Prevention of [Postpartum] Venous Thromboembolism

Ware Branch, MD
Disclosures for Dr. Branch

• No disclosures relevant to this presentation regarding VTE
Today’s Journey

• Brief problem overview / epidemiology
• Standard-of care recommendations - what you should do
• Some nuances of heparin use
• How the study of pregnancy-related VTE is difficult
  • There’s a lot we don’t know!
VTE in Obstetrics

- Obstetric VTE is a major health concern
  - 9-11% of pregnancy-related deaths in U.S. over last 20 years
  - Long term sequelae in non-fatal cases
Risk of Pregnancy-Related VTE

- Retrospective study using large primary care database in United Kingdom
  - 1st VTE within 90 days of delivery (via medical coding and anticoagulant drug prescriptions)
  - 972,683 women, 1987-2004

<table>
<thead>
<tr>
<th>VTE Rate per 100,000 Women Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

Adjusted (age and calendar year) Rate Ratio Compared to Non-Pregnant Women

<table>
<thead>
<tr>
<th>1.6 (0.9-2.8)</th>
<th>2.1 (1.3-3.4)</th>
<th>6.1 (4.7-7.9)</th>
<th>22.1 (18.1-27.1)</th>
<th>1.8 (0.9-3.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 (2.8-4.3)</td>
<td></td>
<td></td>
<td></td>
<td>11.9 (9.8-14.5)</td>
</tr>
</tbody>
</table>

Rate of Postpartum VTE Compared to 1 Year Later

<table>
<thead>
<tr>
<th>Time Interval after Delivery</th>
<th>Case Period</th>
<th>Crossover Period</th>
<th>Absolute Risk Difference (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (rate per 100,000 deliveries)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 0-6</td>
<td>279 (16.5)</td>
<td>23 (1.4)</td>
<td>15.2 (13.1-17.2)</td>
<td>12.1 (7.9-18.6))</td>
</tr>
<tr>
<td>Weeks 7-12</td>
<td>72 (4.3)</td>
<td>33 (2.0)</td>
<td>2.3 (1.1-3.6)</td>
<td>2.2 (1.4-3.3)</td>
</tr>
<tr>
<td>Weeks 13-18</td>
<td>44 (2.6)</td>
<td>28 (1.7)</td>
<td>0.9 (-0.1-2.0)</td>
<td>1.6 (0.8-1.4)</td>
</tr>
<tr>
<td>Weeks 19-24</td>
<td>31 (1.8)</td>
<td>36 (2.1)</td>
<td>-0.3 (-1.3-0.7)</td>
<td>0.9 (0.5-1.4)</td>
</tr>
</tbody>
</table>

Risk Assessment and Management for VTE Prevention
A Standard-of-Care

• Most professional guidelines recommend:
  • VTE risk factor assessment pre-pregnancy or in early pregnancy
  • Repeat assessment upon hospital admission
• Your facility should have a formal / systematic approach to VTE prevention

ACOG Practice Bulletin 196, July 2018

“Each facility should carefully consider the risk assessment protocols available and adopt and implement one …in a systematic way....”
Guidelines Abound!

• ACOG
• RCOG
• ASH
• NPMS
• And others
Guidelines for the Prevention of VTE in Pregnancy

• U.S. Guidelines:
  • American Society of Hematology (ASH)
  • ACOG
  • National Partnership for Maternal Safety

ASH – *Blood Adv 2018; 22:3317*
  • Systematic literature evaluation
  • More emphasis on personal history
  • Less emphasis on thrombophilias
  • Excellent summary table
    (pp 3340-3341)

ACOG – *PB 196, July 2018*
  • More emphasis thrombophilias
  • Usual PB format, with Q&A

NPMS – *Obstet Gynecol 2016; 128:688*
  • Simplified, blended approach
## Guidelines Are Kinda Different

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACOG</th>
<th>RCOG</th>
<th>ASH</th>
<th>NPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum</td>
<td>Risk-based - h/o VTE; thrombophilia</td>
<td>Risk-based - point system</td>
<td>Risk-based</td>
<td>Risk-based</td>
</tr>
<tr>
<td>Antenatal admission</td>
<td>Non-specific</td>
<td>Use heparin agent</td>
<td>Non-specific</td>
<td>Use heparin agent</td>
</tr>
<tr>
<td>Delivery admission and postpartum</td>
<td>Risk-based; universal mechanical for CS</td>
<td>Risk-based - point system</td>
<td>Risk-based</td>
<td>Risk-based or empiric</td>
</tr>
</tbody>
</table>

