INHERITED THROMBOPHILIAS IN PREGNANCY

Week 55

Prepared by: Hemangi P Shukla, DO, MS
with SDH and Epic .phrase slides by: Chloé Altchek, MS4

Reading Assignment:
Practice Bulletin #197, July 2018
Inherited Thrombophilias in Pregnancy
LEARNING OBJECTIVES

• To be familiar with the thrombotic characteristics of pregnancy and how they are exacerbated by inherited thrombophilias

• To be able to identify inherited thrombophilias to be targeted for screening

• To gain an understanding of how to determine risk factors that warrant screening for inherited thrombophilias

• To review the recommendations for prophylactic and therapeutic anticoagulation during and after pregnancy

• To be comfortable counseling the patient about contraceptive options in the setting of an inherited thrombophilia
CASE VIGNETTE

• Ms. V.T. is a 36 y.o. G1P0 woman at 8 weeks 3 days by 1st trimester ultrasound who presents for an initial prenatal visit. She denies any pain or vaginal bleeding. This pregnancy was planned and she’s very excited.

• She asks if she should be concerned that her sister has a genetic condition which required "injections to prevent blood clots"
FOCUSED HISTORY

What will be pertinent in her history?

• **POB:** G1P0
• **PGYN:** Regular menses; No STIs/cysts/fibroids; No abnormal paps
  Contraceptive history: Condoms, **COCs**, DMPA
• **PMH:** **Obesity**
• **PSH:** Denies
• **Meds:** PNV
• **All:** **NKDA**
• **FHx:** **Sister with possible inherited thrombophilia**
What will be pertinent in her physical exam?

- **VS:** P 76  BP 117/74  Wgt: 82kg  Hgt: 160cm  BMI: 32
- **Cor:** Regular rhythm, no M/R/G
- **Pulm:** CTAB b/l
- **Abd:** Soft, NT/ND, +BS x 4Q
- **Pelvic:**
  - **Vulva:** Normal external female genitalia; No lesions
  - **Vagina:** Healthy-appearing mucosa, No discharge
  - **Cervix:** Parous os; L/C/P
  - **Uterus:** NT, ~8wk size, anteverted
  - **Adnexae:** No mass/tenderness b/l
- **Ext:** No calf tenderness b/l; +1 DTR b/l
PHYSIOLOGY OF PREGNANCY

What is the impact of physiologic changes in pregnancy on the following?

- Clotting potential \(\uparrow\)
- Anticoagulant activity \(\downarrow\)
- Fibrinolysis \(\downarrow\)

What is the effect of the pregnant and postpartum state on risk of \textit{VTE} compared with nonpregnant women?

- \textbf{Fourfold to fivefold} increased risk
PREVALENCE

What are the most common inherited thrombophilias?

• Factor V Leiden
  • 1-15% prevalence in general population

• Prothrombin G20210A
  • 2-5% prevalence in general population
Who should be screened for inherited thrombophilias?

**GROUP 1**
- Personal history of VTE
  - AND
- No prior testing +/- recurrent risk factor

**GROUP 2**
- First-degree relative with a history of high-risk inherited thrombophilia

**What are examples of recurrent risk factors?**
- Pregnancy
- Estrogen-containing contraceptives

**What are examples of non-recurrent risk factors?**
- Fractures
- Surgery
- Prolonged immobilization
EVALUATION – PATIENT SELECTION

Which of the following are additional indications for inherited thrombophilia screening?

Women with a history of fetal loss?
  • NO

Women with a history of adverse pregnancy outcomes, e.g. abruption, preeclampsia?
  • NO

Women with a history of fetal growth restriction?
  • NO
For women with a **personal history of VTE**, what is the recommended screening panel?

- Factor V Leiden
- Prothrombin G20210A
- Antithrombin
- Protein S
- Protein C
SCREENING - TIMING

What is the significance of timing of screening?

- Patients should ideally be screened > 6wks after thrombotic event
- Patients should ideally not be pregnant
  - For patients who are pregnant, Free Protein S cutoffs performed

<table>
<thead>
<tr>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>&lt;24%</td>
</tr>
</tbody>
</table>

- Patients should ideally not be taking anticoagulation or hormonal therapy
### Table 2. How to Test for Inherited Thrombophilias

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<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 G20210A mutation</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;65%)</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.

