Maternal Thromboembolic Disease

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Learning Objectives

• Understand the pathophysiology behind pregnancy associated VTE
• Explain the impact of thromboembolism on maternal morbidity and mortality
• Identify risk factors for VTE
• Apply imaging modalities and anticoagulation medications in the setting of acute VTE
• Recognize appropriate candidates for venous thromboembolism prophylaxis and employ appropriate management
Thromboembolism Background

- Prevalence: 1-4/1000 pregnant women
- 80% of events are venous
- Deep Venous Thromboembolism (DVT)
  - 80% of VTE in pregnancy
  - Relatively equal frequency across trimesters
- Pulmonary Embolism (PE)
  - 20% of VTE in pregnancy
  - More commonly occur postpartum, 40-60% in 4-6 weeks (RR 15)
    - 64% of PP VTE occur after cesarean delivery

Pregnancy Physiology

Pathophysiology

- 4-5 times risk of VTE
- Physiologic changes
  - Coagulation
  - Anatomic
  - Hemodynamic
- Protective role against hemorrhage, tolerance to blood loss
  - Hemodilution, Increased RBC production
  - Increased estrogen
  - Vascular remodeling
Virchow’s Triad

- **Hypercoagulability**
- **Venous Stasis**
- **Endothelial Injury**

**Extrinsic Pathway**
- Tissue Factor
- Generates thrombin burst
- Thrombin-feedback activation role

**Intrinsic pathway**
- Contact activation, collagen
- Lesser role

**Common pathway**
- Thrombin driven
- prothrombotic state maintained by by activation of FVIII and FIX =>tenase complex
### Coagulation Factors

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increased</td>
</tr>
<tr>
<td>F VII</td>
<td>Increased</td>
</tr>
<tr>
<td>F VIII</td>
<td>Increased</td>
</tr>
<tr>
<td>F X</td>
<td>Increased</td>
</tr>
<tr>
<td>vWF</td>
<td>Increased</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Increased</td>
</tr>
<tr>
<td>PAI-2</td>
<td>Increased</td>
</tr>
<tr>
<td>F II</td>
<td>No Change</td>
</tr>
<tr>
<td>F V</td>
<td>No Change</td>
</tr>
<tr>
<td>F XI</td>
<td>No Change</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Protein S</td>
<td>Decreased</td>
</tr>
<tr>
<td>Protein C</td>
<td>No Change</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>No Change</td>
</tr>
</tbody>
</table>

### Anatomic

- Compression of inferior vena cava and pelvic veins by gravid uterus
- May-Thurner Syndrome/Anatomy: Left iliac vein compressed by right iliac artery
- LLE >> RLE
  - 78-90% DVT Left leg
- Proximal >> Distal
  - 72% iliofemoral vein
Maternal Morbidity & Mortality

- VTE 5th Leading cause of maternal death worldwide
  - Pregnancy related mortality risk of 0.9/100,000 live births
- VTE accounts for 9.3% of all maternal deaths in the US
  - Pulmonary embolus is leading cause of maternal mortality in the western world
- 20% experience post thrombotic syndrome
- Obstetric PE case mortality rate of 3%, with ~ 25% of all VTE events manifesting as PE, approximately 132 VTE events occur for every one maternal death resulting from PE
2002-2007 (29 maternal deaths)

- 64% obese
  - 25% BMI > 40
- 74% had cesarean section
- 97% of deaths had some chance of preventability
- 52% strong chance of preventability

VTE risk increases with higher BMI

VTE is the “single cause of death most amenable to reduction by systematic change in practice”

- Steven Clark, M.D.
Risk Factors

- **#1 individual risk factor: personal history of thrombosis**
  - 3-4x increased risk recurrent VTE during pregnancy
  - 15-25% VTE in pregnancy are recurrent events

- **#2 individual risk factor: thrombophilia**
  - Present in 20–50% of women with pregnancy associated VTE

- **Primary risk factors:** physiologic changes pregnancy

- **Other Individual risk factors:** Obesity, smoking, AMA, autoimmune disorders, HTN/preeclampsia, multiple gestation, sickle cell anemia

- **Delivery risk factors:** cesarean delivery, hemorrhage, infection

Thrombophilias
Thrombophilia

- 20-50% of women with pregnancy associated VTE
- Inherited vs. Acquired
  - Factor V Leiden
  - Prothrombin mutation
  - Antithrombin 3 deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Anti-phospholipid antibody syndrome (APAS)

Factor V Leiden

Heterozygote:
- prevalence 1-15%
- VTE risk per pregnancy 0.5-1.2%
- VTE risk with history VTE 10%
- 40% all VTE in pregnancy

Homozygote:
- prevalence <1%
- VTE risk per pregnancy 4%
- VTE risk with history VTE 17%
- 2% all VTE in pregnancy
Prothrombin gene mutation

