Thrombophilia in Pregnancy

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Presenter Disclosure

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Learning Objectives

• Review the more common types of thrombophilia in pregnancy

• Review the recommendations for management of thrombophilia in pregnancy

• Discuss clinical scenarios in which may commonly be seen in pregnancy with no clear recommendation for management
Thrombophilia

• Any inherited or acquired disorder associated with an increased risk for thrombosis

• Three types
  • Inherited
    • Antithrombin III, protein S, protein C, Factor V Leiden mutation, prothrombin gene (Factor II) mutation
  • Acquired
    • Antiphospholipid Syndrome (APS)
      • Lupus anticoagulant, anticardiolipin, Beta-2 glycoprotein-1
      • Antithrombin, protein S, and protein C deficiencies
  • Mixed type- combination of inherited and acquired
    • E.g.- Methylene tetrahydrofolate reductase (MTHFR)- genetic mutation + nutritional deficiency of folate and vitamin B12
Thrombophilia

- Inherited thrombophilia - 15% general pop.
  - Factor V Leiden (FVL) heterozygous most common
    - Odds ratio for VTE (no hx) - 1.3 – 4.5 (5-12/1000 del.)
  - Prothrombin gene heterozygous - 3.7 (CI 0.2-78.3)
  - Homozygous for either or family history
    - Approx. 4-fold increase in risk for VTE
  - Ziakas (2015) - May not be difference in VTE rates between hetero- and homozygous for FVL
- Acquired thrombophilia - Odds ratio 15.8 (CI 10.9-22.8)
- Data mainly family-based studies
Venous Thromboembolism

- 1 per 1000 deliveries (0.6 – 1.7 per 1000)
- Maternal mortality- 10-17% of deaths
- Risk is similar both antepartum and postpartum
  - Antepartum- DVT, postpartum- PE
- 50% VTE involves thrombophilia
  - Suggests some patients will not develop VTE in the presence of thrombophilia
  - Factors that increase risk
    - Family history- first degree or multiple members
    - Personal history estrogen related- prior pregnancy or contraception (containing estrogen)
Figure 34-1  Overview of hemostasis. Two pathways can be used to initiate coagulation: the primary extrinsic pathway (shown on the right) and the accessory pathway (historically called the contact or intrinsic pathway, shown on the left). AT, Antithrombin; HWM, high-molecular-weight; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor. (Modified from Brummel-Ziedins K, et al: Chapter 21 In Lee GR, et al, editors: Wintrobe’s clinical hematology, ed 11, Philadelphia, 2003, Lippincott Williams & Wilkins.)
Anticoagulant Systems

- Coagulation tightly regulated to avoid excessive thrombus formation
- Regulated by natural anticoagulants and fibrinolytic systems
- Natural anticoagulant systems
  - Protein C/protein S
  - Plasma serine protease inhibitors (e.g. antithrombin)
  - TFPI (Tissue Factor Pathway Inhibitor)
Anticoagulant Systems

Protein S/Protein C

- Protein C - Enzyme (when activated)
  - Activated by thrombin/thrombomodulin complex
  - Activated protein C (APC) acts as inhibitor to factor Va and VIIa after it binds protein S

- Protein S - Cofactor to protein C (free and bound forms)
  - Free form acts as cofactor to protein C
  - Allows protein C to bind cell surfaces so it is oriented to inactivate Va and VIIa
Anticoagulant Systems
Antithrombin

• Protein that inhibits Factors IIa and Xa
• Found in liver, endothelial cells
• Heparin-binding site to enhance coagulation inhibitor properties
  • Binds endogenous and exogenous heparins
  • Gives heparin its anticoagulant properties
  • Inhibitor effect of antithrombin increased 1000-fold on factor IIa by heparin
Inherited Thrombophilia

Factor V Leiden Mutation (FVL)

- Autosomal dominant, single base substitution
- Detected through genetic testing
- 10-fold longer half-life through resistance of APC
- 2-5% whites; rare in Asian/African populations
  - Homozygous mutation 1 in 2500
- Heterozygous form lower risk of VTE than antithrombin, prot. S or prot. C
  - 0.1 – 0.3% (nonpregnant) vs. 0.3 – 0.5%
Inherited Thrombophilia
Prothrombin gene mutation

