Thrombosis and Pregnancy

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Venous Thromboembolism (VTE) in Pregnancy

- Prevalence
  - Morbidity and Mortality
- Risk factors
  - Pre-existing
  - Obstetric
- Prevention
- Treatment
Prevalence of VTE in obstetrics

- **Antenatal**
  - 4-6x baseline risk compared to non-pregnant
  - Risk approximately equal throughout three trimesters

- **Postnatal**
  - 60x baseline risk compared to non-pregnant
  - Continues for approximately 3 months
  - Risk of PE particularly increased

- **Overall risk 1-2:1000**
  - 700,000 births/year
  - 700-1400 VTE/year

- **Case fatality rate overall 1% (PE 3.5%)**

References:
- Pomp ER, J Thromb Haemost 2008;6: 632-7
- Knight M, BJOG 2008;115:453–61
VTE and Pregnancy

- VTE is 3rd leading cause of maternal death
- Post thrombotic syndrome (PTS) common
- High risk of recurrence in subsequent pregnancies
Mortality

- Confidential Enquiry into Maternal Deaths
  - Started 1952
  - Triennial report
  - Anonymous
  - Scotland since ‘85
  - Informs policy
    - Local
    - National
  - Most recent 2011-13
Deaths from VTE per million maternities 1950 - 2000.

Significant fall during 1960-70s – due to early mobilization
No more ‘lying in’.

http://www.drcog-mrcog.info/
Maternal death rate from VTE (per 100,000)

Centre for Maternal and Child Enquiries (CMACE) BJOG 2011;118(Suppl. 1):1-203
Impact of RCOG guidelines

- RCOG guideline 1995
  - Highlighted risks of C-section and VTE
    - LMWH recommended with additional risk factors

- RCOG guideline 2004
  - Risk assessment following vaginal delivery
  - LMWH recommended with additional risk factors
Importance of body weight

In 2006-2008 report 12/18 women obese ?underdosing of LMWH

<table>
<thead>
<tr>
<th>Weight</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin (75 u/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg</td>
<td>20 mg daily</td>
<td>2500 units daily</td>
<td>3500 units daily</td>
</tr>
<tr>
<td>50–90 kg</td>
<td>40 mg daily</td>
<td>5000 units daily</td>
<td>4500 units daily</td>
</tr>
<tr>
<td>91–130 kg</td>
<td>60 mg daily*</td>
<td>7500 units daily</td>
<td>7000 units daily*</td>
</tr>
<tr>
<td>131–170 kg</td>
<td>80 mg daily*</td>
<td>10000 units daily</td>
<td>9000 units daily*</td>
</tr>
<tr>
<td>&gt; 170 kg</td>
<td>0.6 mg/kg/day*</td>
<td>75 u/kg/day</td>
<td>75 u/kg/day*</td>
</tr>
<tr>
<td>High prophylactic dose for women weighing 50–90 kg</td>
<td>40 mg 12 hourly</td>
<td>5000 units 12 hourly</td>
<td>4500 units 12 hourly</td>
</tr>
</tbody>
</table>

RCOG guideline, No 37a, 2009

Centre for Maternal and Child Enquiries (CMACE) BJOG 2011;118(Suppl. 1):1-203
### Causes of maternal death (per 100,000)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>2009-11</th>
<th>2010-12</th>
<th>2011-13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>All Direct and Indirect deaths</td>
<td>253</td>
<td>10.63</td>
<td>9.36–12.03</td>
</tr>
<tr>
<td>Direct deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis*</td>
<td>15</td>
<td>0.63</td>
<td>0.35–1.04</td>
</tr>
<tr>
<td>Pre-eclampsia and eclampsia</td>
<td>10</td>
<td>0.42</td>
<td>0.2–0.77</td>
</tr>
<tr>
<td>Thrombosis and thromboembolism</td>
<td>30</td>
<td>1.26</td>
<td>0.85–1.80</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td>7</td>
<td>0.29</td>
<td>0.12–0.61</td>
</tr>
<tr>
<td>Early pregnancy deaths</td>
<td>4</td>
<td>0.17</td>
<td>0.05–0.43</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>14</td>
<td>0.59</td>
<td>0.32–0.99</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>3</td>
<td>0.12</td>
<td>0.03–0.37</td>
</tr>
<tr>
<td>All Direct</td>
<td>83</td>
<td>3.49</td>
<td>2.78–4.32</td>
</tr>
</tbody>
</table>
Timing of VTE deaths

- 48 died (43 PE, 5 CVT)
  - Antenatal 24 (50%)
    - 12 (50%) - First trimester
    - 6 (25%) - Second trimester
    - 6 (25%) - Third trimester
  - Postnatal 24 (50%)
    - C-section 12 (50%)
      - 9 (66%) Emergency
      - 3 (33%) Elective
    - 10 (40%) vaginal
    - 2 (10%) post surgical procedures
- 16 - Late deaths (up to one year)
  - 13 PE; 3 CVT

Saving Lives, Improving Mothers’ care UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13 MBRRACE 2015
**Key Issues**

