Anticoagulation in Pregnancy

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No Disclosures
Rise in Pregnancy-Related Mortality
Physiologic Changes During Pregnancy

- Cardiac Output
- Plasma Volume
- RBC Mass
- Delivery
- Hematocrit
Pregnancy is a Pro-coagulant State

The risk is highest in the immediate post-partum period and slowly decreases back to pre-pregnancy levels by 8 to 12 weeks post-partum.
Need for Anticoagulation in Pregnancy

• Prosthetic Heart Valves
• DVT/PE (Venous Thromboembolism)
• Inherited Thrombophilias
• Atrial Fibrillation
• Peripartum Cardiomyopathy and Preexistent DCM
• Women with History of Fetal Loss
Anticoagulants in Pregnancy

Drug of Choice
- LMWH

Ok to Use
- UFH

Rarely Used
- Fondaparinux
- Danaparanoid
- Argatroban

Avoid Use
- Warfarin

Not Studied
- DOACs
## Anticoagulants in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Pre-conception</th>
<th>1(^{\text{st}}) Trimester</th>
<th>2(^{\text{nd}}) / 3(^{\text{rd}}) Trimester</th>
<th>Post Partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Teratogenic</td>
<td>Embryopathy</td>
<td>Fetopathy / Bleeding</td>
<td>Bleeding</td>
</tr>
<tr>
<td>UFH</td>
<td>-</td>
<td>-</td>
<td>Fetopathy / Bleeding</td>
<td>Bleeding</td>
</tr>
<tr>
<td>LMWH</td>
<td>-</td>
<td>-</td>
<td>Bleeding</td>
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</tr>
</tbody>
</table>

**Warfarin Embryopathy**
- 0.6–10%
- Limb defects/Nasal hypoplasia

**Fetopathy**
- Ocular defects
- CNS abnormalities
- Intracranial haemorrhage

**UFH**
- 0.45–0.9% - low-dose

**LMWH**
- 0.6–10%
**TABLE 1.** COMPARATIVE STUDIES OF ANTI-Xa and ANTI-IIa ACTIVITIES OF THE MOTHERS AND THEIR RELATED FETUSES 3 HOURS AFTER THE LMWH INJECTION (Mean and standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>Mothers (n=5)</th>
<th>Fetuses (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>anti-Xa activity</strong></td>
<td>0.175 ± 0.07</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>(IU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>anti-IIa activity</strong></td>
<td>&lt;0.1</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>(IU/ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Forestier F et al. Thromb Res 1984; 34:557*
LMWH in Pregnancy

• Drug Of Choice: Embryopathy/Fetopathy

• Dosage: Early pregnancy body weight
  
  • Enoxaparin 1 mg/kg body weight BID
  
  • Dalteparin 100 IU/kg body BID

• Monitoring: 4–6 h peak anti-Xa - 0.6–1.2 IU/mL
LMWH in Pregnancy

• Risk of recurrent VTE - 1.15%
• Major bleeding - 1.98%
• Markedly lower
  • Heparin-induced thrombocytopenia
  • Heparin-induced osteoporosis (0.04%)
• Dosing less frequent
UFH in Pregnancy

• Low Cost

• Need for rapid reversal is important
  Delivery or Perioperatively

• Severe Renal Insufficiency

• Acute Massive PE

• Risk of Osteoporosis

- LMWH switch to IV UFH 36h before IOL or CS
- Discontinue UFH 4–6h before
- Restart 6 h after
### Mechanical Heart Valves (MHV) in Pregnancy

<table>
<thead>
<tr>
<th>Valve Thrombosis</th>
<th>Venous Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester</td>
<td>Postpartum</td>
</tr>
</tbody>
</table>

- Transition from warfarin to heparins
- Changing pharmacokinetics
- Unidentified homeostatic factors
- Warfarin discontinued by patient

**Valve Thrombosis**

- Transition from warfarin to heparins
- Changing pharmacokinetics
- Unidentified homeostatic factors
- Warfarin discontinued by patient
MHV in Pregnancy - Challenging Situation

- Teratogenic effects of anticoagulants
- Dosing complexities
- Management around labor
- Teratogenic effects during conception
ROPAC Registry

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Valves n=212 (%)</th>
<th>No Prosthetic Valve n= 2906 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Mortality</td>
<td>1.4</td>
<td>0.2</td>
<td>0.025</td>
</tr>
<tr>
<td>Hospital Admission</td>
<td>36.7</td>
<td>24.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6.1</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>23.1</td>
<td>4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscarriage&lt;24 wks</td>
<td>15.6</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscarriage&gt;24 wks</td>
<td>2.8</td>
<td>0.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Van Hagen et al. Circulation 2015
<table>
<thead>
<tr>
<th></th>
<th>Mechanical Valves</th>
<th>Tissue Valve</th>
<th>No Prosthetic Valves</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Mom and Baby</strong></td>
<td>81%</td>
<td>97%</td>
<td>97.7%</td>
</tr>
<tr>
<td><strong>Event Free Live Birth</strong></td>
<td>58%</td>
<td>79%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>
Warfarin vs LMWH in First Trimester

Miscarriage <24 wks

Fetal Loss >24 wks

Van Hagen et al. Circulation 2015
Management of MHV in Pregnancy -
Preconception Counseling