• Genetic mutation at 20210 position in the prothrombin gene- elevated levels of prothrombin (Poort, 1996)
  – More common in Caucasian, less in Asian, Afr. Amer.
  – Homozygous rare

• Mechanism of increasing thrombosis unknown
  – Related to enhanced protein synthesis

• Overall 2.8 fold increased risk for thrombosis
• Increased risk with increased estrogen exposure
Inherited Thrombophilia

Antithrombin Deficiency

• Inherited or acquired
• Inherited- autosomal dominant
  • Type 1- decreased synthesis
    • Decreased protein and activity
  • Type 2- 2 subtypes
    • Normal protein level, decreased activity levels
• Best testing to determine heritable deficiency is functional assay
• VTE most often occurs with increased or synthetic estrogen exposure
Inherited Thrombophilia Antithrombin Deficiency

• Acquired- decreased synthesis, increased clearance or consumption
• Increased synthesis- cirrhosis
• Consumption due to increased thrombin
  • DIC, sepsis, trauma, malignancy
• Clearance- Nephrotic Syndrome
• Pregnancy does NOT decrease antithrombin
  • Pre-eclampsia can decrease levels
Inherited Thrombophilia
Protein S Deficiency

• Both inherited and acquired deficiency
• Inherited- 3 types
  • Decreased synthesis (types 1,3), decreased activity (types 2,3)
• Acquired- decreased synthesis or increased consumption/clearance
• Free protein S decreased in pregnancy
  • More protein bound
  • Decreased synthesis- liver disease, vit. K antagonists
  • Increased consumption/clearance- DIC, nephrotic syndrome
Inherited Thrombophilia
Protein C Deficiency

• Inherited or acquired- vit. K dependent
• Inherited- autosomal dominant, 1:200-1:500 adults
  • 2 types- decreased synthesis(type 1), activity (type 2)
• Acquired- liver disease, DIC, warfarin, sepsis
• Testing- functional assay most reliable
  • Antigen levels vary for normal range
  • Type 2 has normal level, decreased activity
Inherited Thrombophilia
Methylene Tetrahydrofolate Reductase (MTHFR) mutations

• Combined inherited and acquired hypercoagulable abnormality

• Relies on genetic mutation and nutritional deficiency
  • Can result in hyperhomocysteinemia
  • Folate, vitamin B12(cobalamin) and vitamin B6 can reduce homocysteine levels to normal
  • Risk for VTE or arterial thrombosis if homocysteine levels elevated
    • Actual clinical incidence of VTE from MTHFR has significantly reduced through appropriate dietary intake
Thrombophilia in Pregnancy

ACOG Recommendations

• Based on American College of Chest Physicians Evidence-based Practice Guidelines- 2012
• Based on low-to-moderate evidence
  • Few high quality studies to address outcomes or antithrombotic therapy during pregnancy
• Consider fetal/maternal outcomes, burden of treatment, harmful effects
  • How much will it affect patient desire for "normal pregnancy" was one of variables used in determining recommendations for prophylaxis
ACOG Recommendations

Types of Thrombophilia

• Low Risk
  • Factor V Leiden mutation-heterozygous, Prothrombin gene mutation- heterozygous, Protein S or C Deficiency

• High Risk
  • Antithrombin deficiency, homozygous Factor V Leiden mutation, homozygous Prothrombin gene mutation, compound heterozygous Factor V Leiden and prothrombin gene mutations
Anticoagulation Regimens

Antepartum

• Prophylactic LMWH\(^1\)  Enoxaparin, 40 mg SC once daily
• Therapeutic LMWH\(^2\)  Enoxaparin, 1 mg/kg every 12 hours
• Therapeutic UFH\(^3\)  10,000 units or more SC every 8 hours
• Prophylactic UFH
  • Option#1- 7,500 units SC every 12 hours
  • Option#2-
    • 1\(^{st}\) trim- 5,000 units SC every 12 hours
    • 2\(^{nd}\) trim- 7,500 units SC every 12 hours
    • 3\(^{rd}\) trim- 10,000 units SC every 12 hours (unless the aPTT is elevated)