A 2015 study → pharmacological prophylaxis in 1% of CS using ACOG vs 85% of CS using RCOG (Palmerola et al. BJOG 2015)
# Risks Factors for Pregnancy-related VTE

<table>
<thead>
<tr>
<th>Pre-existing risk factors</th>
<th>Obstetric risk factors</th>
<th>Transient risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>Pre-eclampsia</td>
<td>Any surgical procedure in pregnancy or puerperium (e.g. appendicectomy, postpartum sterilization)</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>Assisted conception (antenatal only)</td>
<td>Hyperemesis</td>
</tr>
<tr>
<td>Medical comorbidities (e.g. cancer, heart failure, nephrotic syndrome)</td>
<td>Multiple pregnancy</td>
<td>Ovarian hyperstimulation syndrome</td>
</tr>
<tr>
<td>Family history of unprovoked VTE</td>
<td>Birth by cesarean section</td>
<td>(first trimester only)</td>
</tr>
<tr>
<td>Age (&gt;35 years)</td>
<td>Mid-cavity or rotational operative delivery</td>
<td>Current systemic infection</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m²)</td>
<td>Prolonged labour (&gt;24 h)</td>
<td>Immobility, dehydration</td>
</tr>
<tr>
<td>Parity ≥3</td>
<td>Post partum haemorrhage (&gt;1 l or blood transfusion)</td>
<td>Admission to hospital</td>
</tr>
<tr>
<td>Smoker</td>
<td>Preterm birth in the current pregnancy</td>
<td></td>
</tr>
<tr>
<td>Gross varicose veins</td>
<td>Stillbirth in current pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

Risks Factors for Pregnancy-related VTE

Table 1. Risk of Venous Thromboembolism With Different Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence in General Population (%)</th>
<th>VTE Risk Per Pregnancy (No History) (%)</th>
<th>VTE Risk Per Pregnancy (Previous VTE) (%)</th>
<th>Percentage of All VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden heterozygote</td>
<td>1–15</td>
<td>0.5–3.1</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Factor V Leiden homozygote</td>
<td>&lt;1</td>
<td>2.2–14.0</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombin gene heterozygote</td>
<td>2–5</td>
<td>0.4–2.6</td>
<td>&gt;10</td>
<td>17</td>
</tr>
<tr>
<td>Prothrombin gene homozygote</td>
<td>&lt;1</td>
<td>2–4</td>
<td>&gt;17</td>
<td>0.5</td>
</tr>
<tr>
<td>Factor V Leiden/prothrombin double heterozygote</td>
<td>0.01</td>
<td>4–8.2</td>
<td>&gt;20</td>
<td>1–3</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02</td>
<td>0.2–11.6</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2–0.4</td>
<td>0.1–1.7</td>
<td>4–17</td>
<td>14</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.03–0.13</td>
<td>0.3–6.6</td>
<td>0–22</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviation: VTE, venous thromboembolism.

Screening for Thrombophilias

“...useful only when results will affect management decisions,...not useful in situations in which treatment is indicated for other risk factors...

Targeted assessment for inherited thrombophilia may be considered in the following clinical scenarios:

• A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing.

• A first-degree relative (eg, parent or sibling) with a history of high-risk inherited thrombophilia. ...targeted testing for the known thrombophilia can be considered if testing will influence management.”
Screening for Thrombophilias

- ACOG consensus and expert opinion (Level C)
  “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.”
What Is High-Risk Thrombophilia?

- Antithrombin deficiency
- Homozygosity for FLV or Prothrombin G20120A mutation
- Heterozygosity for both FVL and PT G20210A mutations

- NOT
  - FVL heterozygosity
  - PT G20210A heterozygosity
  - Protein C or S deficiency
  - Presence of an antiphospholipid antibody
What is a Family History of VTE?

