VTE in pregnancy: perils and pitfalls

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Disclosures

• I am lead developer of RCOG Green Top Guideline on thromboprophylaxis in pregnancy

• I have received lecturing fees from Sanofi-Aventis, Leo-Pharma
Lecture Plan

IMPORTANCE (perils)

PREVENTION- the RCOG guideline

CONTROVERSIES IN DIAGNOSIS (pitfalls)

TREATMENT OF ACUTE VTE (pitfalls)
Triennial mortality rates UK 2003-14

- Direct and Indirect maternal death rate
  - P-value for trend across time = 0.018

- Indirect maternal death rate
  - P-value for trend across time = 0.220

- Direct maternal death rate
  - P-value for trend across time = 0.031

Test for trend over period 2003-value for trend across time = 0.003
Figure 2.4: Maternal mortality by cause 2012–14
Maternal deaths from VTE

RCOG Thromboprophylaxis Guidelines

Rate per million maternities

Timing of deaths from VTE

- 50% (24) thromboses occurred antenatally (some died postnatally)
  - 50% (12) delivered by CS (9 emCS; 3 elCS)
  - 10 delivered vaginally
  - 2 post surgical procedures in early pregnancy

- 50% (24) occurred postnatally
Risk factors
(among women who died during or up to six weeks after pregnancy)

- 40 (83%) had risk factors
- 8 (17%) had no risk factors

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<td>3</td>
<td>13</td>
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<td>4</td>
<td>6</td>
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<td>5</td>
<td>3</td>
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<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>
The new RCOG guidelines

Treatment
Prevention

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b
April 2015
Absolute incidence VTE

UK study using prospective primary care database of 972 683 women aged 15–44 years (1987 and 2004):

**107 per 100 000 person years** (95% CI 93-122 per 100 000 person years) *(Sultan et al. BJH 2012)*


**10.7 per 10,000** pregnancy-years during pregnancy

**17.5 per 10,000** puerperal-years during the puerperium


**DVT 12.1 per 10,000 pregnancies**

**PE 5.4 per 10,000 pregnancies**
Pathogenesis: Virchow’s triad

Endothelial injury

↑ Venous distension causing endothelial injury
↑ Trauma during delivery

Thrombosis

↑ Coagulation factors
↓ Natural inhibitors of coagulation
↓ Fibrinolytic activity

Venous stasis

↑ Sluggish blood flow during pregnancy
↑ Compression on inferior vena cava by enlarging uterus
↑ Rest/supine position later in pregnancy

Hypercoagulability

Kyrle and Eichinger Blood 2009;11:1138–9
The distribution of VTE in pregnancy and puerperium

VTE incidence:
- 1st trimester: 10.1%
- 2nd trimester: 10.4%
- 3rd trimester: 28.4%

49.3% of VTE occurred during the first 6 weeks postpartum.

Figure 2: Log$_{10}$ of the rate of VTE and 95% confidence intervals during different time periods during and outside pregnancy

**Outside pregnancy**: Includes time for ever pregnant women spent outside antepartum and postpartum period and all time for women with no recorded pregnancy during study period

**Early postpartum**: First six weeks from date of delivery

**Late postpartum**: Subsequent six weeks postpartum

Age

The diagram shows the rate per 100,000 maternities with 95% CI for different age groups. The age groups are:
- <25
- 25-29
- 30-34
- ≥35

The rates increase with age, with the highest rate seen in the ≥35 age group.
### Rate of VTE per 100,000 person years by antenatal admission to hospital and after hospital stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of VTE</th>
<th>Rate* (95% CI)</th>
<th>Adjusted IRR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time outside hospital</td>
<td>150</td>
<td>97 (83 to 114)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>6</td>
<td>1752 (787 to 3900)</td>
<td>17.5 (7.69 to 40.0)</td>
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<tr>
<td>After discharge</td>
<td>20</td>
<td>676 (436 to 1048)</td>
<td>6.27 (3.74 to 10.5)</td>
</tr>
</tbody>
</table>

**Variation by duration of hospital stay (combining admission/after discharge)**

| Time outside hospital     | 150       | 97 (83 to 114)          | 1.00                   |
| <3 days                   | 13        | 558 (331 to 943)        | 4.05 (2.23 to 7.38)    |
| ≥3 days                   | 13        | 1511 (858 to 2661)      | 12.2 (6.65 to 22.7)    |

