March 24, 2011

**Venous Thromboembolism, Trombophilia Screening, and Anticoagulation: Antepartum and Postpartum Management**

**I: Screening and Management Recommendations**

**Introduction:**
Venous Thromboembolic Events (VTE)-includes DVT and PE

- Incidence of VTE: 0.6-2.0 per 1000 pregnancies
- DVT 3 times more likely than PE
- Occurs equally among trimesters; 5 times more likely postpartum
- Deaths usually occur postpartum, within 30 minutes from the event.

**Inherited Trombophilias: Who Should Be Screened**
1. Personal history of VTE
2. First degree relative (parent or sibling) with history of an inherited high risk thrombophilia (Antithrombin deficiency, Factor V Leiden Homozygous, Prothrombin Homozygous, or Compound Heterozygous for FVL and Prothrombin), or VTE before age 50 in absence of other risk factors.
3. Screening for inherited thrombophilias is otherwise not recommended for recurrent fetal loss, placental abruption, IUGR, or pre-eclampsia.

**Acquired Trombophilias: Who Should Be Screened**
Screen for Lupus Anticoagulant, Anticardiolipin Antibodies, and B2-glycoprotein I Antibodies in patients with:
1. ≥3 consecutive spontaneous abortions <10 wks gestation
2. ≥1 fetal deaths at or beyond 10 wks gestation
3. Severe preeclampsia or placental insufficiency requiring delivery <34 wks gestation
4. Unexplained venous or arterial thrombosis
5. Small vessel thrombosis in any location without evidence of vessel wall inflammation.

**Inherited Trombophilia Work-up:** Should be done ≥6 weeks from thrombotic event, while patient is not pregnant, and while not taking anticoagulation.

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Testing during Pregnancy</th>
<th>Testing with patient on Anti-coagulation</th>
<th>Testing During Acute Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden Mutation</td>
<td>Reliable</td>
<td>Not Reliable if activated protein C resistance assayed&lt;br&gt;Is Reliable if DNA analysis done</td>
<td>Reliable</td>
</tr>
<tr>
<td>Prothrombin gene mutation G20210A</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Reliable</td>
<td>Not Reliable</td>
<td>Not Reliable</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Not Reliable: Instead, use cutoff values of &lt;30% and &lt;24% in 2nd &amp; 3rd trimesters respectively</td>
<td>Not Reliable</td>
<td>Not Reliable</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Reliable</td>
<td>Not Reliable</td>
<td>Not Reliable</td>
</tr>
</tbody>
</table>

Risk Assessment and Management Guidelines: Antepartum (AP) and 6 weeks Postpartum (PP)

- AP anticoagulation should always be equal to or greater than PP anticoagulation
- Low-dose aspirin is not indicated unless specifically stated

*High Risk Thrombophilia: Antithrombin deficiency, Factor V Leiden Homozygous, Prothrombin Homozygous, Compound heterozygous for FVL/Prothrombin
+Low Risk Thrombophilia: Factor V Leiden Heterozygous, Prothrombin Heterozygous, Protein C or S deficiency
#Risk Factors: First degree relative with VTE <50 years of age, obesity, cesarean, prolonged immobility
Other Considerations for Antepartum Management in Antiphospholipid Antibody (APLA) Syndrome

Patients with APLA Syndrome receive ultrasound q4 weeks after 20 wks to assess fetal growth, and fetal testing starting at 32 weeks unless clinically indicated sooner.

II. Anticoagulation: Dosing and Monitoring

General Principles:
- Low molecular weight heparin (LMWH) is the preferred choice for prevention and treatment of VTE secondary to ease of administration and better safety profile. Patients may remain on LMWH if delivery is predictable.
- LMWH is not recommended in patients with renal failure (creatinine >1.5) or with active hemorrhage, or in patients likely to require thrombolytic therapy or emergency surgery.
- If delivery is threatened or unpredictable and patient is hospitalized, therapeutic SC anticoagulation is discontinued and IV UFH is instituted.

Medication Dosing

<table>
<thead>
<tr>
<th>Dose</th>
<th>UFH</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>sc q12 hours:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Up to 20 weeks: 5000 U</td>
<td>Dalteparin 5000 U sc q24h</td>
</tr>
<tr>
<td></td>
<td>20-28 weeks: 7500 U</td>
<td>Enoxaparin 40mg sc q24h</td>
</tr>
<tr>
<td></td>
<td>&gt;28 weeks: 10,000 U</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dalteparin 100 U/kg q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 1mg/kg q12h</td>
<td></td>
</tr>
<tr>
<td>Adjusted dose</td>
<td>UFH sc q12h to target anti-Xa</td>
<td>Pre-Pregnancy Weight</td>
</tr>
<tr>
<td></td>
<td>0.35-0.7 U/mL</td>
<td>Adjusted: Dalteparin 100 U/kg</td>
</tr>
<tr>
<td></td>
<td>*consider changing time</td>
<td>Enoxaparin 1mg/kg q12h</td>
</tr>
<tr>
<td></td>
<td>interval if difficulty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>achieving level.</td>
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</tr>
</tbody>
</table>

