Venous Thromboembolism & Thrombophilias in Pregnancy

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Learning Objectives

• Discuss VTE in pregnancy
• Risk factors for VTE in pregnancy
• Diagnosis for DVT/PE
• VTE treatment and prophylaxis guidelines
  • Antepartum
  • Postpartum
• Various medication options
• Thrombophilia and APS work-up

Background

• Coagulation is tightly regulated to avoid excessive thrombus formation
• Regulated by natural anticoagulants and fibrinolytic systems
  • Natural anticoagulants
    • Protein C/protein S
    • Plasma serine proteinase inhibitors [e.g. antithrombin]
    • TFPI (Tissue Factor Pathway Inhibitor)
Pregnancy & venous thromboembolism (VTE)

• Deep vein thrombosis (DVT) and pulmonary embolism (PE)
  • Collectively referred to as VTE

• VTE complicates approximately 1 in 1600 births
  • VTE is one of the leading causes of maternal mortality in the United States
    • Accounts for 9.3% of all maternal deaths
    • Death from PE occurs about every 1.1 to 1.5 per 100,000 pregnancies

Pregnancy and VTE

• Pregnant women have a 4-fold increased risk of VTE over non-pregnant women

  • ~ 75–80% of cases of pregnancy-associated VTE are caused by DVT
  • ~ 20–25% of cases are caused by PE
  • ~ ½ of these events occur during pregnancy and ½ occur during the postpartum period

Pregnancy-Associated Changes

• Pregnancy is associated with physiologic and anatomic changes that increase the risk of thromboembolism, including
  • Hypercoagulability
  • Increased venous stasis
  • Decreased venous outflow
  • Compression of the inferior vena cava and pelvic veins by the enlarging uterus
  • Decreased mobility

• Thrombotic potential further exacerbated by
  • Hormone-mediated increase in venous capacitance (decreased venous tone)
Hematologic physiology in pregnancy

- Pregnancy is marked by increased clotting potential, decreased anticoagulant activity, and decreased fibrinolysis
- Adaptive mechanism to prevent excessive bleeding at delivery

- Increased fibrinogen
- Increase in procoagulants (Factors VII, VIII, X, and von Willebrand factor)
- Increase in fibrinolytic inhibitors
  - Decreased fibrinolysis
  - Increased plasminogen activator inhibitor (PAI-1 and PAI-2)
- Decrease in Protein S activity
- Increase in resistance to activated Protein C
VTE & Pregnancy

- When DVT occurs during pregnancy, it is more likely to involve the **left lower extremity** and to be more **proximal**, involving the iliac and iliofemoral veins
  - 85% on left side
  - More tortuous course of venous drainage
  - Pelvic compression of left common iliac vein by the overlying right iliac artery

Deep venous thrombosis (DVT)

- Accounts for most cases of pregnancy-associated VTE
- The two most common initial symptoms of DVT
  - Pain and swelling
    - Present in more than 80% of women with pregnancy-associated DVT
  - A difference in calf circumference of 2 cm or more is particularly suggestive of DVT in a lower extremity
- When signs or symptoms suggest new onset DVT, the recommended initial diagnostic test is **compression ultrasonography** of the proximal veins

DVT

- When results are negative or equivocal and iliac vein thrombosis is suspected (swelling of the entire leg, with or without flank, buttock, or back pain), additional imaging with Doppler ultrasonography of the iliac vein, venography, or magnetic resonance imaging is recommended
  - When results are negative and iliac vein thrombosis is not suspected, repeat imaging in 3 days and 7 days should be considered
- Alternatively, depending on the clinical circumstances, empiric anticoagulation may be a reasonable option
Pulmonary Embolism (PE)

- PE
  - Chest pain
  - Shortness of breath
  - Tachycardia
  - Not detected clinically in 70-80% of cases

PE

- The diagnosis of new-onset PE is similar to that in the nonpregnant individual
  - Ventilation-perfusion scanning and computed tomographic (CT) angiography are associated with relatively low radiation exposure for the fetus