IRR=incidence rate ratio.
*Rate calculated per 100,000 person years.
†Adjusted for maternal age, calendar year, BMI, gestational infection, cardiac disease, varicose vein, gestational diabetes, and hyperemesis.
Fig 2 Rate of venous thromboembolism per 100,000 person years by weeks after discharge during antepartum period: 12 events in weeks 1-2 after discharge, 7 events in weeks 3-4 after discharge, and 12 events in weeks 5-10 after discharge.
Risk of a Thrombotic Event after the 6-Week Postpartum Period

Hooman Kamel, M.D., Babak B. Navi, M.D., Nandita Sriram, B.S., Dominic A. Hovsepian, B.S., Richard B. Devereux, M.D., and Mitchell S.V. Elkind, M.D.

California, 2005-2010

1.7 million women, first delivery

1015 thrombotic events in 1 year and 24 weeks post delivery

47 MI; 248 CVA; 720 VTE
<table>
<thead>
<tr>
<th>Weeks Post partum</th>
<th>VTE OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>12.1</td>
<td>7.9 to 18.6</td>
</tr>
<tr>
<td>7-12</td>
<td>2.2</td>
<td>1.4 to 3.3</td>
</tr>
<tr>
<td>13-18</td>
<td>1.6</td>
<td>1.0 to 2.5</td>
</tr>
<tr>
<td>18-24</td>
<td>0.9</td>
<td>0.5 to 1.4</td>
</tr>
</tbody>
</table>

**Figure 1. Risk of a Thrombotic Event, According to the Interval after Delivery.**

Shown are the results of a post hoc exploratory analysis of the risk of a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism across sequential 3-week periods after labor and delivery, as compared with each patient’s risk during the same period 1 year later. The thrombotic risk was still increased during the period of 13 to 15 weeks after delivery (odds ratio, 2.0; 95% CI, 1.1 to 3.6) but was no longer elevated in the period of 16 to 18 weeks after delivery (odds ratio, 1.0; 95% CI, 0.6 to 1.8). The vertical lines indicate 95% confidence intervals.
Appendix I: Obstetric thromboprophylaxis risk assessment and management

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 1 DM with nephropathy, sickle cell disease, current NDU
- Any surgical procedure e.g. appendicectomy
- CHSS (first trimester only)

**HIGH RISK**
Requires antenatal prophylaxis with LMWH

Refer to trust-nominated thrombosis in pregnancy expert/team

**INTERMEDIATE RISK**
Consider antenatal prophylaxis with LMWH

- Obesity (BMI > 30 kg/m²)
- Age > 40
- 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
- NVT/ART

**LOWER RISK**
Mobilisation and avoidance of dehydration

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

Four or more risk factors:
- Prophylaxis from first trimester

Three risk factors:
- Prophylaxis from 28 weeks

Fewer than three risk factors

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

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

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

- 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 NDU

**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 (< 37º weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (> 24 hours)
- PPH > 1 litre or blood transfusion
- PPHH > 30 units/daily

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

- Antenatal and postnatal prophylactic dose of LMWH
- Weight < 50 kg: 50 mg enoxaparin/3000 units dalteparin/3500 units tinzaparin daily
- Weight 50–59 kg: 60 mg enoxaparin/4500 units dalteparin/5000 units tinzaparin daily
- Weight 60–70 kg: 70 mg enoxaparin/6000 units dalteparin/7000 units tinzaparin daily
- Weight 71–100 kg: 80 mg enoxaparin/7500 units dalteparin/10000 units tinzaparin daily
- Weight > 70 kg: 0.6 mg/kg/day enoxaparin/75 units/kg/day dalteparin/75 units/kg/day tinzaparin
### Appendix III: Risk assessment for venous thromboembolism (VTE)