First-degree relative with history of VTE

• Age matters
• Comorbidities matter
<table>
<thead>
<tr>
<th>Factor</th>
<th>Private Insurance</th>
<th>Publically Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE Rate (per 10,000 Deliveries)</td>
<td>Adj OR (95% CI)</td>
</tr>
<tr>
<td>Age 35-39</td>
<td>20.51</td>
<td>1.45 (1.26-1.68)</td>
</tr>
<tr>
<td>Age 40-44</td>
<td>29.13</td>
<td>1.83 (1.51-2.20)</td>
</tr>
<tr>
<td>Obesity</td>
<td>39.01</td>
<td>1.80 (1.51-2.14)</td>
</tr>
<tr>
<td>Smoking</td>
<td>27.73</td>
<td>1.78 (1.34-2.36)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>52.26</td>
<td>2.31 (2.06-2.60)</td>
</tr>
<tr>
<td>Cesarean</td>
<td>27.01</td>
<td>1.54 (1.42-1.68)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47.52</td>
<td>2.40 (2.16-2.67)</td>
</tr>
<tr>
<td>AP Hemorrhage</td>
<td>39.84</td>
<td>1.61 (1.35-1.93)</td>
</tr>
<tr>
<td>PP Hemorrhage</td>
<td>60.16</td>
<td>1.55 (1.30-1.84)</td>
</tr>
<tr>
<td>PP Infection</td>
<td>226.23</td>
<td>6.76 (5.68-8.04)</td>
</tr>
</tbody>
</table>

Tepper et al. Obstet Gynecol 2014; 123:987
Guidelines Abound!

- ACOG
- RCOG
- ASH
- NPMS
- And others
Antepartum VTE Assessment & Care Simplified

Already on Anticoagulation?
- Current VTE?
- Other conditions requiring therapeutic anticoagulation?
- APS?
  - “Benign” conditions for which a heparin agent might be prescribed
    - e.g., prior fetal loss

History of VTE?
- High-risk thrombophilia?
- Multiple VTEs?
- Single prior, unprovoked?
- Related to pregnancy, OCPs, estrogen?
- Single prior, provoked?

Known Thrombophilia?
- High-risk thrombophilia?
- Low-risk thrombophilia with FHx of VTE?
- Low-risk thrombophilia with no FHx of VTE?

High-Risk Therapeutic Anticoagulation
MFM / Hematology

Medium-Risk Thromboprophylaxis

Low-Risk No Thromboprophylaxis
Postpartum VTE Assessment & Care Simplified

Already on Anticoagulation?
- Current or recent VTE?
- Other conditions requiring therapeutic anticoagulation?
- APS?
- “Benign” conditions for which a heparin agent might prescribed
  - e.g., prior fetal loss

History of VTE?
- High-risk thrombophilia?
- Multiple VTEs?
- Single prior, unprovoked?
- Related to pregnancy, OCPs, estrogen?
- Single prior, provoked?

Known Thrombophilia?
- High-risk thrombophilia?
- Low-risk thrombophilia with FHx of VTE?
- Low-risk thrombophilia with no FHx of VTE?

Continue Therapeutic Anticoagulation/ Bridge to Warfarin
Continue Thromboprophylaxis for 6-8 weeks PP
Low-Risk No Thromboprophylaxis
### University of Utah PP Thromboprophylaxis Guideline

#### MAJOR RISK FACTORS
- APS (with prior thrombosis)
- History of VTE
- Medical comorbidities (e.g., heart disease, SLE, IBD)
- High-risk thrombophilia
- Nephrotic range proteinuria (>6g)
- Cesarean hysterectomy (treatment duration 2 weeks)

#### MINOR RISK FACTORS
- BMI >30
- Multiple pregnancy
- PPH >1L
- Smoking >10 cig/d
- Preeclampsia
- Emergency cesarean or cesarean in labor
- Infection – sepsis or triple I around time of delivery
- Preterm delivery <37 weeks
- Low-risk thrombophilia

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- 1 or more major risk factors
- 2 or more minor risk factors

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Thromboprophylaxis
Rates of LMWH Use Post Cesarean – U of U
Postnatal assessment and management (to be assessed on delivery suite)

- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

Caesarean section in labour
BMI ≥ 40 kg/m²
Readmission or prolonged admission (> 3 days) in the puerperium
Any surgical procedure in the puerperium except immediate repair of the perineum
Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type 1 DM with nephropathy, sickle cell disease, current IVDU