What are considered “low-risk” thrombophilias?
- Factor V Leiden heterozygous
- Prothrombin G20210A heterozygous
- Protein C or Protein S deficiency

What are considered “high-risk” thrombophilias?
- Antithrombin
- Factor V Leiden homozygosity
- Prothrombin G20210A homozygosity
- Heterozygosity for Factor V Leiden + Prothrombin G20210A
How is the need for anticoagulation therapy determined?
Table 3. 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(^a) without previous VTE</td>
<td>Surveillance without anticoagulation therapy</td>
<td>Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors(^1)</td>
</tr>
<tr>
<td>Low-risk thrombophilia(^a) with a family history (first-degree relative) of VTE</td>
<td>Surveillance without anticoagulation therapy or prophylactic LMWH/UFH</td>
<td>Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH</td>
</tr>
<tr>
<td>Low-risk thrombophilia(^a) with a single previous episode of VTE—Not receiving long-term anticoagulation therapy</td>
<td>Prophylactic or intermediate-dose LMWH/UFH</td>
<td>Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH</td>
</tr>
<tr>
<td>High-risk thrombophilia(^a) without previous VTE</td>
<td>Prophylactic or intermediate-dose LMWH/UFH</td>
<td>Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH</td>
</tr>
<tr>
<td>High-risk thrombophilia(^a) with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy</td>
<td>Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH</td>
<td>Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)</td>
</tr>
<tr>
<td>Thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy</td>
<td>Intermediate-dose or adjusted-dose LMWH/UFH</td>
<td>Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)</td>
</tr>
<tr>
<td>Thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy</td>
<td>Adjusted-dose LMWH/UFH</td>
<td>Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.</td>
</tr>
</tbody>
</table>
What are the recommended anticoagulants to be used during pregnancy?

- Low Molecular Weight Heparin (LMWH) > Unfractionated heparin
  - Longer T1/2
  - Dose response more predictable
  - Improved maternal safety profile

- Antithrombin concentrate: Antithrombin-deficient patients refractory to standard therapy
MANAGEMENT - DOSING

How is **dosing** determined and **classified**?

- **Dosing**
  - Thrombophilia severity
  - VTE risk factors (eg Obesity, CD, FHx, VTE Hx)

- **Classification**
  - Prophylactic
  - Intermediate
  - Therapeutic (weight-based)
PERIPARTUM PLANNING - IOL

Is the presence of a thrombophilia an indication for induction of labor?
- No

Is there a role for induction of labor for a patient on anticoagulation for an inherited thrombophilia?
- Yes: induction at term can be utilized to time discontinuation of anticoagulation to facilitate neuraxial anesthesia
PERIPARTUM – PLANNING DISCONTINUATION

How would you counsel your patient to **discontinue their anticoagulation** in anticipation of a scheduled delivery?

- **LMWH**
  - Hold for **24 hours** if adjusted dose
  - Hold for **12 hours** if prophylactic

- **Unfractionated Heparin**
  - Hold for **12 hours** if >7500 units
  - Verify normal aPTT

- **Spontaneous labor**
  - Instruct patients on anticoagulation to withhold their injections at the onset of labor
POSTPARTUM

What are the considerations when a patient requires postpartum anticoagulation for an inherited thrombophilia?

• **Dosing**
  • Equal to antepartum therapy

• **Timing**
  • Vaginal delivery: 4-6 hours after delivery
  • Cesarean delivery: 6-12 hours after delivery

• **Patients requiring warfarin**
  • **Bridging** with LMWH or unfractionated heparin avoids paradoxical thrombosis and skin necrosis from warfarin’s early anti-Protein C effect
  • End point of achieving **INR 2.0 - 3.0 for 2 days**
What are the considerations when providing contraceptive counseling for women with an inherited thrombophilia?

- Estrogen-containing OCs increase VTE risk
- Consider alternative methods
  - IUD
  - Progestin-only pills and implants

Should routine screening for inherited thrombophilia be employed before initiation combination contraception?

- No

How many women would need to be screened to prevent one death from VTE?

- ~ ½ million
Prevalence of inherited thrombophilias varies by race

**Factor V Leiden Rates by Race in US**
- Caucasians: 5.27%
- Hispanic Americans: 2.21%
- Native Americans: 1.25%
- African Americans: 1.23%
- Asian Americans: 0.45%

**Prothrombin G20210A Rates by Race in US**
- Caucasians: 3.6%
- Hispanic Americans: 3.5%
- Native Americans: 0.9%
- African Americans: 0.3%

**Differences in the prevalence of protein C deficiency and antithrombin deficiency by racial or ethnic group are not delineated.**

**The prevalence of protein S deficiency in the general population remains unknown.**
Pt w/ ***[inherited thrombophilia] was counseled on her contraceptive options. The increased risk of VTE with estrogen-containing OCs was discussed and education on alternative options including IUD and progestin-only pills and implants was provided.
# CODING AND BILLING

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin gene mutation</td>
<td>D68.52</td>
</tr>
<tr>
<td>Primary thrombophilia</td>
<td>D68.5</td>
</tr>
<tr>
<td>Other primary thrombophilia</td>
<td>D68.59</td>
</tr>
<tr>
<td>Other thrombophilia</td>
<td>D68.6</td>
</tr>
</tbody>
</table>
EVIDENCE