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>Risk factors for VTE</th>
<th>Tick</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-existing risk factors</strong></td>
<td></td>
<td></td>
</tr>
<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 I 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*</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*</td>
<td></td>
</tr>
<tr>
<td>Parity &gt; 3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>History of varicose veins</td>
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<td></td>
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<tr>
<td><strong>Obstetric risk factors</strong></td>
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<tr>
<td>Pre-eclampsia in current pregnancy</td>
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<tr>
<td>ART/ IVF (antenatal only)</td>
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<tr>
<td>Multiple pregnancy</td>
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<td></td>
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<tr>
<td>Caesarean section in labour</td>
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<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>PPV (&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>
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<tr>
<td><strong>Transient risk factors</strong></td>
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<td></td>
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<tr>
<td>Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendectomy, postpartum sterilization</td>
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<tr>
<td>Hypertension</td>
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<td>OHSS (first trimester only)</td>
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<tr>
<td>Current systemic infection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Immobility, dehydration</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.

**BMI**: 18 ≤ BMI < 25 = 1; 25 ≤ BMI < 30 = 2; 30 ≤ BMI = 3
Case 1

39 yr old multip, 38 weeks
Secondary infertility; IVF pregnancy
Admission for ovarian hyperstimulation syndrome
A+E: C/O swollen, painful left leg for 3 weeks
Sudden onset left sided pleuritic pain last night
SOB since
O/E dyspnoeic, RR 34, SOBOE undressing
Pulse 118, BP 104/66
Oxygen saturation 92%
Diagnosis of DVT in Pregnancy

88% on left (vs. 55% in non pregnant)
71% proximal (vs. 9% in non pregnant)
  • 64% were restricted to the iliac and/or femoral vein.

Chan WS et al. CMAJ 2010; 182:657-60
Diagnosis

DVT
  Doppler US
PE
  CXR
  V/Q Lung scan
  CTPA

D dimers are useless!!

Unless pregnancy specific ranges are used
US may miss below knee / above inguinal ligament. Solution:

If US negative and high level of clinical suspicion of DVT......

• stop anticoagulation and repeat US day 3 and 7
• Do MR venogram

Prevalence of ultimately diagnosed PE in pregnant women with suspected PE is 2–6%. Solution:

• Stop irradiating women without good history!
• Half dose perfusion only
35 year old
1 day post first normal vaginal delivery
C/O chest pain
Obstetric SHO requests CTPA
Medical registrar asked to review - told CXR normal
Not all chest pain / SOB is a PE
Clinicians should be aware that, at present, there is no evidence to support the use of pretest probability assessment in the management of acute VTE in pregnancy. [New 2015]

**DiPEP:** collect data 18 months all UK hospitals, 150 women diagnosed with PE in pregnancy using UKOSS

250 pregnant women attending 8 selected hospitals who have suspected PE.

Identify which patient characteristics predict whether a woman actually has PE or not.

Test whether existing clinical prediction rules can identify PE in pregnancy, and whether a new or improved rule works better in pregnancy.
Systematic Review and Meta-analysis of Pregnant Patients Investigated for Suspected Pulmonary Embolism in the Emergency Department

Jeffrey A. Kline, MD, Danielle M. Richardson, Martin P. Than, MBBS, Andrea Penaloza, MD, PhD, and Pierre-Marie Roy, MD

frequency of VTE non-preg 12.4% (95% CI = 9.0% to 16.3%)

frequency of VTE 506 preg 4.1% (95% CI = 2.6% to 6.0%)
## Radiation exposure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rads</th>
<th>mGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Perfusion scan</td>
<td>&lt;0.08</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Ventilation scan</td>
<td>&lt;0.01</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>CTPA / Helical CT</td>
<td>&lt;0.013</td>
<td>&lt;0.13</td>
</tr>
<tr>
<td>Max recommended</td>
<td>&lt;0.5</td>
<td>5</td>
</tr>
</tbody>
</table>
Increased risk of fatal childhood cancer to the age of 15 following in utero radiation exposure = 0.006% per mGy, (1 in 17 000 per mGy).

The fetal radiation exposure associated with CTPA = 0.1 mGy
V/Q = 0.5 mGy

- 10 mGy radiation (CTPA) to a woman’s breast increases lifetime risk of developing breast cancer by 13.6% above her background risk

- V/Q investigation of first choice for young women especially if FH of breast CA or patient has had previous chest CT scan

- Higher rate of nondiagnostic scans in pregnancy with CTPA (37.5%) V/Q (4%)

(may be related to the imaging protocol employed).

