Diagnosis and Management of Venous Thromboembolic Disorders in Pregnancy

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Conflict of Interest Disclosure Agreement

I have no financial interest or other relationships with industry relevant to the topics being discussed.
Learning Objectives

1) Understand the factors that render pregnancy a pro-thrombotic state.
2) Understand the work up of patients at risk for acute pulmonary embolism.
3) Know the evidence base for prevention and treatment of VTE.
VTE in Pregnancy

• Overall incidence is 1/1600
  – **DVT 0.71/1000** (70% antepartum; 30% postpartum), 7-10 X rate over age-matched controls.
  – **PE 0.15/1000** (47% antepartum; 53% postpartum), 15-35 X rate of age-matched controls.

• Risk highest first 6 wks postpartum (OR 11; 95%CI: 8-15), declines but still elevated at 7 to 12 wks (OR 2; 95% CI 1.5-3.1). Prevalence dropping in postpartum but increasing in antepartum period x 30 yrs.

Unique features of VTE in Pregnancy

• Isolated pelvic vein thrombosis account for 11% of DVT in pregnancy vs. 1% in non-pregnant women.
• 90% of DVTs in pregnancy are left-sided.
• PE accounts for 9.2% of maternal mortality; AA women have 4X mortality vs. whites.
• 75% of fatal PE’s occur after C-sections.

VTE: How to DX and TX

• Physiologic Regulation of Hemostasis
• Risk factors for VTE
• Diagnosis of VTE
• Treatment of VTE
• Prevention of VTE
Pregnancy-Associated Changes in Hemostatic and Fibrinolytic Proteins

• Increase in Clotting Factors: 20 to 200% increase in levels of fibrinogen and factors II, VII, VIII, IX, and X.

• Decrease in Anticoagulant Activity: Protein S levels decrease by 40%.

• Increase in Anti-fibrinolytic activity: PAI-1 levels increase two to three-fold in pregnancy; placental derived PAI-2 appears.

Pregnancy-Associated Factors Predisposing to VTE

• **Venous Stasis:** Compression of iliac veins by uterus, of left iliac vein by right iliac artery, general venous dilation due to P4, NO, and Pgl₂, **50% decrease** in lower extremity venous flow by **25 weeks**.

• **Vascular damage:** Placentation, delivery

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Risk Factors for VTE during Pregnancy

• Multiple births
• Varicose veins/STP
• Medical Complications (DM, IBD, UTIs, CRD)
• Increased parity
• Age ≥35 years
• BMI ≥ 30 kg/m²
• Antenatal hospitalization > 3 days

Risk Factors for Puerperal VTE

- Cesarean delivery (emergency)
- Postpartum endomyometritis
- Preeclampsia, IUGR and IUFD
- Medical complications
- Varicose veins/STP
- Ob hemorrhage
- BMI $\geq 30$ kg/m$^2$
### Risk of maternal VTE for a given thrombophilia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>VTE Risk No Hx</th>
<th>VTE Risk (+) Hx</th>
<th>% of VTE</th>
<th>RR of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL (heteroz.)</td>
<td>0.5%-1.2%</td>
<td>10%</td>
<td>40%</td>
<td>7X</td>
</tr>
<tr>
<td>FVL (homoz.)</td>
<td>4%</td>
<td>17%</td>
<td>2.2%</td>
<td>25X</td>
</tr>
<tr>
<td>PGM (heteroz.)</td>
<td>&lt;0.5%</td>
<td>&gt;10%</td>
<td>17%</td>
<td>9X</td>
</tr>
<tr>
<td>PGM (homoz.)</td>
<td>2 - 4%</td>
<td>&gt;17%</td>
<td>0.50%</td>
<td>&gt;25X</td>
</tr>
<tr>
<td>FVL/PGM</td>
<td>4.7%</td>
<td>&gt;20%</td>
<td>1-3%</td>
<td>84X</td>
</tr>
<tr>
<td>Disorder</td>
<td>VTE Risk No Hx</td>
<td>VTE Risk (+) Hx</td>
<td>% of VTE</td>
<td>RR of VTE</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>AT def activity &lt; 60%</td>
<td>3-7%</td>
<td>40%</td>
<td>1%</td>
<td>&gt;100X</td>
</tr>
<tr>
<td>PC def activity &lt; 50%</td>
<td>0.1-0.8%</td>
<td>4-17%</td>
<td>14%</td>
<td>13X</td>
</tr>
<tr>
<td>PS def free Ag &lt; 55%</td>
<td>0.1%</td>
<td>0-22%</td>
<td>3%</td>
<td>5X</td>
</tr>
</tbody>
</table>

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- Physiologic Regulation of Hemostasis
- Risk factors for VTE
- Diagnosis of VTE
- Treatment of VTE
- Prevention of VTE
Clinical Diagnosis of DVT

- **90%** False Positive rate with calf or thigh tenderness and pain, erythema and edema.
- Differential diagnosis includes cellulitis, ruptured or strained muscle or tendon, trauma, ruptured popliteal (Baker’s) cyst, cutaneous vasculitis, superficial thrombophlebitis, and lymphedema.