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Table 8. Fetal Radiation Dose Associated With Selected Radiologic Examinations:

<table>
<thead>
<tr>
<th>Type of Examination</th>
<th>Fetal Dose (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium enema (cystoscopy) (4.0 Gy)</td>
<td>0.05</td>
</tr>
<tr>
<td>Renal ultrasonography (6.0 Gy)</td>
<td>0.05</td>
</tr>
<tr>
<td>Sonogram (7.0 Gy)</td>
<td>0.10</td>
</tr>
<tr>
<td>MRI (for imaging)</td>
<td>0.05</td>
</tr>
<tr>
<td>CT (including chest CT)</td>
<td>0.05</td>
</tr>
<tr>
<td>Radionuclide scans (bone scans, 1.0 Gy)</td>
<td>0.10</td>
</tr>
<tr>
<td>Angiography (4.0 Gy)</td>
<td>0.50</td>
</tr>
<tr>
<td>Interventional procedures (angiography)</td>
<td>0.50</td>
</tr>
<tr>
<td>Ultrasound (transabdominal) (1.0 Gy)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ultrasound (transvaginal) (1.0 Gy)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ultrasound (transrectal) (1.0 Gy)</td>
<td>0.10</td>
</tr>
<tr>
<td>Fluoroscopy (1.0 Gy)</td>
<td>0.05</td>
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</tbody>
</table>
Although D-dimer levels is a useful screening tool to exclude VTE in the nonpregnant population, pregnancy is accompanied by a progressive increase in D-dimer levels, such that a high D-dimer level does not reliably predict VTE. False negative D-dimers also have been reported in pregnant women with DVT or PE. D-dimer is not recommended as part of the evaluation of VTE in pregnancy or the postpartum period.

### Risk Factors
- Personal History of VTE (most important risk factor)
- Inherited or Acquired Thrombophilia (2nd most important)
- Family History of VTE
- Medical factors or pregnancy complications
  - Obesity
  - Hypertension
  - Autoimmune disease
  - Heart disease
  - Nephrotic syndrome
  - Stable vascular disease
  - Preeclampsia
- Advanced Maternal Age
- Multiple Gestation
- Increased Parity
- Smoking
- Immobility – travel, bedrest
- Surgery (C/S) or Trauma

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**Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis**

<table>
<thead>
<tr>
<th>Gestational Period</th>
<th>Effects</th>
<th>Estimated Threshold Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before implantation</td>
<td>Death of embryo or no consequence (all or none)</td>
<td>50-100 mGy</td>
</tr>
<tr>
<td>Organogenesis (D–8 weeks after fertilization)</td>
<td>Congenital anomalies (skeletal, eyes, genitalia) Growth restriction</td>
<td>200 mGy 200–250 mGy</td>
</tr>
<tr>
<td>Fetal period</td>
<td>Effects</td>
<td>Estimated Threshold Dose*</td>
</tr>
<tr>
<td>8–15 weeks</td>
<td>Severe intellectual disability (high risk) Intellectual deficit Microcephaly</td>
<td>60–310 mGy 25-10-point loss per 1,000 mGy 200 mGy</td>
</tr>
<tr>
<td>10–25 weeks</td>
<td>Severe intellectual disability (low risk)</td>
<td>250–280 mGy*</td>
</tr>
</tbody>
</table>
**Treatment**

- Unfractionated Heparin
- Low Molecular Weight Heparin
  - *Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta and both are considered safe in pregnancy*
- Warfarin (Coumadin)
- Inferior Vena Cava Filters
- Thrombolytic Agents
- Embolectomy

**Unfractionated Heparin (UFH)**

- Mechanism of Action
  - Stimulation of Antithrombin III activity
  - Direct Factor X inhibition
- Half Life of 1.5 hours
- Approximately 3% of pregnant women develop HIT
- Risk of osteopenia and vertebral fractures with long term use
- No risk of teratogenicity
- Protamine Sulfate – can reverse the effects of UFH