Postpartum

• LMWH 40mg daily or UFH 5000 units q12 hours x 6 weeks or
• Coumadin for 4–6 weeks with a target INR of 2.0–3.0; initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days

Notes

1- LMWH: anti-Xa level in prophylactic range of 0.3 – 0.6 units/ml
2- LMWH: anti-Xa level in the therapeutic range of 0.6–1.0 units/mL
3- Adjust UFH to target aPTT in the therapeutic range (1.5–2.5x normal) 6 hours after injection; can also use anti-factor Xa level for management
ACOG Recommendations
Low-Risk Thrombophilias

- No previous VTE, no family/personal hx
  - No prophylaxis- antepartum or postpartum
- Family hx VTE (first degree relative)
  - Antepartum- observe, Postpartum- prophylaxis x 6 weeks
- Personal hx VTE- single episode
  - Antepartum- prophylaxis or surveillance
  - Postpartum- prophylaxis for 6 weeks
- Personal Hx of 2 or more VTE events
  - Antepartum- prophylaxis indicated
  - Postpartum- prophylaxis for 6 weeks
ACOG Recommendations
High-Risk Thrombophilias

• No previous VTE
  • Antepartum-no prophylaxis
  • Postpartum- prophylaxis for 6 weeks

• Previous VTE or family history (1st deg. rel.)
  • Prophylaxis antepartum and postpartum
ACOG Recommendations

No Thrombophilia, Prior VTE

- Prior VTE with transient risk (not estrogen related)
  - Antepartum- surveillance, postpartum- prophylaxis
- Prior VTE- risk associated with estrogen
  - Antepartum/postpartum- prophylaxis
- Prior VTE- no identifiable risk (idiopathic)
  - Antepartum/postpartum- prophylaxis
ACOG Recommendations

Controversial Issues

• Are we sure about low-risk vs. high risk thrombophilias?
  • Ziakas (2015) - meta-analysis utilizing odds ratio to assess VTE risk of inherited thrombo.
  • Published after ACCP guidelines (2012)
  • FVL heterozygous similar genetic risk of thrombosis as homozygous
    • Anticoagulation prophylaxis for both types??
  • Heterozygous prothrombin gene mutation shows similar effect to homozygous
ACOG Recommendations

Controversial Issues

• Studies used for guidelines may not reflect current practice management of anticoagulants in pregnancy
  • Monitoring of anti-factor Xa level with Lovenox dose adjustment
    • May explain the lack of difference in outcomes

• Should recommendations be based on maternal desire for “normalcy” with VTE responsible for significant maternal mortality?
  • 10-17% cases of maternal mortality
  • Should be informed discussion on weighing risks of maternal morbidity with risk of treatment
Acquired Thrombophilia

• Described in 1906 (Wasserman) in association with positive RPR test

• Antiphospholipid Syndrome
  • Autoimmune- either isolated or with other immune disorder (e.g. SLE)
  • Involves antibodies to proteins that bind phospholipids
    • Prolongs phospholipid-dependent assays (lupus anticoagulants)
    • Antibodies to cardiolipin and Beta-2 glycoprotein-1
Acquired Thrombophilia

Antiphospholipid Syndrome

• Based on clinical and laboratory criteria
  • Problems with each set of criteria
  • Based on analysis on weaker level studies
  • Clinical criteria also controversial
    • Multiple losses do not always account for other etiologies (i.e.- hormonal, uterine anomaly)

• Risk of VTE during pregnancy/postpartum is 5-12%
• Nonpregnant- VTE, arterial thrombosis (i.e. stroke), thrombocytopenia
• Pregnancy- pregnancy loss, pre-eclampsia, IUGR
Acquired Thrombophilia Antiphospholipid Syndrome