- Consider bioprosthetic valves
- Discuss risk profile
- Eliminate modifiable risk factors
  - Smoking
  - Atrial arrhythmia
- Start ASA
### Management of MHV in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; &amp; 3&lt;sup&gt;rd&lt;/sup&gt; Trimesters</th>
<th>Peripartum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACC/AHA</strong></td>
<td>Warfarin if dose ≤ 5 mg/d (IIa) or Dose-adjusted LMWH* (IIb) or Dose-adjusted IV UFH† (IIb)</td>
<td>Warfarin + daily Aspirin (I)</td>
<td>Dose-adjusted IV UFH (I)</td>
</tr>
<tr>
<td><strong>ESC</strong></td>
<td>Warfarin if dose &lt; 5 mg/d (IIa) or &gt; 5 mg/d (IIb) or Dose-adjusted LMWH (IIb) or Dose-adjusted IV UFH (IIb)</td>
<td>Warfarin (I)</td>
<td>Dose-adjusted LMWH or IV UFH (I)</td>
</tr>
</tbody>
</table>

*LMWH: Low Molecular Weight Heparin
†IV UFH: Intravenous Unfractionated Heparin

Alshwabkeh et al. JACC 2016
<table>
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<tr>
<th>Prosthesis thrombogenicity</th>
<th>Patient Related Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Low</td>
<td>2.5</td>
</tr>
<tr>
<td>Medium</td>
<td>3.0</td>
</tr>
<tr>
<td>High</td>
<td>3.5</td>
</tr>
</tbody>
</table>

- MVR
- TVE
- H/O TE
- Afib
- Any MS
- LVEF <35%

Low- Carbomedics, Medtronic Hall, ATS, or Medtronic Open-Pivot, St Jude Medical, On-X, or Sorin Bicarbon

High- Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Björk-Shiley and other tilting-disc valves; any pulmonary valve prosthesis.
MHV in Pregnancy - Surveillance

• Pregnancy heart team in an expert center
• Anticoagulation - Weekly or every 2 weeks
• Clinical follow-up + echocardiography - monthly
Anticoagulation for MHV in Pregnancy

- ↑ maternal and fetal mortality
- ↑ thrombotic and hemorrhagic complications
- Most MVTs - first trimester
- All MVTs in women on some form of heparin
- Warfarin (even low dose) – miscarriage /fetal demise
- No regime safe
<table>
<thead>
<tr>
<th>Prosthesis thrombogenicity</th>
<th>Anti-Xa Peak</th>
<th>Anti-Xa Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤1.5</td>
<td>≥0.6</td>
</tr>
<tr>
<td>High</td>
<td>≤1.5</td>
<td>≥0.7</td>
</tr>
</tbody>
</table>

Goland et al. Cardiol Clin 2012
VTE During Pregnancy

• VTE is highest in post-partum period with rates - 0.5%
• In women with previous VTE, recurrence rates - 7.6%
• High index of suspicion + low threshold for investigation

Regitz-Zagrosek et al. EHJ 2018
Post-Partum Management VTE

• Heparin treatment should be restarted
  • 6 h after a vaginal birth and
  • 12 h after a caesarean delivery
• Warfarin may be started on the second day after delivery
• Atleast 3 months, or for 6 months if PE occurred later
• INR 2-3, 1–2 weekly check
• Warfarin safe for breastfeeding
Prevention of VTE During Pregnancy

High-risk for VTE

- prophylactic enoxaparin - 0.5 IU/kg daily or equivalent

- Previous unprovoked recurrent VTEs
- Previous VTE—unprovoked or estrogen-related
- Thrombophilia + FH VTE

Regitz-Zagrosek et al. EHJ 2018
Atrial Fibrillation In Pregnancy

• Not been systematically studied
• Some experts recommend anticoagulation if Afib>48hrs
• ESC guidelines- Same rules apply as Afib in non-pregnant
• Warfarin should not be given
• Cardiovert within 48 hrs to reduce TE risk

Regitz-Zagrosek et al. EHJ 2018
Goland et al. Cardiol Clin 2012
Mitral Stenosis- Suggested Indications for Anticoagulation in Pregnancy

• Atrial Fibrillation
• Prior thromboembolism
• Enlarged left atrium > 55 mm

Goland et al. Cardiol Clin 2012
Peripartum Cardiomyopathy and Pre-existent Dilated Cardiomyopathy

- Atrial Fibrillation
- Prior thromboembolism
- LV thrombus
- Bromocriptine use for PPCM

Goland et al. Cardiol Clin 2012
Inherited Thrombophilias

Factor V Leiden
Prothrombin 20210A

- FH
  - Antepartum + Postpartum AC
- No FH
  - Postpartum AC only

Other Thrombophilias

- FH
  - Postpartum AC
    - Consider antepartum
- No FH
  - Postpartum AC only

Antepartum: LMWH or UFH
Postpartum: LMWH, UFH or Warfarin

Bates et al. Chest 2012
Some Other Scenarios

• Severe ovarian hyperstiumaulation syndrome
  • LMWH 3 months

• APLA - UFH or LMWH + ASA 81 mg

• At risk for preeclampsia- ASA 81 mg
Neuraxial Anesthesia

- Not be done if patient anticoagulated - risk of spinal/epidural hematoma
- >95% CS and >65% VD in US
- Prophylactic LMWH-12 hrs last dose
- Intermediate and Therapeutic LMWH – 24 hrs
- Prophylactic and therapeutic UFH – Once the aPTT has normalized
  - 6 hours after IV
  - 24 hours SQ

Gogarten W et al. Eur J Anaesthesiol 2010
Conclusion

- Pregnancy is a procoagulant state
- Anticoagulation - Increased maternal & fetal morbidity + mortality
- MHV - increased risk of valve thrombosis - first trimester
- LMWH is the drug of choice in pregnancy
- LMWH and UFH carry a high risk of MVT
- Warfarin lower risk of MVT but high risk of adverse fetal outcome
- Warfarin, LMWH and UFH are safe in post partum period
- DOACs have not been studied in pregnancy
Thank you