**Low Molecular Weight Heparin (LMWH)**

- Mechanism of Action
  - Stimulation of Antithrombin III activity
  - Inhibition of Factor X
- Half Life is 4-7 hours
- Lower risk of HIT and osteopenia
- May consider monitoring with anti-factor Xa levels
  - Therapeutic 0.6 to 1.0 U/mL, 4-6 hours after injection
Coagulation cascade

Warfarin

- Vitamin K antagonist – inhibits factors II, VII, IX, and X and decreases levels of protein C and S
- Crosses the placenta – can cause bleeding and teratogenicity
- May be recommended in patients with mechanical heart valves
  - Warfarin Embryopathy
    - 4-5% of fetuses if exposure between 6 and 9 weeks gestation
    - Stippled epiphyses, nasal, and limb hypoplasia

Inferior Vena Cava Filter

- Have been used safely and effectively in pregnancy
- Placement typically suprarenal
- Indications for use are same as in nonpregnant:
  - Any contraindication to anticoagulant therapy
  - Serious complication of anticoagulation
  - Recurrence of PE in patients with adequate anticoagulation therapy
Thrombolytic Agents

- Limited to life-threatening situations due to risk of substantial maternal bleeding
- Risk of placental abruption and fetal death is currently unknown

Embolectomy

- Treatment option when conservative measures fail
- Indicated to prevent death in patients who are hemodynamically unstable despite anticoagulation and treatment with vasopressors
- Associated with 20 to 40% incidence of fetal loss

VTE during pregnancy

- Adjusted-dose anticoagulation is recommended for all women with acute VTE during pregnancy
- After initial treatment (3–6 months dependent upon the type of VTE event), anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum for a minimum total duration of therapy of 3–6 months depending on the clinical scenario
VTE during pregnancy

• Management of newly diagnosed VTE consists of initiation of adjusted-dose (therapeutic) subcutaneous low-molecular-weight heparin
• Hospitalization for the initiation of anticoagulation therapy may be indicated in cases of hemodynamic instability, large clots, or maternal comorbidities

VTE during pregnancy

• Intravenous unfractionated heparin can be considered in the initial treatment of PE and in situations in which delivery, surgery, or thrombolysis (indicated for life-threatening or limb-threatening thromboembolism) may be necessary
• When patients appear to be hemodynamically stable, low-molecular-weight heparin can be substituted in anticipation of discharge from the hospital

VTE during pregnancy

• No need for antenatal testing
Anticoagulation at time of delivery

- For women who are receiving prophylactic low-molecular-weight heparin, discontinuation is recommended at least 12 hours before scheduled induction of labor or cesarean delivery
- A 24-hour interval is recommended for patients on an adjusted-dose regimen
- For unfractionated heparin doses of 7,500 units subcutaneously twice a day or more, a 12-hour interval as well as evaluation of coagulation status with laboratory testing are recommended

Anticoagulation at time of delivery

- Women receiving anticoagulation therapy may be converted from low-molecular-weight heparin to the shorter half-life unfractionated heparin in anticipation of delivery
  - Depends on the institution's protocol
- An alternative option may be to stop anticoagulation and induce labor within 24 hours

Anticoagulation at time of delivery

- The purpose of conversion to unfractionated heparin has less to do with any risk of maternal bleeding at the time of delivery, but rather the risk of an epidural or spinal hematoma with regional anesthesia
Postpartum

• Resume anticoagulation therapy no sooner than 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery

• Consider delaying initiation of therapeutic anticoagulation with low-molecular-weight heparin for at least 24 hours after neuraxial blockade and 4 hours after catheter removal
  - Recommended in the Society for Obstetric Anesthesia and Perinatology
  - If therapeutic anticoagulation is desired more rapidly after delivery, intravenous heparin may be an alternative

• When reinstitution of anticoagulation therapy is planned postpartum, pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation therapy is restarted

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Table 1: Anticoagulation Regimen Definitions