Age > 35 years
Obesity (BMI ≥ 30 kg/m²)
Parity ≥ 3
Smoker
Elective caesarean section
Family history of VTE
Low-risk thrombophilia
Gross varicose veins
Current systemic infection
Immobility, e.g. paraplegia, PGP, long-distance travel
Current pre-eclampsia
Multiple pregnancy
Preterm delivery in this pregnancy (< 37th weeks)
Stillbirth in this pregnancy
Mid-cavity rotational or operative delivery
Prolonged labour (> 24 hours)
PPH > 1 litre or blood transfusion

Antenatal and postnatal prophylactic dose of LMWH
Weight ≤ 50 kg = 30 mg enoxaparin/5500 units dalteparin/3500 units tinzaparin daily
Weight 50–90 kg = 40 mg enoxaparin/5500 units dalteparin/6500 units tinzaparin daily
Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily
Weight > 130 kg = 0.6 mg/kg/day enoxaparin/ 75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin daily

HIGH RISK
At least 6 weeks' postnatal prophylactic LMWH

INTERMEDIATE RISK
At least 10 days' postnatal prophylactic LMWH
NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

LOWER RISK
Early mobilisation and avoidance of dehydration

Two or more risk factors

Fewer than two risk factors
Postpartum VTE Prophylaxis

• RCOG
  • LMWH after all CD in labour and for women birthing vaginally with any two risk factors
    • e.g, BMI > 30, age >35 years, parity >3, smoking or preterm delivery
  • Large proportion of women with cesarean delivery now treated with LMWH after cesarean postpartum
    • Recommended for 10 days
“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 thromboprophylaxis with [UFH] or [LMWH] unless there is a specific contraindication. This approach is consistent with the RCOG recommendations.”

Pneumatic Compression Devices

- Retrospective comparison of VTE-related maternal deaths before and after policy of intra-and post-partum pneumatic compression devices for cesarean delivery

<table>
<thead>
<tr>
<th></th>
<th>2000-2006 (N=1,461,270)</th>
<th>2007-2012 (N=1,256,020)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>1</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Clark et al. AJOG 2014; 211:32
Pregnancy and Heparin Agents

• Confusing terminology?
• Monitoring effect?
• Physiologic changes
  • Increased blood volume
  • Changes in protein binding
  • Increased GFR
• Population changes
  • Increasing rate of obesity
  • Increasing rates of other risk factors
What Is Prophylactic-dose and Intermediate-dose Heparin?

- ASH
  - Prophylactic-dose: enoxaparin 40 mg once daily
  - Anything else shy of treatment dose is “intermediate”

- ACOG (Table 2 in PB 196)
  - Prophylactic-dose: enoxaparin 40 mg once daily or UFH 5,000-10,000 U every 12 hours
  - Intermediate-dose: enoxaparin 40 BID

- Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy (NCT01828697)
Anti-Xa Levels for Therapeutic LMWH?

- ASH / ACCP
  - Not routinely recommended
- RCOG
  - Recommended for extremes of maternal weight, renal impairment, or in patients with recurrent VTEs
Weight-based LMWH Dosing in Pregnancy

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>20 mg daily</td>
<td>2500 units daily</td>
<td>3500 units daily</td>
</tr>
<tr>
<td>50–90</td>
<td>40 mg daily</td>
<td>5000 units daily</td>
<td>4500 units daily</td>
</tr>
<tr>
<td>91–130</td>
<td>60 mg daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7500 units daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7000 units daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>131–170</td>
<td>80 mg daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 000 units daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9000 units daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;170</td>
<td>0.6 mg/kg/day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75 units/kg/day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75 units/kg/day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Booking Weight (kg)</th>
<th>Anti-Xa limits 0.2–0.4 (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Below</td>
</tr>
<tr>
<td>50–90</td>
<td>13 (34%)</td>
</tr>
<tr>
<td>91–130</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>131–170</td>
<td>0</td>
</tr>
<tr>
<td>&gt;170</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>16 (21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Third dose</th>
<th>Below</th>
<th>Within</th>
<th>Above</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–90</td>
<td>8 (23%)</td>
<td>25 (71%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>91–130</td>
<td>3 (13%)</td>
<td>19 (79%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>131–170</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&gt;170</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>12 (18%)</td>
<td>47 (71%)</td>
<td>7 (11%)</td>
</tr>
</tbody>
</table>

Weight-based LMWH Dosing in Pregnancy

Stephenson et al. J Perinatol 2016; 36:95
VTE in Obstetrics
Juxtaposition of Difficulties

• Obstetric VTE is a major health concern
  • 9-11% of pregnancy-related deaths in U.S. over last 20 years
  • Long term sequelae in non-fatal cases

• Obstetric VTE relatively infrequent
  • Studies require very large numbers

• >1 risk factor frequently present
  • Additive vs multiplicative?

