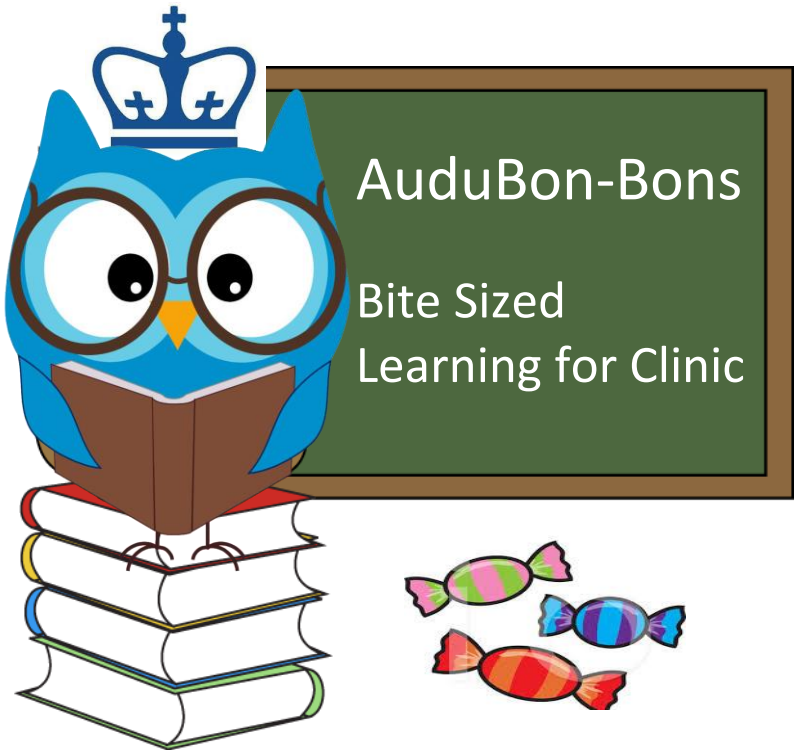
INHERITED THROMBOPHILIAS IN PREGNANCY



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**

PERTINENT PHYSICAL EXAM FINDINGS

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 ⬆
- Anticoagulant activity ⬇
- Fibrinolysis ⬇

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

- **Four**fold to **five**fold 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

EVALUATION – PATIENT SELECTION

Who should be screened for inherited thrombophilias?

GROUP 1

- **Personal history of VTE**

  AND

- No prior testing +/- recurrent risk factor

What are examples of recurrent risk factors?

Pregnancy
Estrogen-containing contraceptives

What are examples of non-recurrent risk factors?

Fractures
Surgery
Prolonged immobilization

GROUP 2

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

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

SCREENING – TARGETS

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

Second Trimester	Third Trimester
<30%	<24%

- Patients should ideally not be taking anticoagulation or hormonal therapy

SCREENING - TIMING

Table 2. How to Test for Inherited Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable With Anti-coagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin G20210A mutation	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<65%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No*	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

*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.

Inherited thrombophilias in pregnancy. ACOG Practice Bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e18—34

MANAGEMENT - STRATIFICATION

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

MANAGEMENT

How is the need for anticoagulation therapy determined?

Table 3. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophilia† with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Intermediate-dose or adjusted-dose LMWH/UFH	Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Adjusted-dose LMWH/UFH	Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.

Inherited thrombophilias in pregnancy. ACOG Practice Bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e18—34

MANAGEMENT - ANTICOAGULANTS

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

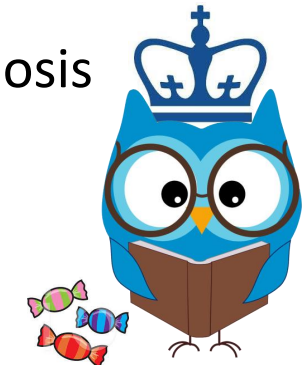
How would you counsel your patient to discontinue their anticoagulation in anticipation of a scheduled delivery?

- **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



CONTRACEPTION

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?

