Thrombophilias, Venous Thromboembolism (VTE), and Pregnancy

University of Utah Health Sciences and Intermountain Healthcare

Salt Lake City, Utah
How to Make a Seemingly Complicated Area Simple using evidence and professional guidelines

University of Utah Health Sciences and Intermountain Healthcare

Salt Lake City, Utah
Risk Factors for VTE in Pregnancy

• Thrombophilia
  – High risk
    • Homozygosity for FVL or prothrombin 20210
    • Compound heterozygosity for same
    • Antithrombin deficiency
    • *Lupus anticoagulant*
  – Low risk
    • Heterozygosity for FVL or prothrombin 20210, protein C or S deficiency
<table>
<thead>
<tr>
<th>Condition</th>
<th>Type of Assay</th>
<th>Possible Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FV Leiden</td>
<td>DNA-based</td>
<td>Negative, heterozygote, homozygote</td>
<td></td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td>Functional clotting</td>
<td>Negative, positive</td>
<td>May be substituted for FV Leiden</td>
</tr>
<tr>
<td>Prothrombin 20210 mutation</td>
<td>DNA based</td>
<td>Negative, heterozygote, homozygote</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Functional clotting</td>
<td>Negative, positive</td>
<td>Must be off of oral and parenteral anticoagulants</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Functional clotting</td>
<td>Negative, positive</td>
<td>Must be off of oral anticoagulants; test is sensitive to certain clinical conditions</td>
</tr>
<tr>
<td>Anti-thrombin deficiency</td>
<td>Enzymatic, chromogenic</td>
<td>Negative, positive</td>
<td></td>
</tr>
</tbody>
</table>
Risk Factors for VTE in Pregnancy

• “...there is insufficient evidence to support assessment of MTHFR polymorphisms or measurement of fasting homocysteine levels in the evaluation of a thrombophilic etiology for venous thromboembolism and, therefore, it is not recommend.”

ACOG Practice Bulletin 124, September 2011
Heritable Thrombophilia Testing OUTSIDE of Pregnancy

• Somewhat controversial in setting of acute VTE!
  – Most commonly found heritable thrombophilias do not alter treatment
  – Most commonly found heritable thrombophilias do not substantially increase the risk of recurrent thrombosis
  – Likelihood of finding a high-risk heritable thrombophilia is small
  – Testing is costly
Heritable Thrombophilia Testing with Regard to Pregnancy

• ACOG (PB 123, 2011): “Screening may be considered in...[women with]”:
  – A personal history of VTE associated with a nonrecurrent risk factor
  – A first-degree relative with a history of a high-risk thrombophilia or VTE before age 50 years in the absence of other risk factors
VTE Prevention
Brill-Edwards Study

• Subjects: 125 women with single prior VTE
• Methods:
  – Antepartum heparin withheld
  – Anticoagulant therapy 4-6 weeks postpartum
  – Laboratory testing to identify thrombophilia
• Results:
  – 2.4% recurrent VTE in antepartum period
  – No recurrent VTE in 44 women (1) negative for thrombophilia, and (2) with prior thrombosis in association with a transient risk factor
Heritable Thrombophilia Testing with Regard to Pregnancy

- **Antiphospholipid antibodies**
  - Lupus anticoagulant (LA)
  - Anticardiolipin (aCL) IgG and IgM
  - Anti-\(\beta_2\)-glycoprotein I (anti-\(\beta_2\)-GPI) IgG and IgM

- **What’s a positive test?**
  - LA is either positive or negative
  - aCL positive = 40 or more units
  - anti-\(\beta_2\)-GPI positive = greater than 99\(^{th}\) percentile for the lab
  - Repeatedly positive more than 12 weeks apart
Approach to Thromboprophylaxis

Patient Categories

• VTE
  – Acute VTE
  – Recurrent VTE
  – Single prior VTE
• Family history of thrombophilia or VTE without personal history of VTE
• Adverse pregnancy outcome or recurrent miscarriage
• Peripartum - postpartum
Recurrent VTE

- Most important consideration is whether or not the patient is on long-term anticoagulation
History of 2 or More Prior VTEs

- On long-term anticoagulation:
  - Adjusted dose LMWH/UFH
  - Resumption of long-term anticoagulation

- Not on long-term anticoagulation:
  - Intermediate or adjusted dose LMWH/UFH
  - Postpartum (6 wks) intermediate or adjusted dose LMWH/UFH or warfarin
Single Prior VTE

• Considerations:
  – Prior VTE without provocation vs. with transient risk factor
  – Prior VTE associated with estrogen treatment or pregnancy
  – Prior VTE associated with thrombophilia
Unprovoked, pregnancy or estrogen, high-risk thrombophilia