- Just over 50% care suboptimal
- Just over 50% not compliant with RCOG guideline
- Risk assessment as early as possible in pregnancy
  - 52% women were not either not risk assessed or LMWH was under-dosed
  - 50% deaths in first trimester
    - Too early for current risk assessment
- Careful consideration of symptoms remains essential
  - Involve obstetricians when pregnant and post partum women present with symptoms of VTE to emergency care
- Avoid late and missed doses
  - Prescribe full course of LMWH for post partum period from secondary care
## Risk factors for VTE in pregnancy

Modified from RCOG guideline, No 37a, 2015

<table>
<thead>
<tr>
<th>Pre-existing</th>
<th>Previous VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombophilia</strong></td>
<td><strong>Heritable</strong></td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td></td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td></td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>Persistent lupus anticoagulant and/or persistent moderate/high titre anticardiolipin antibodies and/or $\beta_2$-glycoprotein 1 antibodies</td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities e.g. cancer; heart failure; active SLE, inflammatory polyarthritis or IBD; nephrotic syndrome; type 1 diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user</td>
<td></td>
</tr>
<tr>
<td>Age $\geq$ 35 years</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI $\geq$ 30 kg/m²) either prepregnancy or in early pregnancy</td>
<td></td>
</tr>
<tr>
<td>Parity $\geq$ 3 (a woman becomes para 3 after her third delivery)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)</td>
<td></td>
</tr>
<tr>
<td>Paraplegia</td>
<td></td>
</tr>
</tbody>
</table>
# Risk factors for VTE in pregnancy

Modified from RCOG guideline, No 37a, 2015

| Obstetric risk factors                                      | Multiple pregnancy  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current pre-eclampsia</td>
</tr>
<tr>
<td>Caesarean section</td>
<td></td>
</tr>
<tr>
<td>Prolonged labour (&gt; 24 hours)</td>
<td></td>
</tr>
<tr>
<td>Mid-cavity or rotational operative delivery</td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
</tr>
<tr>
<td>Postpartum haemorrhage (&gt; 1 litre/requiring transfusion)</td>
<td></td>
</tr>
</tbody>
</table>

| New onset/transient                                         | Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone fracture</td>
</tr>
<tr>
<td><strong>These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve and therefore what is important is an ongoing individual risk assessment</strong></td>
<td>Hyperemesis, dehydration</td>
</tr>
</tbody>
</table>
|                                                             | Ovarian hyperstimulation syndrome (first trimester only)  
|                                                             | Assisted reproductive technology (ART), in vitro fertilisation (IVF) |
|                                                             | Admission or immobility (≥ 3 days’ bed rest)  
|                                                             | e.g. pelvic girdle pain restricting mobility                                                                                     |
|                                                             | Current systemic infection (requiring intravenous antibiotics or admission to hospital)  
|                                                             | e.g. pneumonia, pyelonephritis, postpartum wound infection                                                                   |
|                                                             | Long-distance travel (> 4 hours)                                                                                                 |
Evidence for use of antepartum LMWH

- Some evidence
  - PMH
    - Idiopathic/estrogen induced
    - Associated thrombophilia
  - FH
    - Idiopathic/estrogen induced with associated thrombophilia
  - Synergism of risk factors
    - Very little
      - ART/multiple pregnancy (additive)
      - Immobility/BMI (multiplicative)

Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or estrogen-provoked VTE in a first-degree relative when aged under 50 years should be considered for thrombophilia testing. This will be more informative if the relative has a known thrombophilia. [New 2015]

- **Hypothesis**
  - Thrombophilia has a strong phenotype
  - Thrombophilia affected relative
  - Therefore thrombophilia might affect you
Antenatal assessment and management (to be assessed at booking and repeated if admitted)

Any previous VTE except a single event related to major surgery

Hospital admission
Single previous VTE related to major surgery
High-risk thrombophilia + no VTE
Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
Any surgical procedure e.g. appendicectomy
OHSS (first trimester only)

Obesity (BMI > 30 kg/m²)
Age > 35
Parity ≥ 3
Smoker
Gross varicose veins
Current pre-eclampsia
Immobility, e.g. paraplegia, PGP
Family history of unprovoked or estrogen-provoked VTE in first-degree relative
Low-risk thrombophilia
Multiple pregnancy
IVF/ART

Transient risk factors:
Dehydration/hyperemesis; current systemic infection; long-distance travel

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

INTERMEDIATE RISK
Consider antenatal prophylaxis with LMWH

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

LOWER RISK
Mobilisation and avoidance of dehydration

Modified from RCOG guideline, No 37a, 2015
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

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

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

Two or more risk factors

LOWER RISK
Early mobilisation and avoidance of dehydration

Fewer than two risk factors

Modified from RCOG guideline, No 37a, 2015
Appendix III: Risk assessment for venous thromboembolism (VTE)

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score ≥ 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (> 3 days) or readmission to hospital within the puerperium consider thromboprophylaxis.