• Database-driven research complicated
  • PPV of ICD discharge codes may be <65%
  • Chart review is critical
The Power Dilemma for Pregnancy-related VTE

Overall VTE
1:1000

Antepartum VTE
1:2000

Postpartum VTE
1:2000

Outpatient VTE
1:4000

Inpatient VTE
1:4000

Outpatient VTE
1:4000

Inpatient VTE
1:4000
Cochrane Systematic Review, 2014
Bain et al. CD001689

• 16 trials included: 6 antenatal, 9 post CS, 1 postnatal
• Of the 10 postpartum studies (<2500 patients)
  • Only 1 reported on mortality – no deaths
  • No differences for symptomatic VTE
  • One study → increased rate of bleeding complications with heparin
• Judged studies to be of low quality
• Concluded evidence is insufficient for recommendations
Table 2.1. Direct deaths from thrombosis and thromboembolism and rates per 100 000 maternities; UK: 1985–2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Pulmonary embolism</th>
<th>Cerebral vein thrombosis</th>
<th>Thrombosis and thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>1985–87</td>
<td>30</td>
<td>1.32</td>
<td>0.83–1.89</td>
</tr>
<tr>
<td>1988–90</td>
<td>24</td>
<td>1.02</td>
<td>0.68–1.51</td>
</tr>
<tr>
<td>1991–93</td>
<td>30</td>
<td>1.30</td>
<td>0.91–1.85</td>
</tr>
<tr>
<td>1994–96</td>
<td>46</td>
<td>2.09</td>
<td>1.57–2.79</td>
</tr>
<tr>
<td>1997–99</td>
<td>31</td>
<td>1.46</td>
<td>1.03–2.07</td>
</tr>
<tr>
<td>2000–02</td>
<td>25</td>
<td>1.25</td>
<td>0.85–1.85</td>
</tr>
<tr>
<td>2003–05</td>
<td>33</td>
<td>1.56</td>
<td>1.11–2.19</td>
</tr>
<tr>
<td>2006–08</td>
<td>16</td>
<td>0.70</td>
<td>0.43–1.14</td>
</tr>
</tbody>
</table>

8th Report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011; 118:S1
VTEs per 100,000 Deliveries
Abe et al. Sem Perinatol 2019; 43:200

Cesarean

Vaginal
Postpartum VTE Prophylaxis
More Harm / Cost Than Good?

- Overestimation of risk from case-control studies
- Inadequate accounting for chronology of VTE across postpartum period
- Difficulties in risk stratification
- Inadequate assessment of harms of treatment

Kotaska. BJOG 2018; 125:1109
Risk Prediction Model for VTE in Postpartum Women

- Developed and validated using national health databases in England and Sweden
  - 433,353 deliveries in English cohort; 662,387 in Swedish
  - Absolute rates of VTE in 1st 6 weeks PP: 7.2/10,000 and 7.9/10,000
- MLR analysis using candidate predictors \(\rightarrow\) risk equation for predicted absolute risk of PP VTE
- Final model – excellent discrimination (C statistic 0.70)

Sultan et al. BMJ 2016; 355:i6253
Postpartum Thrombosis Risk

The aim of this program is to accurately predict the risk of Venous thromboembolism (VTE) among postpartum women within six weeks of delivery.

Please enter risk factors information:

- Previous VTE/Thrombophilia/Family Hx of VTE
- Varicose veins before delivery
- Comorbidities (Cardiac disease, renal disease or inflammatory bowel disease)
- Eclampsia/Pre-eclampsia
- Smoker
- Postpartum haemorrhage
- Stillbirth
- Postpartum Infection
- Diabetes in pregnancy

Please select antenatal parity:
- Party 3 or more

Enter age at delivery: 35

Pre-pregnancy weight (Kg): 80

Height in meters: 1.52

Baby’s Weight (grams): 3500

Please select delivery method:
- Emergency c-section

Output parameters:

Predicted probability of VTE: 0.0300

Body Mass Index used: 34.5260

Age of delivery assumed: 

Birth weight assumed: 

Interpretation:

If 1000 postpartum women are followed with same risk factors, 30 will develop VTE within 6 weeks of delivery.
Postpartum VTE Prophylaxis
More Harm / Cost Than Good?