Intermediate or adjusted dose LMWH/UFH

Postpartum (6 wks) intermediate or adjusted dose LMWH/UFH or warfarin

Transient risk factor; low-risk thrombophilia

Antepartum surveillance or prophylactic LMWH/UFH

Postpartum (6 wks) prophylactic or intermediate dose LMWH/UFH or warfarin
Family History of High Risk Thrombophilia or VTE Without Personal History of VTE

- ACOG (PB 123, 2011): “Screening may be considered in...[women with]”:
  - A first-degree relative with a history of a high-risk thrombophilia or VTE before age 50 years in the absence of other risk factors
High risk thrombophilia

Prophylactic or intermediate dose LMWH/UFH

Postpartum (6 wks) prophylactic or intermediate dose LMWH/UFH or warfarin

Low risk thrombophilia

Antepartum surveillance or prophylactic LMWH/UFH

Postpartum surveillance or prophylactic or intermediate dose LMWH/UFH or warfarin (6 wks)

FHx of high-risk thrombophilia or 1st degree relative with VTE <50 yrs of age

No Prior VTE
Approach to Thromboprophylaxis

Patient Categories

• VTE
  – Acute VTE
  – Recurrent VTE
  – Single prior VTE
• Family history of thrombophilia or VTE without personal history of VTE
• Adverse pregnancy outcome or recurrent miscarriage
• Peripartum - postpartum
Heparin for the Prevention of Adverse Pregnancy Outcomes

- RCT of LMWH in women with one or more of the following adverse outcomes in the immediately prior pregnancy:
  - Severe preeclampsia $\rightarrow$ delivery $<$35 weeks
  - Unexplained SGA infant ($<$5 percentile)
  - Abruption $\rightarrow$ delivery $<$35 weeks
  - One or more unexplained fetal deaths $\geq 20$ weeks
  - Two unexplained fetal deaths 12-20 weeks

Heparin for the Prevention of Adverse Pregnancy Outcomes

- No thrombophilia (FVL, PT 20210, LA, aCL)
- All enrolled before 17 weeks (mean = 11 weeks); most also took LDA
- Intervention
  - Dalteparin, 4000 U – 6000 U daily
  - No dalteparin

## Heparin for the Prevention of Adverse Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Group</th>
<th>Dalteparin N=55</th>
<th>Controls N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PE</td>
<td>1 (2%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Severe SGA</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Abruptio</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fetal death &lt;20 wk</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fetal death &gt;20 wk</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Composite</td>
<td>3 (6%)</td>
<td>13 (24%)</td>
</tr>
</tbody>
</table>

Heparin for the Prevention of Adverse Pregnancy Outcomes

- RCT (multicenter) of LMWH in women with one or more of the following adverse outcomes in prior pregnancies:
  - Preeclampsia (any)
  - SGA infant (BW <10th percentile + AC < 60th percentile)
  - Abruption → delivery >24 weeks

- Primary outcome: composite of preeclampsia, eclampsia, HELLP, fetal death, FGR, abruption

Heparin for the Prevention of Adverse Pregnancy Outcomes

- Long list of exclusions, including prior VTE or arterial thrombosis
  - Thrombophilia not an exclusion
- Intervention
  - Nadroparin, 3800 IU daily
  - No nadroparin

Heparin for the Prevention of Adverse Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Group</th>
<th>Nadroparin N=63</th>
<th>Controls N=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreE</td>
<td>5 (8%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HELLP</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Fetal death</td>
<td>2 (3%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>FGR</td>
<td>5 (8%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Abruption</td>
<td>0</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Composite</td>
<td>13 (21%)</td>
<td>12 (18.5%)</td>
</tr>
</tbody>
</table>

Thrombophilias and Abnormal Placentation

- ACOG (PB 124, 2011)

  “...there is insufficient evidence of an association and, therefore, insufficient evidence to either screen for or treat women with inherited thrombophilias and obstetric histories that include complications such as IUGR or preeclampsia.”
Heparin for the Prevention of Recurrent Miscarriage

- Clark et al (SPIN Study)
  - Study Population: ≥ 2 losses < 24 weeks
    - Unexplained RM; aPL antibody negative
    - N=294 (13 centers)
  - Trial: LMWH + ASA + intense surveillance vs. intense surveillance alone started at documentation of viable pregnancy

Heparin for the Prevention of Recurrent Miscarriage

• Kaandorp et al
  – Study Population: ≥ 2 losses < 20 weeks
    • Unexplained by conventional evaluation; aPL antibody negative
    • N=364
    • Trial: LMWH + LDA vs. LDA vs. Placebo started < 6 weeks gestation ASA or Placebo; LMWH started with documentation of viable pregnancy