- Heterozygote:
  - prevalence 2-5%
  - VTE risk per pregnancy <0.5%
  - VTE risk with history VTE >10%
  - 17% all VTE in pregnancy

- Homozygote:
  - prevalence <1%
  - VTE risk per pregnancy 2-4%
  - VTE risk with history VTE >17%
  - 0.5% all VTE in pregnancy

Anti-thrombin III Deficiency

- Antithrombin III (ATIII)-nonvitamin K-dependent protease that inhibits coagulation by neutralizing the enzymatic activity of thrombin (factors IIa, IXa, Xa)
  - prevalence 0.02%
  - VTE risk per pregnancy 3-7%
  - VTE risk with history VTE 40%
  - 1% all VTE in pregnancy
Protein C Deficiency

- Inhibitor of FV and FVIII
- Quantitative defect v. qualitative defect
- Most are heterozygotes
- Prevalence 0.2-0.4%
- VTE risk per pregnancy 0.1-0.8%
- VTE risk with history VTE 4-17%
- 14% all VTE in pregnancy

Protein S Deficiency

- Vitamin K dependent anticoagulant
- Cofactor to activate Protein C to degrade FV and FVIII
  - Decreased levels/function -> decreased degradation -> increased clots
- Prevalence 0.03-0.13%
- VTE risk per pregnancy 3-7%
- VTE risk with history VTE 40%
- 1% all VTE in pregnancy
**High Risk Thrombophilia**
- Homozygous FVL
- Homozygous PT gene mutation
- Antithrombin III Mutation
- Compound heterozygote (PT/FVL)

**Low Risk Thrombophilia**
- Heterozygous FVL
- Heterozygous PT gene mutation
- Protein C deficiency
- Protein S Deficiency

**Anticoagulant Medications**
Heparins

- **Unfractionated Heparin**
  - Inactivates thrombin and activated factor X through antithrombin dependent mechanism
  - Reversal with protamine sulfate
  - Renal clearance, dose related
  - Does not cross placenta
  - Safe in Lactation

- **Low Molecular Weight Heparin (LMWH)**
  - Inactivates activated factor X through antithrombin dependent mechanism
  - Not as readily reversible
  - Renal clearance, dose independent
  - Do not cross the placenta
  - Safe in Lactation

Warfarin

- Vitamin K antagonist
  - Inhibits vitamin K epoxy reductases
  - Wide dosing range, narrow therapeutic window
  - Highly influenced by environmental factors
  - Contraindicated in severe liver disease, anemia, vitamin K deficiency

- Crosses placenta
  - Warfarin embryopathy
    - Occurs in 5% exposed 6-12 weeks gestation
    - Dose dependent (>5mg/day)
    - Hypoplasia of nasal bridge, congenital heart defects, ventriculomegaly, agenesis of the corpus callosum, stippled epiphyses

- Safe in lactation
Factor Xa inhibitors

- Fondaparinux, Apixaban, Rivaroxaban
- Inhibit Factor Xa -> preventing thrombin generation
- Not recommended in pregnancy
- Not recommended in lactation

Direct Thrombin Inhibitors

- Desirudin, Bivalirudin, Argatroban
- Direct, selective, and reversible binding to the active site of thrombin
  - Inhibition of thrombin induced reactions
- Not recommended in pregnancy
- Not recommended in lactation
Pregnancy Specific Issues

- 40-50% increase in maternal blood volume = Increased volume of distribution
- Increased GFR => higher renal excretion of heparin and increase in protein binding
  - UFH and LMWH have shorter half lives and lower peak plasma concentrations
  - Higher dosing, more frequent administration

Heparin Dosing

- **Prophylactic Heparin**
  - LMWH 40mg daily
  - LMWH 40mg q 12 hr (intermediate dosing)
  - UFH trimester specific
    - 5000 U BID Frist
    - 7500 U BID Second
    - 10000 U BID Third
  - UFH low dose 5000 IU SQ BID

- **Therapeutic Heparin**
  - LMWH 1mg/kg BID
  - UFH 10,000 IU or more SQ q 12 hrs adjusted to target aPTT (1.5-2.5) 6 hrs after injection
Heparin Induced Thrombocytopenia

- Risk <0.1%
- 50% decrease in platelet count occurring 4–10 days after the initiation of UFH or LMWH
- Most obstetric patients will not require platelet monitoring
- If HIIT present consider fondaparinux

Acute VTE
DVT

- Sx: 80% with pain and extremity swelling
  - Left>>Right
  - Proximal>>Distal
- Testing: Compression ultrasonography of the proximal veins
  - If negative/equivocal -> Doppler US, venography, or MRI
  - Consider repeat imaging in 3-7 days
- May consider empiric anticoagulation
- D-Dimer:
  - Progressive increase in pregnancy
  - Not reliable predictor of VTE, false negative