Studies to Diagnose DVT in Pregnancy

1) Serial Compression Color Doppler Venous Ultrasonography (VUS) on days 3 and 7: highly predictive of proximal vein DVT Sensitivity of 94.1% and FNR of 0.7%

2) Lower efficacy for isolated calf vein DVT (sensitivity 92.5%, specificity 98.7%).

Studies to Diagnose DVT in Pregnancy

2) **D-dimer**: Study of 149 at risk pregnancies with DVT prevalence of 8.7%, SimpliRED D-dimer assay had efficacy of:

- Sensitivity of **100%** (77% to 100%)
- Specificity of **60%** (52% to 68%)
- Negative predictive value of **100%** (95% to 100%)

Source: (Chan et al. Ann Intern Med. 2007; 147:165-70)
Imaging Studies to Diagnose DVT in Pregnancy

3) **Venous Magnetic Resonance (MR) imaging** efficiency is equivalent to VUS.

- Sensitivity in non-pregnant patients approaches 100%, Specificity 96%, NPV 100%, PPV 90%.

- May be very useful in cases of iliac DVT

LEFt clinical prediction rule

1) Symptoms in left leg (L for left), Calf circumference difference ≥2 cm (E for edema) & First trimester presentation (Ft for 1st tri.)

2) Among patients presenting with 0, 1, and 2/3 variables, DVT was diagnosed in 0, 16, and 58%.

Patient with Signs and Symptoms of DVT

Assess VUS and D-Dimer

VUS (-) and D-Dimer (-)

Low risk patient?

(-) D/C Patient

VUS (-) but D-Dimer (+)

High risk patient?

Consider serial VUS
Venous MRI

(-) D-dimer < 500 ng/mL

VUS (+)

Treat
Symptoms of PE in pregnancy include:
- Dyspnea (62%)
- Pleuritic Chest pain (55%)
- Tachycardia (54%)
- Abn alveol.-art. grad >14 mmHg (41%)
- Cough (24%)
- Diaphoresis (18%)
- Hemoptysis (8%)
- Syncope (5%)

Ancillary tests for PE

1) **D-Dimers**: Study of 37 at risk women found sensitivity only 73% with low specificity (15%); also literature contains multiple false negative case reports

2) **Compression VUS**: Lower extremity DVT seen in 36%-82% of non-pregnant pts with PE

Ancillary tests for PE

3) EKG findings: RBBB, Right axis deviation, Q waves in lead III and aVF, S waves in lead I and aVL >1.5 mm, T wave inversions in leads III and aVF and/or new-onset A-fib.

4) Echocardiographic findings: RV dilation and hypokinesis, Tricuspid regurgitation and PA dilation.
Signs of Pulmonary Embolus

5) Ventilation-Perfusion (V/Q): In setting of normal CXR, V/Q scan diagnostic in 75-93% of pregnant women vs. 64.3% for CTPA.
   - Very low risk of subsequent VTE if normal
   - Sensitivity >85%, specificity > 95%, NPV 100%
   - Perfusion component alone has comparable efficacy but lower fetal radiation

Signs of Pulmonary Embolus

6) CT Pulmonary Angiography (CTPA): multi-detector-row machines yield false negative results < 1%:

- More diagnostic than V/Q when CXR is abnormal but technically inadequate in 17 to 28% of all cases.
- Other clinically significant findings found in 12-13% of patients including pneumonia and pulmonary edema.

# Radiation Exposures CTPA vs. V/Q

<table>
<thead>
<tr>
<th>Exposure</th>
<th>CTPA</th>
<th>V/Q</th>
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<tbody>
<tr>
<td>Fetus</td>
<td>0.003-0.131 mGy</td>
<td>0.32-0.74 mGy</td>
</tr>
<tr>
<td>Maternal Breast</td>
<td>35.0 mGy</td>
<td>0.25 mGy</td>
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V/Q vs. CTPA

• If CXR Normal - V/Q preferred because it is more diagnostic than CTPA, has lower breast radiation, and because of uncertainty over clinical import of subsegmental PE more commonly found on CTPA.
• If CXR Abnormal - CTPA preferred because it can r/o other life-threatening diagnoses (e.g., aortic dissection) and exposes fetus to less radiation than V/Q.