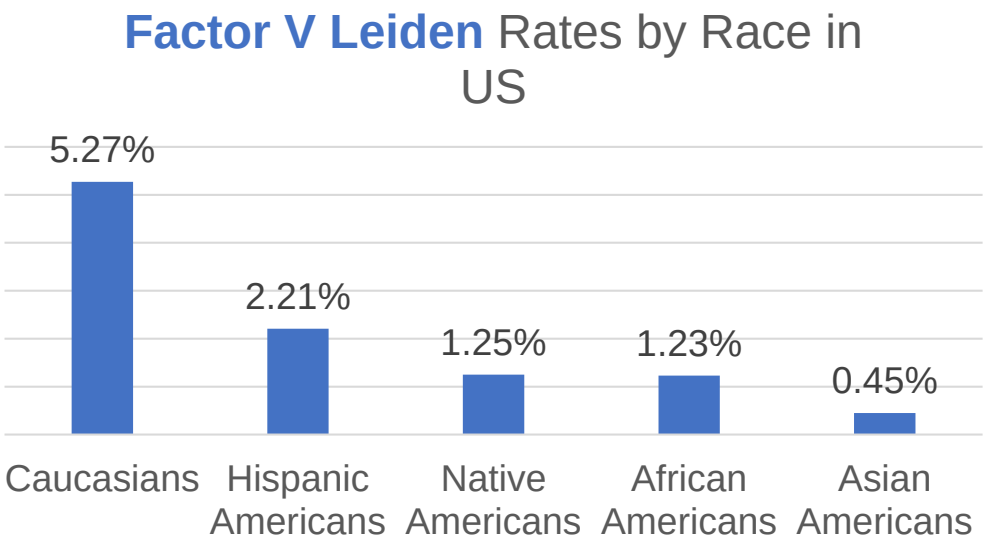
- No

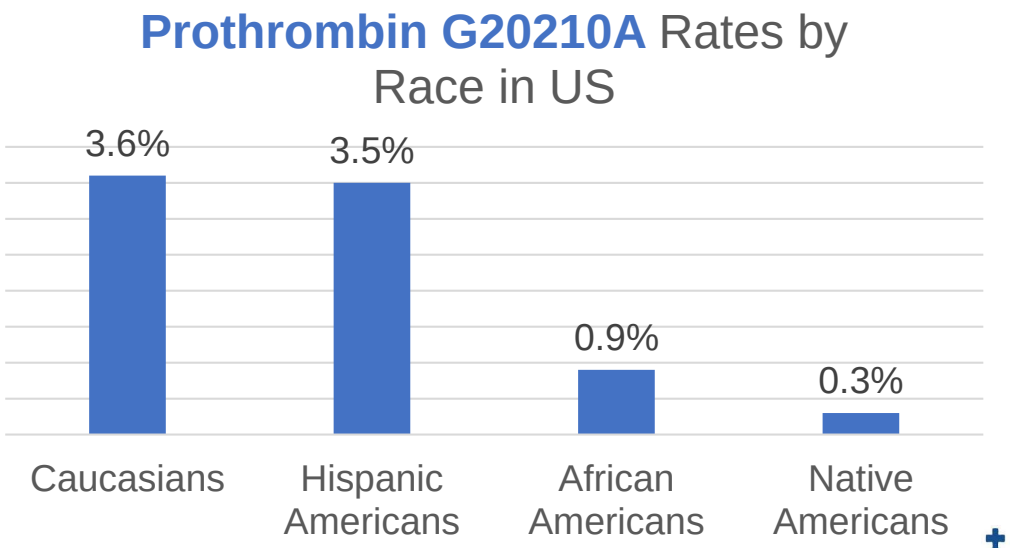
How many women would need to be screened to prevent one death from VTE?

- ~ ½ million

SOCIAL DETERMINANTS OF HEALTH

Prevalence of inherited thrombophilias varies by race





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.

Epic .phrase

BBonThrombophiliaContraception

Description: Contraceptive counseling for patient with inherited thrombophilia

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

Prothrombin gene mutation	D68.52
Primary thrombophilia	D68.5
Other primary thrombophilia	D68.59
Other thrombophilia	D68.6

EVIDENCE

- Inherited thrombophilias in pregnancy. ACOG Practice Bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e18—34
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