Pulmonary Embolism

- Shortness of breath, chest pain, tachycardia, swollen leg
- Testing:
  - Ventilation-perfusion scanning (VQ scan):
    - Fetal radiation 0.32-0.64 mGy
    - Lower Breast Radiation dose
  - CT angiography
    - 0.0033-0.13 mGy dependent on trimester
Acute treatment

Low Molecular Weight Heparin
• First line therapy
  • better bioavailability, longer plasma half life
  • more predictable dose response
    • improved maternal safety
    • More convenient
• Weight adjusted dosing

Unfractionated Heparin
Use with renal dysfunction
(1) initial IV therapy followed by adjusted-dose subcutaneous UFH given every 12 h
(2) BID adjusted-dose subcutaneous UFH
• Less reliable in pregnancy

Treatment Duration

• Treatment throughout pregnancy and postpartum period for a minimum total of 3 months
• No studies on optimal duration of anticoagulant therapy for pregnancy-related VTE
Delivery and Anesthesia Considerations

- If planned delivery
  - Hold adjusted dose UFH or BID LMWH 24 h before Induction or Cesarean
  - If daily dose LMWH take 50% of dose on the morning of the day prior to delivery

Peripartum Anticoagulation and Neuraxial Blockade

<table>
<thead>
<tr>
<th>UFH dose ≤ 10,000 IU/day</th>
<th>No contraindications if &gt;4-6hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH daily dose &lt;20,000 IU/day</td>
<td>&gt;12 hrs after last dose, check aPTT, risk benefit discussion</td>
</tr>
<tr>
<td>LMWH prophylaxis</td>
<td>≥ 12 hrs after last dose</td>
</tr>
<tr>
<td>LMWH therapeutic dose</td>
<td>≥ 24 hrs after last dose</td>
</tr>
</tbody>
</table>
### Postpartum Dosing

<table>
<thead>
<tr>
<th>Type</th>
<th>Time After Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH prophylaxis</td>
<td>≥ 1 hr</td>
</tr>
<tr>
<td>UFH therapeutic</td>
<td>≥ 1 hr</td>
</tr>
<tr>
<td>LMWH prophylaxis</td>
<td>≥ 12 hrs</td>
</tr>
<tr>
<td>LMWH therapeutic</td>
<td>≥ 24 hrs</td>
</tr>
</tbody>
</table>

**Guidelines**
VTE prophylaxis is Joint Commission Quality Measure
Minimal resources, easily implementable
Success in the UK
2003-2005: 1.94 deaths per 100,000 births
2006-2008: 0.79 deaths per 100,000 births
2011-2013: 1.01 deaths per 100,000 births
• Lower than any of the seven periods from 1985 to 2005

Antepartum Anticoagulation

ACCP/ASH
• Hx VTE (not provoked)
• High risk thrombophilia +/- hx clot
• No specific recs for Antepartum admission

ACOG
• Hx VTE (not provoked)
• High risk thrombophilia +/- hx clot
• No specific recs for Antepartum admission

RCOG
• Hx VTE (not provoked)
• High risk thrombophilia +/- hx clot
• Medical co-morbidities, surgery
• ≥4 RF (obese, AMA, >P3, smoker, varicose veins, PrE, immobility, FHx VTE, thrombophilia, IVF, multiples
• Antepartum admission

CMQCC
• Hx VTE (not provoked)
• High risk thrombophilia +/- clot
• Antepartum admission

NPMS
• Hx VTE (not provoked)
• High risk thrombophilia +/- clot
• Antepartum admission
Postpartum Anticoagulation

Vaginal Delivery

- Postpartum pharmacologic prophylaxis based on risk factors
  - History of VTE or high risk thrombophilia (All support)
  - Already receiving outpatient anticoagulation (All support)
- Consider pharmacologic prophylaxis based on multiple risk factors, Caprini/Padua Score (RCOG, NPMS)
- CMQCC considers BMI >40 and either low risk thrombophilia and/or antepartum admission, Low risk thrombophilia and Fam Hx VTE
- ACCP-no specific recommendations
Cesarean Section

- Independent risk factor
- Elective cesarean ~2x risk compared to vaginal delivery
- Emergency cesarean ~2x that of elective cesarean (4x vaginal delivery)
- RR 2-6.7

Obesity and Cesarean

- Risk Factor for VTE in nonpregnant population
- UK Triennial report 9/16 deaths in obese women
  - OR 1.7-5.3
- CMQCC: 61% had BMI ≥ 35 (all deliveries)
  - In those obese women who died of VTE 75% had undergone cesarean section
- Pharmacologic PPx supported by RCOG, NPMS
  - ACCP, ACOG for “high risk”
ACOG