Monitoring Levels

- If on low dose anticoagulation, monitoring of levels is not indicated.
- If on adjusted dose anticoagulation, levels need to be monitored.
  - **LMWH**: Check anti-Xa 4-6 hours after 3rd dose; therapeutic level 0.6-1.0 U/mL; increase/decrease dose 10-25% as needed to achieve level; once therapeutic recheck monthly
  - **UFH**: Check anti-Xa 4-6 hours after 3rd dose; therapeutic level 0.35-0.7 U/mL; increase/decrease dose 10-25% as needed to achieve level
  - Weekly assessment of platelet count first 3 weeks after initiating heparin
  - In the morbid obese, consider changing sites if difficulty achieving level.
Complications with Heparin Use:
  Bleeding, Skin necrosis, Osteoporosis

Heparin Induced Thrombocytopenia (HIT)
  • Very rare in pregnancy but potentially life and limb threatening
  • Two types: Type 1 is benign and resolves by five days, Type 2 immune form occurs days 5-14 and may result in widespread thrombosis
    Stop Treatment if platelets <100,000 and consult Hematologist for alternative therapy

III. Intrapartum and Postpartum Management

1. Induction of Labor
   Patients on Anticoagulation outpatient should be instructed to discontinue as follows:
   1. UFH
      a. Adjusted dose: Discontinue 12 hours prior to induction of labor (i.e. on day prior may take am dose but not pm dose)
      b. Low dose: May continue until presents for induction. (i.e. may take both doses on day prior)
   2. LMWH
      a. Adjusted dose: Discontinue 24 hours prior to delivery (i.e. on day prior do not take evening dose or am dose the morning of induction, surgery)
      b. Low dose: Discontinue 12 hours prior to delivery (i.e. on day prior, may take am dose but hold evening dose)

2. Spontaneous Labor - If necessary, reversal of adjusted dose heparin anticoagulation may be accomplished with protamine sulfate. Only minimally effective in LMWH.

   -Protamine sulfate use is contraindicated in patients who have shown previous intolerance to the drug or with salmon sperm allergy.

   -If labor begins unexpectedly in a fully anticoagulated pregnancy, most patients will not have excessive intrapartum bleeding. Reversal of heparin is rarely required, and is not indicated for low dose anticoagulation.

3. Admission for C-section
   The American Society of Regional Anesthesia and Pain Medicine recommends that spinal/epidural anesthesia should not be given until 12 hours after administration of low dose of LMWH, 24 hours after the last adjusted dose LMWH dose, and 12 hours after the last adjusted dose subcutaneous unfractionated heparin dose (if patient on UFH and aPTT normal, regional anesthesia acceptable).

4. Post Partum Management
   *Post Partum anticoagulation should always be equal to or greater than antepartum anticoagulation.
   1. S/P NSVD: restart LMWH/UFH  6 hours after delivery and at least 2 hours after epidural catheter removal
   2. S/P C-Section: restart LMWH/UFH 12 hours after delivery
   3. If on Coumadin: (use if patient requires anticoagulation >6 weeks postpartum)
      a. Start 5mg daily for 2 days
      b. Adjust dose by 2.5 or 5mg daily to achieve INR of 2-3 for 2 days
c. Continue of adjusted dose LMWH/UFH for at least 5 days until INR is therapeutic for 2 days to prevent paradoxical thrombosis and skin necrosis.
d. Check INR/CBC weekly for 2 weeks, then q4 weeks.
e. Refer to Hematology for follow-up.

IV. Diagnosis and Treatment of Acute VTE in Pregnancy:

Symptoms:  
- **DVT**: lower extremity swelling, pain; most likely located left lower extremity.  
- **PE**: dyspnea, tachypnea, tachycardia, pleuritic chest pain

Clinical diagnosis of DVT and PE is notoriously insensitive and non-specific; clinical prediction rules have not been validated in pregnancy.

- **Arterial blood gases** are neither sensitive nor specific for the diagnosis of PE, and respiratory alkalosis is a common feature in pregnancy and PE
- **D-Dimer** is a breakdown product of cross-linked fibrin, limited use in pregnancy because levels are increased, rising with gestational age, and peaking at delivery and early post-partum.

* If high clinical suspicion for acute PE, **empiric anticoagulation is indicated** prior to the diagnostic evaluation and treatment may be discontinued if VTE is excluded

Diagnostic Imaging:

- **DVT**: doppler ultrasound as initial test: highly sensitive and specific for symptomatic proximal vein thrombosis. If testing is non-diagnostic, may consider contrast venography with shielding or MRV.

