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>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting Factors</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor V</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor X</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Protein C</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Protein S</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Protein Z</td>
<td>Increased</td>
<td>Increased</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
- 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–ß2-glycoprotein I
  - Maternal & obstetric complications may still occur despite therapy
    - VTE 5%
    - Pregnancy loss 27%
    - PIH 17%
    - IUGR 15%
### APS: Who to screen?

- Hx of ≥ 1 vascular thrombosis (arterial or venous)
- Hx of ≥ 1 fetal death (>10wks) normal morphology
- Hx of ≥ 1 preterm births (<34wks) normal morphology, due to eclampsia, severe PET, or placental insufficiency
- Hx of ≥ 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

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Risk of VTE with Thrombophilias

Table 1. Risk of Venous Thromboembolism With Different Thrombophilias

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Prevalence in General Population (%)</th>
<th>VTE Risk per Pregnancy (% lifetime)</th>
<th>VTE Risk per Pregnancy (Thrombus VTE) (%)</th>
<th>Percentage of All VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden heterozygote</td>
<td>1-15</td>
<td>&lt;0.1</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Factor V Leiden homogygote</td>
<td>1</td>
<td>1.5</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombin gene heterozygote</td>
<td>2-5</td>
<td>0.0-5</td>
<td>&gt;18</td>
<td>17</td>
</tr>
<tr>
<td>Prothrombin gene homozygote</td>
<td>1-2</td>
<td>2.0-4</td>
<td>&gt;17</td>
<td>0.5</td>
</tr>
<tr>
<td>Factor V Leiden/prothrombin</td>
<td>0.85</td>
<td>4.7</td>
<td>&gt;28</td>
<td>3-5</td>
</tr>
<tr>
<td>Protein C activity (U/L)</td>
<td>2.2-4.4</td>
<td>2.1-5</td>
<td>&gt;28</td>
<td>3-5</td>
</tr>
<tr>
<td>Antithrombin III activity (U/L)</td>
<td>0.82</td>
<td>3-5</td>
<td>&gt;28</td>
<td>3-5</td>
</tr>
<tr>
<td>Protein S free antigen (U/L)</td>
<td>0.0-0.13</td>
<td>0.1-0.13</td>
<td>&gt;28</td>
<td>3-5</td>
</tr>
</tbody>
</table>


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How to Test for Thrombophilias

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Testing Method</th>
<th>In Testing Reliable During Pregnancy?</th>
<th>In Testing Reliable During Acute Thrombosis?</th>
<th>In Testing Reliable With Anti-coagulation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td>Advanced assays (Cassette)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Activated partial thromboplastin assay (APT)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>Activated partial thromboplastin assay (APT)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Protein C deficiency</td>
<td>Activated partial thromboplastin assay (APT)</td>
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</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>Activated partial thromboplastin assay (APT)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Testing is pregnancy and delivery labors for key protein C antigen levels in the second and third trimesters have been identified at less than 30% and less than 30%, 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

- 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
### 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 0.5–1 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
  - 1’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 thrombophilies 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.....

**THANK YOU!**

**References**