## Heparin for the Prevention of Recurrent Miscarriage

<table>
<thead>
<tr>
<th>Group</th>
<th>LMWH + LDA</th>
<th>LDA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al (SPIN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>77.6%</td>
<td>NA</td>
<td>79.3%</td>
</tr>
<tr>
<td>Kaandorp et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>69.1%</td>
<td>61.6%</td>
<td>67%</td>
</tr>
</tbody>
</table>
# Heparin for the Prevention of Recurrent Miscarriage

<table>
<thead>
<tr>
<th>Group</th>
<th>Enoxaparin + Placebo</th>
<th>Enoxaparin + LDA</th>
<th>LDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=68</td>
<td>N=63</td>
<td>N=76</td>
</tr>
<tr>
<td>Live Births</td>
<td>48 (71%)</td>
<td>41 (65%)</td>
<td>46 (61%)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.17 (0.92-1.48)</td>
<td>1.08 (0.83-1.39)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Thrombophilias and Recurrent Miscarriage or Fetal Death

• ACOG (PB 124, 2011)
  “Testing for inherited thrombophilias in women who have experienced recurrent fetal loss … is not recommended.”
Peripartum Thromboprophylaxis

- Change patients on LMWH to UFH at 36 to 37 weeks – **now debated**
  - Shorter half-life
  - Increased opportunity for neuraxial anesthesia if labor occurs
  - Reversible with protamine sulfate
- Advise patients to stop UFH or LMWH if labor is suspected
- Discontinue adjusted-dose and intermediate-dose LMWH 24 hrs prior to scheduled induction or c-section
- Discontinue UFH at least 12 hours prior to scheduled admission
ASRA Guidelines

• UFH
  – No contraindications to neuraxial techniques for BID UFH with total dose ≤10,000 u per day
  – Safety neuraxial blockade for >10,000 u per day or > twice daily dosing not established
    • Individualized risk / benefit assessment
      – No sooner than 12 hours after most recent SC dose of heparin and with a normal aPTT
  – Prophylactic UFH can be re-initiated no sooner than 1 hr after neuraxial catheter removal

Horlocker et al, ASRA Practice Advisory, Regional Anesthesia and Pain Medicine, 2010; 35:64.
ASRA Guidelines

- **LMWH**
  - Anti-Xa is not predictive of risk of bleeding
  - Needle placement at least 10-12 hrs after last prophylactic LMWH dose
  - Regional anesthesia contraindicated <24hrs from last adjusted-dose (therapeutic) dose
  - Prophylactic LMWH can be re-initiated no sooner than 2 hrs after neuraxial catheter removal

Horlocker et al, ASRA Practice Advisory, Regional Anesthesia and Pain Medicine, 2010; 35:64.
Peripartum Thromboprophylaxis

• Cesarean delivery (ACOG)
  – “Placement of pneumatic compression devices before cesarean delivery is recommended for all women not already receiving thromboprophylaxis”
Peripartum Thromboprophylaxis

- Cesarean delivery (ACCP, 2012)
  - If no additional risk factors, early mobilization is acceptable
  - If one major or two minor risk factors
    - Perioperative mechanical OR pharmacological thromboprophylaxis while in hospital
  - If higher risk
    - Perioperative mechanical AND pharmacological thromboprophylaxis
  - In selected high-risk patients with persistent risk factors for VTE should extended prophylaxis for up to 6 weeks postpartum
Peripartum Thromboprophylaxis

• Major Risk Factors
  – Immobility (≥ 1 week in antepartum period)
  – PPH ≥ 1,000 ml with surgery
  – Previous VTE
  – Preeclampsia with FGR
  – Thrombophilia (FVL, PTM, AT def)
  – Medical conditions
    • SLE
    • Heart disease
    • Sickle cell disease
  – Blood transfusion
  – Postpartum infection
Peripartum Thromboprophylaxis

• Minor Risk Factors
  – BMI > 30
  – Multiple pregnancy
  – PPH > 1,000 ml
  – Smoking > 10 cigs per day
  – FGR
  – Thrombophilia
    • Protein C or S def
  – Preeclampsia
Peripartum Thromboprophylaxis

- Cesarean delivery (ACCP, 2012)
  - If no additional risk factors, early mobilization is acceptable
  - If one major or two minor risk factors
    - Perioperative mechanical OR pharmacological thromboprophylaxis while in hospital
  - If higher risk
    - Perioperative mechanical AND pharmacological thromboprophylaxis
  - In selected high-risk patients with persistent risk factors for VTE should extended prophylaxis for up to 6 weeks postpartum
Prevention
Postpartum Thromboprophylaxis

• UFH or LMWH
  – Restart 4-6 hrs after vaginal birth or 6-12 after cesarean delivery if clinically stable (ACOG)

• LMWH option

• Warfarin option
  – Treat with LMWH until INR therapeutic for 2 days
  – Start either 5-10 mg per day for first 2 days, then 5 mg per day
  – Check INR on day 3, 4, and 5 to attain INR 2-3