• 20 year old with BMI of 32 having cesarean in labor
  • Calculated VTE risk of 1.1/1000 during 6 weeks PP
  • Risk in 1\textsuperscript{st} week PP 0.3/1000

• Assuming 70\% effectiveness of LMWH
  • NNT: 4300 women to prevent 1 VTE
  • In U.S. costs $\rightarrow$ approx $2,225,000 to 3,000,000 per VTE avoided!

Kotaska. BJOG 2018; 125:1109
Postpartum VTE Prophylaxis
More Harm / Cost Than Good?

• Of obstetric VTEs, 30% are pulmonary embolism events (PEs)
  • 2% are fatal
  • Avg woman having a cesarean $\rightarrow$ risk of death from PE in first week
    PP is 0.4/100,000

• If LMWH is 70% effective, NNT to prevent one death is $\sim$360,000

• If LMWH increases risk of major hemorrhage by 0.5% $\rightarrow$ $>$1,000 major hemorrhages per PE death avoided!

Kotaska. BJOG 2018; 125:1109
There’s A Lot We Don’t Know!

• Are current PP thromboprophylactic regimens effective?
  • For how long PP?
• What is the proper balance of the rate of PP VTE versus complications and costs of thromboprophylaxis?
  • How do you risk stratify?
  • Do you treat for an estimated 0.5% rate of PP VTE, 1%, 2%, etc?
• Are there less expensive / safer approaches?
Work Underway

• Retrospective cohort – VTE Incidence
  • Inclusion: All delivered women at 5 institutions
  • Compare women receiving LMWH v no LMWH
  • Outcome: VTE events

• Prospective cohort – LE Doppler
  • Inclusion: Obese (BMI >30 kg/m²) women post-cesarean delivery receiving mechanical but not chemical prophylaxis
  • Outcome: Incidence of asymptomatic DVT identified via Lower extremity Doppler ultrasound on POD# 10-18

• Small RCT – LMWH dosing
  • Inclusion: Women undergoing cesarean delivery & meet facility guidelines for chemical VTE prophylaxis
  • Intervention: Standard dosing v weight-based LMWH dosing
  • Outcome: Prophylactic anti-Factor Xa level

• Future: multi-center RCT – LMWH v Placebo
  • Inclusion: Post-cesarean with risk factors
  • Intervention: Placebo v LMWH (dosing TBD based on prior work)
  • Outcome: VTE (measurement metric TBD based on prior work)
Appendix II: Obstetric antithrombotic risk assessment and management

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

- **HIGH RISK**
  - Requires antenatal prophylaxis with LMWH
  - Refer to trust-nominated thrombosis in pregnancy expert/team

- **INTERMEDIATE RISK**
  - Consider antenatal prophylaxis with LMWH

- **LOWER RISK**
  - No antenatal prophylaxis

Postnatal assessment and management (to be assessed on delivery suite)

- **HIGH RISK**
  - At least 6 weeks' postnatal prophylactic LMWH

- **INTERMEDIATE RISK**
  - At least 60 days' postnatal prophylactic LMWH

- **LOWER RISK**
  - Early mobilisation and avoidance of dehydration

### Antenatal Assessment and Management

- **Any previous VTE except a single event related to major surgery**
- **Hospital admission**
- **Single previous VTE related to major surgery**
- **High-risk thrombophilia**
- **Medical comorbidities e.g., cancer, heart failure, active SLE, IBD or inflammatory polyarthritis, nephritis/nephrotic syndrome, type 1 DM with nephropathy, sickle cell disease, current IVDU**
- **Any surgical procedure e.g., appendicectomy, OHSS (first trimester only)**

### Postnatal Assessment and Management

- **Cessation of breastfeeding**
- **Obesity (BMI > 30 kg/m²)**
- **Age > 35**
- **Parity > 3**
- **Smoker**
- **Gross varicose veins**
- **Current pre-eclampsia**
- **Preeclampsia, e.g., paraplegia, PXP**
- **Family history of unprovoked or new-thrombosis-related VTE in first-degree relative**
- **Low-risk thrombophilia**
- **Multiple pregnancy**
- **FVEART**