Patient with Signs and Symptoms of Acute PE

*If hemodynamically unstable consider TE-echo at bedside
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Who to treat in Pregnancy

Therapeutic LMWH x 4 months (20 weeks) followed by Prophylactic LMWH
Therapeutic LMWH

Dose

• Dalteparin sodium (Fragmin) 200 U/kg s.q. once daily; or 100 U/kg s.q., every 12 hrs. (up to 5,000 U)

• Enoxaparin (Lovenox) 1 mg/kg up to 100 mg in s.q., every 12 hrs.

• Titrate dose of LMWH to target anti-factor Xa levels of 0.6 to 1.0 IU/ml 4 hours after 3rd or 4th dose for twice daily Rx; or 1 to 2 IU/ml 4 hours after 2nd or 3rd dose for once daily Rx.
Prophylaxis with LMWH

- **Dose:** Dalteparin: 5000 U s.q. once daily; or enoxaparin: 40 mg s.q., once daily; adjust both to maintain anti-factor Xa levels at 0.1 –0.2 U/ml 4 hrs after 3rd or 4th injection dose.

- **Risk of epidural anesthesia:** due to reports of epidural hematomas associated with LMWH heparin therapy, such therapy should be discontinued at 36-37 weeks or earlier if delivery is anticipated, and unfractionated heparin therapy resumed to permit regional anesthesia.
Intrapartum Management: Patients on Unfractionated Heparin

- Vaginal or cesarean delivery not accompanied by significant risks bleeding if procedure occurs > 6 hrs after a prophylactic UFH dose, or > 12 hrs after prophylactic dose of LMWH or > 24 hrs after therapeutic dose of LMWH.

- If patient on therapeutic UFH an aPTT should be checked pre-operatively. Protamine may be given to reverse a prolonged aPTT at the time of delivery.
Intrapartum Management (Con’t)

➢ AT concentrates can be used in AT deficient patients in the peripartum period.

➢ UFH or LMWH should be resumed 4-6 hours after a vaginal delivery and 8-12 hours after a cesarean delivery.
# Postpartum treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>PE or Iliofemoral DVT in index pregnancy</td>
<td>4-6 months</td>
</tr>
<tr>
<td>DVT in index pregnancy or</td>
<td>12 weeks ATIII deficiency</td>
</tr>
<tr>
<td>DVT or PE in a prior pregnancy or other inherited thrombophilia</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>
Postpartum treatment

a) Warfarin can be initiated immediately post-partum, titrating dose to maintain INR at $\geq 2$

b) Because of Warfarin’s more rapid inhibitory effect on protein C compared with clotting factors, *heparin should always be maintained during the initial 5 days of Warfarin therapy* and heparin should not be stopped until INR $\geq 2 \times 48\text{ hrs.}$
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ACOG recommendations prevention of postpartum VTE

• ACOG recommends pneumatic compression devices for all patients before, during and after C-section
• Low risk thrombophilia (LMWH if additional risk factors – C-section, prior VTE, FHx, BMI > 30)
• High risk thrombophilia (LMWH, - x 6 weeks if prior VTE)
• No thrombophilia but prior VTE (LMWH)
National Partnership for Maternal Safety has called for more aggressive use of pharmacological thromboprophylaxis in pregnancy.

- **Patients with Antepartum Hospitalizations:** Prophylactic heparin in all patients, not receiving LMWH, admitted to hospital > 72 hrs and not at risk for bleeding. If at risk for bleeding, patients should receive pneumatic compression devices in lieu of heparin.

- **Patients with Vaginal Deliveries:** Use intrapartum pneumatic compression devices with a history of VTE or thrombophilia followed by heparin based on RCOG or Padua criteria.

National Partnership for Maternal Safety has called for more aggressive use of pharmacological thromboprophylaxis in pregnancy.

- **Patients with Cesarean Deliveries:** All patients should use pneumatic compression devices until fully ambulatory. Heparin thromboprophylaxis for women with risk factors based on RCOG or Caprini criteria.

- **Given the challenges in consistently identifying women with risk factors and issues related to poor compliance with mechanical devices, hospitals may choose a strategy in which all women undergoing cesarean birth receive postoperative heparin thromboprophylaxis.**

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