<table>
<thead>
<tr>
<th>Anticoagulation Regimen</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic (LP)</td>
<td></td>
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</tbody>
</table>
- Norepinephrine 0.01–0.05 μg/kg/min
- Precordial thump
- Thrombin
- Heparin
- Prothrombin time (PT) above normal range |
| Therapeutic (LMWH) | 
- LMWH 0.01–0.05 mg/kg/min
- Precordial thump
- Thrombin
- Heparin
- PT above normal range |
| Therapeutic (LMWHR) | 
- LMWH 0.01–0.05 mg/kg/min
- Precordial thump
- Thrombin
- Heparin
- PT above normal range |
| Therapeutic (LMWHX) | 
- LMWH 0.01–0.05 mg/kg/min
- Precordial thump
- Thrombin
- Heparin
- PT above normal range |
| Therapeutic (LMWHD) | 
- LMWH 0.01–0.05 mg/kg/min
- Precordial thump
- Thrombin
- Heparin
- PT above normal range |
| Therapeutic (LMWHF) | 
- LMWH 0.01–0.05 mg/kg/min
- Precordial thump
- Thrombin
- Heparin
- PT above normal range |

Prior VTE

- Women with a history of thrombosis who have not had a complete evaluation of possible underlying etiologies should be tested for antiphospholipid antibodies and for inherited thrombophilias.

Thrombophilia

- Inherited
- Acquired

- Both associated with increased risk of VTE
- Up to 50% of women who have thrombotic events during pregnancy possess an underlying congenital or acquired thrombophilia.

Inherited thrombophilia

- Genetic conditions that increase the risk of VTE and possibly some pregnancy complications
- 15% general population
  - Most common: Factor V Leiden (FVL) heterozygous
Inherited thrombophilia

- Factor V Leiden mutation
- Prothrombin G2021A mutation
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Factor V Leiden mutation

- Mutation arises from a G to A mutation in nucleotide 1691 of the factor V gene's 10th exon
  - Substitution of a glutamine for an arginine at position 506
- Autosomal Dominant
- Prevalence
  - 5-10% in Europeans
  - 3% in African Americans
  - Rare in Asian and African populations

- The mutation renders factor V Leiden refractory to proteolysis by activated protein C

Coagulation cascade
Factor V Leiden mutation

- Women heterozygous for factor V Leiden account for ~40% of cases of VTE during pregnancy
  - Risk of VTE among pregnant women heterozygous for factor V Leiden without history of VTE or a first-degree relative with a thrombotic episode is increased above the baseline pregnancy risk
  - This risk increases to up to 10% in women heterozygous for the factor V Leiden mutation with a personal history of VTE
  - A woman heterozygous for factor V Leiden with affected first-degree relative, but with no personal history of VTE, has a slightly higher risk of VTE during pregnancy (15/1,000 deliveries) than that conferred by her thrombophilia alone

Factor V Leiden mutation

- Pregnant women who are homozygous for factor V Leiden without a personal history of VTE or an affected first-degree relative have a 1–2% risk for VTE, whereas those with such a history have a 17% risk

Prothrombin G2021A mutation

- Mutation in the promoter of the prothrombin gene leads to increased (1.5-2x) circulating levels of prothrombin and increased risk of VTE
- Autosomal Dominant
- The combination of factor V Leiden and prothrombin G2021A mutations has synergistic hypercoagulable effects
Coagulation cascade

Antithrombin III

• Protein that inhibits Factors Ila and Xa
  • Found in liver, endothelial cells
  • Binds endogenous and exogenous heparins
    • Gives heparin its anticoagulant properties

Antithrombin III deficiency

• The most thrombogenic of the inherited thrombophilias with a 70-80% lifetime risk of VTE
• Can result from numerous point mutations, deletions, and insertions
• Autosomal Dominant
• Cutoff for activity level is <60%
Protein C