### Risk Factors

- **Four or more risk factors:** prophylaxis from first trimester
- **Three risk factors:** prophylaxis from 28 weeks

### Risk Factor Categorization

- **Lower Risk:** Mobilisation and avoidance of dehydration
- **Intermediate Risk:** At least 60 days' postnatal prophylactic LMWH
- **High Risk:** At least 6 weeks' postnatal prophylactic LMWH
## RCOG Recommendations for Antenatal and Postpartum VTE Prophylaxis

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk Factors</th>
</tr>
</thead>
</table>
| 4      | Previous VTE (except for single event related to major surgery)  
        | Ovarian hyperstimulation syndrome (1st trimester only) |
| 3      | Previous VTE provoked by major surgery  
        | Known high-risk thrombophilia  
        | Surgical procedure in pregnancy or puerperium (except repair of perineum)  
        | Hyperemesis  
        | Medical comorbidities, eg, SLE, heart failure, cancer, inflammatory bowel disease, current IV drug user |
| 2      | Cesarean in labor  
        | Obesity (BMI >40) |
| 1      | Family history of unprovoked or estrogen-related VTE in 1st degree relative  
        | Known low-risk thrombophilia  
        | Age >35 years  
        | Obesity (BMI >30)  
        | Parity ≥3  
        | Smoker  
        | Gross varicose veins  
        | Preeclampsia in current pregnancy  
        | ART – IVF (antenatal only)  
        | Multiple pregnancy  
        | Elective cesarean  
        | Mid-cavity rotational operative birth  
        | Prolonged labor (>24 hours)  
        | PPH (>1 liter or transfusion)  
        | Preterm birth <37 weeks in current pregnancy  
        | Stillbirth in current pregnancy  
        | Current systemic infection  
        | Immobility, dehydration |
## Prevention of VTE in Pregnancy

### Personal history of VTE, not on long-term anticoagulation

<table>
<thead>
<tr>
<th>Issue / Scenario</th>
<th>ASH</th>
<th>ACOG</th>
</tr>
</thead>
</table>
| 1 VTE, provoked, nonhormonal* | No AP prophylaxis¹  
Yes PP (pro dose)² | No AP prophylaxis  
No / Yes³ PP (pro dose) |
| 1 VTE, unprovoked or hormonal risk factor** | Yes AP (pro dose)²  
Yes PP (pro dose)² | Yes AP (pro/intrm dose)  
Yes PP (pro/intrm dose) |
| >2 VTEs, on long-term anticoagulation | Yes AP (adj dose)  
Yes PP (adj dose) | Yes AP (adj dose)  
Yes PP (adj dose) |
| Low risk thrombophilia; 1 VTE, not on long-term anticoagulation | Yes AP (pro/intrm dose)  
Yes PP (pro/intrm dose) | Yes AP (pro/intrm dose)  
Yes PP (pro/intrm dose) |
| High-risk thrombophilia; >2 VTEs, not on long-term anticoagulation | Yes AP (pro/intrm/adj dose)  
Yes PP (pro/intrm/adj dose) | Yes AP (pro/intrm/adj dose)  
Yes PP (pro/intrm/adj dose) |

¹ ASH “suggestion”.
² ASH “recommendation”.
³ If additional risk factors are present.
* Strong recommendation; low certainty in evidence.
** Conditional suggestion; low certainty in evidence.
# Prevention of VTE in Pregnancy

**No personal history of VTE; Pos family history of VTE**

<table>
<thead>
<tr>
<th>Issue / Scenario</th>
<th>ASH</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Heteroz FLV or PTm</td>
<td>No AP prophylaxis(^1) No PP prophylaxis(^1)</td>
<td>No / Yes AP (pro dose) Yes PP (pro/intrm dose)</td>
</tr>
<tr>
<td>PC or PS deficiency</td>
<td>No AP prophylaxis(^1) Yes PP (pro dose)(^1)</td>
<td>No / Yes AP (pro dose) Yes PP (pro/intrm dose)</td>
</tr>
<tr>
<td>AT deficiency</td>
<td>Yes AP (pro dose)(^1) Yes PP (pro dose)(^2)</td>
<td>Yes AP (pro/intrm/adj dose) Yes PP (pro/intrm/adj dose)</td>
</tr>
<tr>
<td>Homoz FVL or combined</td>
<td>Yes AP (pro dose)(^1) Yes PP (pro dose)(^1)</td>
<td>Yes AP (pro/intrm/adj dose) Yes PP (pro/intrm/adj dose)</td>
</tr>
<tr>
<td>Homoz PTm</td>
<td>Yes AP (pro dose)(^1) Yes PP (pro dose)(^1)</td>
<td>Yes AP (pro/intrm/adj dose) Yes PP (pro/intrm/adj dose)</td>
</tr>
</tbody>
</table>

\(^1\) ASH “suggestion”.

