HOT TOPIC / Pregnancy-Related Venous Thromboembolism:

Risk Factors and Management

Presenter:
Ariela L. Marshall, MD
Senior Associate Consultant
Division of Hematology/Coagulation and Core Consultative Hematology Groups at Mayo Clinic, Rochester, Minnesota

Disclosure
• None
Utilization Message

As you view this presentation, consider the following important points regarding testing:

- How is the testing going to be used in your practice?
- When should the tests be used?
- How will results impact patient management?

Case Presentation: 31-year old woman with history of VTE who wants to become pregnant

- 31-year-old, G2, P1011, premenopausal woman with polycystic ovarian syndrome
  - 2011: Possible lower extremity DVT (acute right leg pain/swelling after a long drive, smoking, using NuvaRing for contraception); treated empirically with enoxaparin and symptoms resolved
  - 2011 – 2015: Used minipill and combined oral contraceptives
  - 2015: Successful pregnancy; restarted NuvaRing postpartum
  - 3 weeks postpartum woke with lower extremity pain and dyspnea on exertion, diagnosed with left lower extremity DVT and bilateral pulmonary emboli; transitioned to Lovenox and then warfarin
  - Thrombophilia testing was negative for factor V Leiden and prothrombin gene mutation, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-beta 2 GPI antibodies), deficiencies of proteins C, S, and antithrombin
  - Has been on warfarin for 1 month, notes increased menstrual bleeding but otherwise tolerating well
  - Wants to discuss future pregnancies including risk of hormone stimulation (for infertility related to PCOS) and role of prophylactic anticoagulation

Epidemiology

- Incidence
  - 1-2 per 1,000 pregnancies
  - Antenatal = 5-fold higher incidence than nonpregnant women (DVT more common)
  - Postnatal = up to 20-fold higher (PE more common)

- Consequences
  - One of the leading causes of pregnancy-related death in the developed world
  - Mortality 1 in 100,000 (US and Europe)
HOT TOPIC  / Pregnancy-Related Venous Thromboembolism

Risk Factors: Virchow’s Triad

- **Stasis:** “May-Thurner” physiology
  - Compression of left iliac vein by right iliac artery or ovarian artery
  - 90% DVT on left (versus 55% nonpregnant)
  - 70% in iliofemoral veins (versus 9% nonpregnant)
  - <10% of VTE in pregnancy are isolated calf DVTs

- **Hypercoagulability**
  - Increased factors V, VII, VIII, X, VWF, and fibrinogen
  - Decreased protein S; acquired resistance to activated protein C
  - Reduced fibrinolysis via reduced tPA and increased PAI (placental)
  - Acquired ATIII deficiency (preeclampsia → proteinuria)

- **Endothelial Injury**
  - Compression by uterus (and edema)
  - Vascular damage during delivery

Other Risk Factors

- **Antepartum:**
  - Age >35
  - Gestational diabetes
  - Assisted reproduction (ovarian hyperstimulation)
- **Postpartum:**
  - Preeclampsia/ eclampsia
  - Placental previa/abruption
  - Planned/ emergency C-section
  - Thrombophilia and/or previous VTE are high risk factors at all times
Treatment: Overall Points

• Low-molecular weight heparin preferred
• UFH and fondaparinux are alternative options
• Avoid warfarin and DOACs

Prophylaxis after prior VTE: Rationale

• Patients with prior VTE are at higher risk of recurrent VTE in subsequent pregnancies than when not pregnant
• Lifetime risk of recurrent VTE lower if first VTE pregnancy-associated
• BUT risk of recurrent VTE in subsequent pregnancy higher if first VTE pregnancy-associated

Prophylaxis: No Thrombophilia

<table>
<thead>
<tr>
<th>Prior VTE, provoked</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
<td>Vigilance</td>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior VTE, estrogen-associated</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior VTE, unprovoked</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
<td>Pluripotent or Intermediate dose (1.500 UI or variable 30 3-4 5-6 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On warfarin baseline</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjust dose (INR 2.5 for first trimester dose (350 UI)</td>
<td>Resume warfarin</td>
<td>Adjust dose (INR 2.5 for first trimester dose (350 UI)</td>
</tr>
</tbody>
</table>
About 50% of patients with VTE in pregnancy have at least one inherited thrombophilia.

### Prophylaxis: Thrombophilias

<table>
<thead>
<tr>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior VTE, HOMOzygous FVL or prothrombin, + FHx</td>
<td>Prophylactic or intermediate dose LMWH or varifant INR 2-3 x 6 weeks</td>
</tr>
<tr>
<td>No prior VTE, HOMOzygous FVL or prothrombin, No FHx</td>
<td>Vigilance</td>
</tr>
<tr>
<td>Prior VTE, HOMOzygous FVL or prothrombin</td>
<td>Prophylactic, intermediate, or full dose LMWH or varifant INR 2-3 x 6 weeks</td>
</tr>
<tr>
<td>No prior VTE, all other Thrombophilias, + FHx*</td>
<td>Vigilance</td>
</tr>
<tr>
<td>No prior VTE, all other Thrombophilias, No FHx*</td>
<td>Vigilance</td>
</tr>
<tr>
<td>Prior VTE, all other Thrombophilias</td>
<td>Prophylactic or intermediate dose LMWH or varifant INR 2-3 x 6 weeks</td>
</tr>
</tbody>
</table>

*N.B. Some practitioners use ppx post-partum (or even antepartum) LMWH for all patients with thrombophilia even without personal or family history
Case Discussion: Recommendations

- First DVT: Provoked in setting of hormone exposure, smoking, inactivity
- Second DVT/PE: Provoked in the postpartum setting
- History of PCOS and may need hormone therapy to become pregnant
- Evidence suggests that women on therapeutic anticoagulation do not have increased risk of recurrent VTE when exposed to hormone therapy
- Once future pregnancy attained:
  - Antepartum prophylaxis with enoxaparin 40mg daily for duration of pregnancy
  - Postpartum prophylaxis with enoxaparin 40mg daily (or warfarin) for at least 6 weeks after delivery, up to 8+ weeks if she has a Cesarean section

References
10. ACOG, Obstet Gynecol, 2013