304 women with a clinical suspicion of PE

Primary outcome =

nondiagnostic study for PE (CTPA)

"low or intermediate probability" in the V/Q group.

Initial diagnostic test =

CTPA in 108 (35.1%)

V/Q in 196 (64.9%)

Higher rate of nondiagnostic study CTPA (17.0% compared with 13.2%, P=.38)

Subgroup of women with a normal chest X-ray,

CTPA more likely to yield a nondiagnostic result than V/Q even after adjusting

30.0% cf 5.6%, adj OR = 5.4, 95% CI 1.4-20.1, P<.01).

Diagnostic algorithm for PE in pregnancy

**Suspected PE**
- ABG, ECG, CXR

**Start anticoagulation LMWH treatment dose**

**UNSTABLE**
- Clinically urgent (out of hours)

**STABLE**
- DOPPLER USS LEGS
  - +ve
    - Portable echo
      - Suggestive of massive PE
      - +ve
        - Thrombolysis/i.v. heparin/thrombectomy
      - -ve
        - Stop anticoagulation
        - Still suspicious of PE
          - -ve
            - CTPA
              - +ve
                - Thrombolysis/i.v. heparin/thrombectomy
              - -ve
                - Stop anticoagulation
                - +ve
                  - Anticoagulate with LMWH

- -ve
  - V/Q scan
    - +ve
      - Anticoagulate with LMWH
    - -ve
      - CXR normal
      - CXR abnormal
        - -ve
          - Anticoagulate with LMWH
          - +ve
            - Thrombolysis/i.v. heparin/thrombectomy

ABG, arterial blood gas; ECG, electrocardiogram; CXR, Chest X-ray; USS, ultrasound sonography; CTPA, computerised tomography pulmonary angiography

Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small.

Recent studies have shown a superior sensitivity and specificity when using V/Q single photon emission computed tomography (SPECT) in diagnosing PE than conventional planar V/Q scintigraphy and this may safely be performed in pregnancy.
6.2 What is the therapeutic dose of LMWH in pregnancy?

LMWH should be given in doses titrated against the woman’s booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. [C]

There should be clear local guidelines for the dosage of LMWH to be used. [GPP]
Treatment: Dose of LMWH

Give while waiting for confirmation

Enoxaparin 1mg/kg/bd

NOT 1.5 mg/kg od (= non-pregnant dose)

Higher doses of dalteparin also recommended

Usual dose of tinzaparin 175 u/kg/day

LMWH should be given in doses titrated against the woman’s booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. [New 2015] C
**Thrombolysis**

For massive life threatening PE with haemodynamic compromise

**Systematic review** - 29 articles, 189 patients

No maternal deaths

1.6% major bleeding events in largest series (122 pts)

67 other pts

- 3 major, 2 minor bleeding events,
  - 3 fetal deaths

_Ahearn et al. Arch Int Med 2002_

_Eric J Gartman. Obstetric Medicine 2013;6:105-111_
Consideration should be given to the use of a temporary inferior vena cava filter in the peripartum period for patients with iliac vein VTE to reduce the risk of PE or in patients with proven DVT and who have recurrent PE despite adequate anticoagulation. D
Intrapartum management

Treat for as long as possible before delivery

Liaise with obstetric anaesthetist

OK to interrupt LMWH for 24hrs if > 2/52 Rx

Consider siting epidural at this time

? Convert to UH

No place for a caval filter
Indications, Complications, and Management of Inferior Vena Cava Filters

The Experience in 952 Patients at an Academic Hospital With a Level I Trauma Center

Shayna Sarosiek, MD; Mark Crowther, MD; J. Mark Sloan, MD

**Conclusion and Relevance:** Our research suggests that the use of IVC filters for prophylaxis and treatment of venous thrombotic events, combined with a low retrieval rate and inconsistent use of anticoagulant therapy, results in suboptimal outcomes due to high rates of venous thromboembolism.
Post partum management acute VTE

Drop dose to 1.5 mg/kg/day
Continue LMWH for 6 weeks
Switch to warfarin > 5 days post delivery
Contraceptive issues
Did you know that blood clots are more common in the first few weeks after giving birth?

Have you asked about your anti-clot injection?

Check with your midwife or with your doctor whether you need one.