estrogen OCP’s
  - ↑’s 35–99–fold w/ heterozygous Factor V Leiden & 16–fold w/ prothrombin G20210A mutations
- Consider alternative methods (e.g.IUD’s, progestin–only pills or implants)
- Screening all women for thrombophilias prior to initiating combination contraception NOT recommended
Preconceptional Counseling

- Discuss pros & cons of medical therapy
- Acknowledge the unproven efficacy of thromboprophylaxis
- Difficult to give precise #’s for risk of thrombosis or OB complications
- Review specific logistics of either thromboprophylaxis or full anticoagulation with UFH or LMWH
- Switch Coumadin to LMWH before conception
Preconceptional Counseling

- Discuss obstetric management and long-term medical implications
- Address emotional needs of families, especially with regard to prior adverse obstetric events
- Consultation & f/u with hematologist
A suggested approach.....

**Figure 1.** Thrombophilia and pregnancy. *High risk VTE: APS, AT III deficiency, homozygous FVL, homozygous prothrombin gene mutation, compound heterozygous FVL and prothrombin gene mutations, recent thrombosis, recurrent thrombosis, PC, and PS deficiency. **Low risk VTE: Heterozygous FVL, heterozygous prothrombin gene mutation, hyper-homocysteinemia.*
Questions??

THANK YOU!
References