- **PE**: If DVT confirmed, no need to document PE; Spiral CT using IV contrast is the non-invasive study of choice with sensitivity of 83% and specificity of 96%; if contraindication to radiocontrast and leg studies are negative, do V/Q scan.

Diagnostic Approach in Pregnancy: Patients may be evaluated with above tests taking into consideration their limitations in pregnancy. Clinical picture must be taken into consideration along with diagnostic findings. Chest x-ray may be done initially if mild hypoxia present and clinical picture may be consistent with other lung pathology (pneumonia, pulmonary edema, etc)

- If symptoms of DVT and PE are present, start with LE ultrasound. If confirmed, then exposure to CT/VQ scan not necessary.
- For suspected PE- may order CT or VQ scan based on availability
  
  **CT Scan:**  
  Positive- treat  
  Negative- consider LE ultrasound- if positive then treat

  **VQ Scan:**  
  Normal-withhold anticoagulation  
  High Probability- treat  
  Non-Diagnostic- get LE u/s- if positive then treat

Treatment of Acute VTE Diagnosed in or around Pregnancy:
If DVT is diagnosed, patient may be started on subcutaneous adjusted dose anticoagulation in outpatient setting (See dosing above). Draw baseline CBC and coagulation profile.
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If diagnosis of PE is made, admit patient and obtain baseline CBC and Coagulation panel. Do not place SCD’s until DVT has been ruled out. Monitor patients pulse ox. Initiate adjusted dose anticoagulation (see dosing above).

-SC LMWH is preferred over IV UFH or SC UFH except in patients with renal failure (creatinine >1.5) active hemorrhage, or in patients likely to require thrombolytic therapy or emergency surgery.
  -In stable patient, use SC therapeutic LMWH
  -If potentially unstable or have above risks, initiate IV therapeutic UFH.

Anticoagulation should be continued for at least 6 weeks postpartum and total treatment length at least 6 months

ADDENDUM:
Special Considerations: Mechanical Heart Valves and Warfarin (Coumadin) Use in Pregnancy

Warfarin is an oral vitamin K antagonist and suppresses the intrinsic pathway of coagulation. It crosses the placenta and can cause fetal wastage, fetal hemorrhagic complications, and teratogenicity.

-Use throughout pregnancy is assoc with congenital anomalies usually occurring after in utero exposure between 6-13 weeks gestation.

-Coumarin Embryopathy:
  - nasal hypoplasia and/or stippled epiphyses
  - limb hypoplasia in up to 1/3 of cases with embryopathy

Also associated with CNS abnormality after exposure during any trimester- dorsal midline dysplasia and ventral midline dysplasia leading to optic atrophy, mental retardation, spasticity, and hypotonia

-The substitution of heparin before 6 weeks appears to eliminate the risk

In 2002, the FDA issued warnings that LMWH was not recommended for thromboprophylaxis in pregnant women with mechanical heart valves, and this was endorsed by ACOG. However, the alternative warfarin therapy carries substantial fetal risks, especially in the 1st trimester. Any potential regimen chosen should minimize both maternal and fetal complications, and LMWH may be indicated in some circumstances for fetal benefit. Vitamin K antagonists may be indicated in pregnancy when maternal benefits justify the fetal risks.

There is a lack of agreement as to the optimal treatment of pregnant women with prosthetic heart valves due to the absence of adequate prospective controlled trials.

☐ Risk Factors that increase thromboembolic risk are mechanical vs. bioprosthetic valve, prior thromboembolic event, Afibb, mitral position, or multiple prostheses.
☐ Valve thrombosis is a potentially catastrophic complication in pregnancy with treatment options being surgical thrombectomy or thrombolysis, both of which carry substantial maternal and fetal risks.
☐ Several studies concluded risk is elevated with heparin compared to warfarin although dosing was not well controlled.

Several Approaches Remain Acceptable:

- Women with mechanical valves need to be assessed for additional risk factors of thromboembolism, and thoroughly counseled on the risks and benefits of the type of anticoagulation employed.
  1. In very high risk patients, vitamin K antagonist use throughout pregnancy may be considered with LMWH/UFH substitution close to term.
  2. For those with lower risk profiles, may consider switching patients to therapeutic LMWH/UFH at the time of positive pregnancy test until 13th week gestation. Coumadin is then resumed until 36 weeks, when patients can be switched to heparin.
  3. Aggressive Adjusted-dose LMWH/UFH anticoagulation throughout pregnancy

- For those at very high risk, addition of 75-100mg ASA may be beneficial.
- If on coumadin and urgent delivery is necessary, C/S is preferable due to fetal risk. If time allows, Vitamin K can be given to get INR to 2.0 which should permit safe C/S. If emergent, give FFP to get INR to 2.0