**Laboratory Criteria**

- Any of the labs must be verified with repeat testing 12 weeks apart
  - Lupus anticoagulant - positive
  - Anticardiolipin Ab - IgM and IgG medium/high positive
  - Beta-2 glycoprotein-1 Ab - IgM and IgG >99th percentile (usually medium/high positive)
Acquired Thrombophilia Antiphospholipid Syndrome

Clinical Criteria

• Vascular thrombosis- arterial or venous, any size vessel

• Pregnancy morbidity
  • Unexplained fetal death at or beyond 10 wks
  • Unexplained fetal losses x 3 < 10 wks with chromosomal abnormalities excluded
  • Preterm delivery < 34 wks due to pre-eclampsia or placental insufficiency (IUGR)
Antiphospholipid Antibodies
Non-APS Labs

• Antibodies to negatively charged phospholipids
  • Phosphatidic acid, phosphatidylserine (anti-PS), phosphatidylglycerol, phosphatidylinositol
  • Anti-PS most commonly studied
    • Inhibition of trophoblast development/invasion through binding of syncytiotrophoblast- decreased hCG levels
    • Heparin shown to decrease binding of anti-PS and ACL to syncytiotrophoblasts
    • Testing not standardized
    • Studies lacking to allow for inclusion in the APS lab criteria
**Antiphospholipid Antibodies**

### Non-APS Labs

- IgA- anticardiolipin and Beta-2 glycoprotein-1
  - May be useful with African Americans, obstetrical APS
  - Lee (2001) showed IgA-type ACL more common in pregnancy loss when typical APS labs normal
  - Can be considered in patients with negative APS-labs and poor pregnancy outcome (i.e. multiple pregnancy losses or late pregnancy complications)
Antiphospholipid Syndrome

Controversial Issues

• Using the stringent criteria in real world setting
  • Patient awareness of testing options available that include those lab studies outside of the APS criteria and strong desire to avoid “another miscarriage” or early delivery due to pre-eclampsia
    • Several 1\textsuperscript{st} trim. losses with no genetic testing on the products of conception in a 40 y/o patient with no children; “money is no object”…”wants all testing performed”
    • Do you test? All labs related to phospholipids or just ACOG criteria? What do you do with positive result?
    • If has positive lupus anticoagulant or medium/high ACA IgG, do you wait 12 more weeks before committing to diagnosis of APS? Would you withhold treatment if second test is negative? BE HONEST....
Antiphospholipid Syndrome
Controversial Issues

• What about low-positive antiphospholipid antibodies?

• Mekinian (2012) studied outcomes with patients with low level antibodies and no treatment
  • Similar poor outcomes as patients with untreated APS per criteria
  • Obstetrical APS may be related to 1 positive test versus 2 with APS-related thrombosis
Thrombophilia in Pregnancy Clinical dilemmas

• Most important- PLAN AHEAD!!!
  • Consider genetic studies for ANY loss when products of conception is available
  • Commercial testing available to minimize testing error

• Testing after 1 miscarriage <10wks with normal genetic testing? No

• Multiple losses, patient desires heparin therapy...What to do?
  • Consider other reasons- Uterine and hormonal evaluation
  • Standard recommendation- therapy not indicated
  • Some small studies show improvement in outcomes
  • Need to have strong informed discussion concerning risk of medication versus questionable benefit with negative APS workup
Thrombophilia in Pregnancy
Clinical dilemmas

• If low level APS-related antibodies then need to discuss with patient the lack of data to recommend heparin...however...
  • If OB clinical complications similar to APS criteria then reasonable to offer anticoagulation, especially if Beta-2 glycoprotein-1 antibodies

• Test non-APS lab studies? How will you treat?
  • Should develop standard panel of non-APS labs if this will be part of your practice
  • Need to have open dialogue with patient so it is understood that testing and possible tx outside of accepted practice of care for APS workup and management
Thrombophilia in Pregnancy Summary

• Thrombophilias can occur as inherited or acquired or in some cases as both types.
• Management during pregnancy and postpartum may depend on type of thrombophilia and history involved.
• Both types of thrombophilia should be part of the workup of VTE—inherited and acquired.
• It is important to know APS criteria but also to be aware of additional studies that patients may request so testing/treatment options may be discussed.