- Natural anticoagulant
- Vitamin K dependent polypeptide synthesized primarily in the liver
- Activated by thrombin/thrombomodulin complex
- Activated Protein C combines with free Protein S to inhibit Factors V and VIII

Protein C deficiency

- Deficiency can result from numerous mutations
- Autosomal Dominant
- Functional Assay cutoff of <65%

Protein S

- Natural anticoagulant
- Vitamin K Dependent polypeptide synthesized primarily in the liver
- Cofactor to protein C (free and bound forms)
  - Allows protein C to bind cell surfaces so it is oriented to inactivate Va and Vila
Protein S deficiency

- Autosomal Dominant
- Free PS Antigen <55% in non-pregnant should be detected at least twice
- Decrease in pregnancy due to estrogen
  - 2nd Trimester: <30%
  - 3rd Trimester: <24%

Methylenetetrahydrofolate Reductase Mutations

- There is insufficient evidence to support assessment of methylenetetrahydrofolate reductase (MTHFR) polymorphisms or measurement of fasting homocysteine levels in the evaluation of a thrombophilic etiology for VTE

* Whenever possible, laboratory testing should be performed remote (after 6 weeks) from the thrombotic event and while the patient is not pregnant and not taking anticoagulation or hormonal therapy
Who are candidates for thrombophilia evaluation?

• Screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors

• Assessment for inherited thrombophilia may be considered in the following scenarios:
  • A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing
  • A first-degree relative (e.g., parent or sibling) with a history of high-risk inherited thrombophilia

Who are candidates for thrombophilia evaluation?

• In other situations, thrombophilia testing is not routinely recommended
  • Screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-weight heparin prevents recurrence in these patients, and a causal association has not been established
  • Keep in mind, testing for the acquired antibodies present in antiphospholipid syndrome should be considered in the setting of recurrent pregnancy loss or stillbirth
Antepartum surveillance

- No or little association between thrombophilias and adverse pregnancy outcomes
  - Importantly, the vast majority of women with thrombophilias and no prior adverse pregnancy outcomes have uncomplicated normal pregnancies
  - Accordingly, such women should be reassured regarding pregnancy
- No antenatal testing
- Induction at 39 weeks – to coordinate medications

Acquired thrombophilias

- Antiphospholipid syndrome (APS)
  - An autoimmune disorder defined by the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies
  - Diagnosis requires that at least one clinical and one laboratory criterion are met
  - Because transient positive test results may occur, the diagnosis of APS requires two positive antiphospholipid antibody test results at least 12 weeks apart
The goals of treatment for APS during pregnancy are to improve maternal and fetal–neonatal outcomes.

Treatment broken into 2 categories:
1) Those with a history of thrombotic events
2) Those without a history of thrombotic events

For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum.

Patients can also receive low-dose aspirin, but the benefit of adding aspirin for this indication is unknown.

Anticoagulation should be continued for a minimum of 6 weeks postpartum to minimize the risk of maternal thromboembolism.
Treatment - patients with no hx of thrombotic event

- The optimal treatment of women with APS without a preceding thrombotic event has not been well studied
- Expert consensus suggests that clinical surveillance or prophylactic heparin may be used antepartum and 6 weeks postpartum
- For women with recurrent pregnancy loss and antiphospholipid antibodies, prophylactic use of heparin and low-dose aspirin may reduce pregnancy loss by 50%
  - For women with a history of sporadic fetal loss or any type of recurrent pregnancy loss, but no prior thrombotic history, consider prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks postpartum

Antepartum surveillance

- Antepartum testing has been suggested because of the potential risk of fetal growth restriction and stillbirth in pregnancies of women with APS
  - The data are insufficient to support or refute a specific practice, but many experts recommend serial ultrasonographic assessment and antepartum testing in the third trimester
- Induction at 39 weeks

Long term risks of APS

- Long-term risks for women with APS include thrombosis and stroke
  - In studies of women with APS, including women without prior thrombosis, ½ developed thromboses during 3–10 years of follow-up, and 10% developed lupus
The END

Questions?

References