\(^2\) ASH “recommendation”.

All ASH suggestions or recommendations are conditional and based on very low certainty in evidence except for PP prophylaxis in women with AT deficiency and a family history of VTE (moderate certainty).
## Prevention of VTE in Pregnancy

**No** personal history of VTE; **No** family history of VTE

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<tr>
<td></td>
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<tr>
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<td>Yes PP (pro dose)(^1)</td>
<td>Yes PP (pro/intrm dose)</td>
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\(^1\) ASH “suggestion”.

\(^2\) If additional risk factors are present.

All ASH suggestions are conditional and based on very low certainty in evidence.
<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple prior VTE's</td>
<td>Treatment-dose LMWH or UFH</td>
</tr>
<tr>
<td>Prior VTE with high-risk thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Prior VTE with acquired thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Idiopathic prior VTE</td>
<td>Prophylactic-dose LMWH or UFH</td>
</tr>
<tr>
<td>Prior VTE with pregnancy or on OCP's</td>
<td></td>
</tr>
<tr>
<td>Prior VTE with low-risk thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Family history of VTE with high-risk thrombophilia</td>
<td></td>
</tr>
<tr>
<td>High-risk thrombophilia (including acquired)</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia</td>
<td>No treatment</td>
</tr>
<tr>
<td>Prior VTE provoked</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia and FHx of VTE</td>
<td></td>
</tr>
</tbody>
</table>

### National Partnership for Maternal Safety, 2016
#### Postpartum Recommendations

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple prior VTE's</td>
<td>6 wk treatment-dose LMWH or UFH</td>
</tr>
<tr>
<td>Prior VTE with high-risk thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Prior VTE with acquired thrombophilia</td>
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<tr>
<td>Prior VTE provoked</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia and FHx of VTE</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

# Neuraxial Block in Pregnant Women


<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop low dose UFH, 5000 u BID or TID</td>
<td>Neuraxial block 4 - 6 hours after UFH or coag status be assessed</td>
</tr>
<tr>
<td>Postop low dose UFH</td>
<td>Catheter removal 4 - 6 hours after UFH; subsequent UFH administration may occur 1 hour after catheter removal</td>
</tr>
<tr>
<td>Preop “higher dose” UFH, 7500-10,000 BID (&lt;20,000 daily)</td>
<td>Neuraxial block 12 hours after UFH and assessment of coag status</td>
</tr>
<tr>
<td>Postop “higher dose” UFH</td>
<td>Thoughtful individualization of care with neurologic monitoring</td>
</tr>
</tbody>
</table>

Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition), 2018
Neuraxial Block in Pregnant Women

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop prophylactic LMWH</td>
<td>Neuraxial block &gt;12 hours after LMWH</td>
</tr>
<tr>
<td>Postop prophylactic LMWH</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; dose of LMWH the following day and no earlier than 12 hours after</td>
</tr>
<tr>
<td></td>
<td>needle/catheter placement; remove indwelling catheters prior to LMWH and delay</td>
</tr>
<tr>
<td></td>
<td>LMWH for 4 hours after catheter removal</td>
</tr>
<tr>
<td>Preop higher dose LMWH</td>
<td>Neuraxial block &gt;24 hours after LMWH</td>
</tr>
<tr>
<td>Postop higher dose UFH</td>
<td>LMWH may be resumed 24 hours after non–high-bleeding risk surgery and 48 to 72</td>
</tr>
<tr>
<td></td>
<td>hours after high-bleeding-risk surgery; remove indwelling neuraxial catheters</td>
</tr>
<tr>
<td></td>
<td>4 hours prior to the first postoperative dose and at least 24 hours after</td>
</tr>
<tr>
<td></td>
<td>needle/catheter placement, whichever is greater</td>
</tr>
</tbody>
</table>

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