- High risk thrombophilia
- Prior VTE
- Low risk thrombophilia and Fam Hx VTE

ACCP

### Major Risk Factors (Risk 0.3%)
- Immobility
- PPH with surgery
- Previous VTE
- Preeclampsia with IUGR
- Antithrombin deficiency
- Factor V Leiden
- Prothrombin G20210A
- Systemic lupus erythematosus
- Heart disease
- Sickle cell disease
- Blood transfusion
- Postpartum infection

### Minor Risk Factors (≥ 2 or one in the setting of emergent CS) Risk 0.3%
- BMI 30
- Multiple gestation
- PPH 1000mL
- Smoking
- Fetal growth restriction
- Protein C deficiency
- Protein S deficiency
- Preeclampsia

≥ 1 Major or ≥ 2 minor Risk Factors
• Broad, risk-factor based assessments for both antepartum and postpartum patients
NPMS

- Modified Caprini
- Modified Padua
  - High Risk Thrombophilia
  - Hx VTE
  - Low risk thrombophilia with Fam Hx VTE
- Not for low risk thrombophilia w/o additional RF

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Appendix 1. Modified Caprini Risk Assessment Model for Pregnancy*

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60</td>
<td>1</td>
</tr>
<tr>
<td>Minor surgery (less than 45 minutes)</td>
<td>1</td>
</tr>
<tr>
<td>Visible varicose veins</td>
<td>1</td>
</tr>
<tr>
<td>Swollen legs (current)</td>
<td>1</td>
</tr>
<tr>
<td>Overweight or obese (body mass index above 23 kg/m²)</td>
<td>1</td>
</tr>
<tr>
<td>Currently on bed rest</td>
<td>1</td>
</tr>
<tr>
<td>Serious lung disease including pneumonia (&lt;1 month)</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy or postpartum (&lt;1 month)</td>
<td>1</td>
</tr>
<tr>
<td>History of unexplained stillbirth infant, recent spontaneous abortion</td>
<td>1</td>
</tr>
<tr>
<td>Eq. N: premature birth with low birth weight or growth restricted infant</td>
<td>1</td>
</tr>
<tr>
<td>Other risk factors (smoking, diabetes, BMI=40kg/m², blood transfusions)</td>
<td>1</td>
</tr>
<tr>
<td>Central venous access</td>
<td>2</td>
</tr>
<tr>
<td>Major surgery (&gt;45 minutes)</td>
<td>2</td>
</tr>
<tr>
<td>Patient confined to bed (&gt;72 hours)</td>
<td>2</td>
</tr>
<tr>
<td>Family history of thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>History of DVT/PE</td>
<td>3</td>
</tr>
<tr>
<td>Factor V Leiden or Factor V Proaccelerator (20%)</td>
<td>3</td>
</tr>
<tr>
<td>Lupus anticoagulant or elevated antiphospholipid antibodies</td>
<td>3</td>
</tr>
<tr>
<td>Elevated serum homocysteine</td>
<td>3</td>
</tr>
<tr>
<td>Other congenital or acquired thrombophilia</td>
<td>3</td>
</tr>
</tbody>
</table>

* Original Caprini scoring system condensed to include conditions commonly encountered in obstetric patients. Source: Steven L. Clark

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Percentage of Women Receiving Pharmacologic Anticoagulation Post Cesarean

- ACOG 1% HxVTE Thrombophilia
- CMQCC 25% Simplified Qualitative Major/minor Risk Factors
- ACCP 35% Emergency CS, PreE, Obesity, multiples, PPH
- RCOG 85% Complex Scoring system Extensive List

CMQCC, Palmerola et al
Duration Postpartum Anticoagulation

- Continued for 6 weeks in high-risk women
- 10 days in intermediate-risk women (RCOG) v. only during hospitalization (ACOG)

Safety bundles

- Readiness
  - Standardized risk assessment
- Recognition and Prevention
  - Education, Standardized tools
- Response
  - Mechanical /pharmacologic prophylaxis
- Reporting and Systems Learning
  - Review events, metrics and complications

NPMS 2016
References

- ACOG. Thromboembolism in Pregnancy. VOL. 132, NO. 1, JULY 2018
- Hameed AB, Montgomery D, Peterson N, Morton CH, and A Friedman. Improving Health Care Response to Maternal Venous Thromboembolism. Developed under contract #11-1006 with the California Department of Public Health, Maternal, Child and Adolescent Health Division. Published by the California Department of Public Health, 2017.
- Steven Clark, M.D., Semin Perinatol 2012;36(1):42
- Sultan, et al. The association between admission and venous thromboembolism remained when we restricted our analysis to women without medical comorbidities including obesity, cardiac disease, and varicose veins. BMJ. (2013 Nov); 7: 347
Questions?