For patients with an identified bleeding risk, the balance of risks of bleeding and thrombosis should be discussed in consultation with a haematologist with expertise in thrombosis and bleeding in pregnancy.

<table>
<thead>
<tr>
<th>Pre-existing risk factors</th>
<th>Risk factors for VTE</th>
<th>Risk factors for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE (except a single event related to major surgery)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Previous VTE provoked by major surgery</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Known high-risk thrombophilia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthritis or inflammatory bowel disease; nephrotic syndrome; type 1 diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Family history of unprovoked or estrogen-related VTE in first-degree relative</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Known low-risk thrombophilia (no VTE)</td>
<td>1^2</td>
<td></td>
</tr>
<tr>
<td>Age (&gt; 35 years)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1 or 2^3</td>
<td></td>
</tr>
<tr>
<td>Parnity ≥ 3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gross varicose veins</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obstetric risk factors</th>
<th>Risk factors for VTE</th>
<th>Risk factors for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia in current pregnancy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ART/IVF (antenatal only)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Caesarean section in labour</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Elective caesarean section</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mid-cavity or rotational operative delivery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prolonged labour (&gt; 24 hours)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PPH (&gt; 1 litre or transfusion)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt; 37th weeks in current pregnancy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stillbirth in current pregnancy</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transient risk factors</th>
<th>Risk factors for VTE</th>
<th>Risk factors for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hyperemesis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>OHSS (first trimester only)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Current systemic infection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Immobility, dehydration</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL 10
VTE treatment
Significant changes in 2015 RCOG guidelines
Diagnosis – Significant changes

- If ultrasound negative and a high level of clinical suspicion
  - Anticoagulant treatment should be discontinued
  - Repeat USS on days 3 and 7
- Safe to discontinue anticoagulation
- Similar method used in non-pregnant population
- If do not discontinue anticoagulation between scans, extension will be prevented and false reassurance obtained

RCOG guideline 37b, April 2015
Chan et al., CMAJ 2013;185:E194–200
Diagnosing PE

- Perform CXR and ECG

- Suspected PE with symptoms and signs of DVT
  - Compression duplex ultrasound should be performed

- Suspected PE without symptoms and signs of DVT
  - Ventilation/perfusion (V/Q) lung scan
  - Computerised tomography pulmonary angiogram (CTPA) (preferred if CXR abnormal)

- Advice to women with suspected PE
  - Compared with CTPA
    - V/Q scanning slightly increased risk of childhood cancer
    - Lower risk of maternal breast cancer
    - In both situations, the absolute risk is very small

RCOG guideline 37b, April 2015
Treatment – Significant changes

• LMWH can be given once daily or in two divided doses
  ◦ Multicentre study - 60% units give once daily
  ◦ UKOSS study - 49% units give once daily
  ◦ Aus/NZ guidelines state no evidence to prefer either
  ◦ Data for once daily dosing with tinzaparin
  ◦ Half life of LMWH increases during pregnancy with once daily dosing regimen

• Advantages
  ◦ Patient satisfaction
  ◦ Improved chance of safe regional anaesthesia use

Dosing of LMWH in pregnancy

<table>
<thead>
<tr>
<th>Booking or early pregnancy weight</th>
<th>Initial dose of enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg</td>
<td>40 mg twice daily or 60 mg once daily</td>
</tr>
<tr>
<td>50–69 kg</td>
<td>60 mg twice daily or 90 mg once daily</td>
</tr>
<tr>
<td>70–89 kg</td>
<td>80 mg twice daily or 120 mg once daily</td>
</tr>
<tr>
<td>90–109 kg</td>
<td>100 mg twice daily or 150 mg once daily</td>
</tr>
<tr>
<td>110–125 kg</td>
<td>120 mg twice daily or 180 mg once daily</td>
</tr>
<tr>
<td>&gt; 125 kg</td>
<td>Discuss with haematologist</td>
</tr>
</tbody>
</table>

**Issues**

- Syringe sizes not available in 90 mg
- Check antiXa if syringe size is >10% from 1.5mg/kg dose
  - e.g. 55kg = 1.5x55 = 82.5 mg
  - 100mg, 17.5% larger than recommended dose

RCOG guideline 37b, April 2015
Treatment

• Postpartum warfarin should be avoided until at least the fifth day (for longer in women at increased risk of postpartum haemorrhage)
  ◦ No evidence for advice
  ◦ Higher doses may be required with associated close monitoring

• Direct oral anticoagulants
  ◦ Suitable alternative if not breastfeeding
  ◦ More convenient for mother
    • No monitoring
    • Not affected by diet/most drugs
  ◦ Probably should also wait 5 days
    • Possible signal of increased menstrual loss
Treatment – new information

- Following a DVT, graduated elastic compression stockings should be worn on the affected leg to reduce pain and swelling
  - Role of compression stockings in the prevention of post-thrombotic syndrome remains unclear.

- SOX study
  - Placebo vs. compression stocking
  - No difference in outcomes at 2 years

Kahn et al., Lancet 2014, 383: 880
Any Questions??

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