Venous Thromboembolism (VTE) in Pregnancy

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Pathogenesis of VTE in Pregnancy

Virchow’s triad of factors underlying VTE all occur in pregnancy

**Hypercoagulability**

- Increase Fibrin generation
- Decrease fibrinolytic activity
- Increase II, VII, VIII, X
- Decrease free protein S levels
- Acquired APCR

**Venous Stasis**

- Progesterone-mediated increases in venous distensibility cause an increase in venous stasis.

  Reduction in venous flow velocity up to 50% occurs in the legs by 3rd trimester and lasts until approximately 6 weeks after delivery

**Endothelial Damage**

Endothelial damage to pelvic vessels can occur secondary to compression of the inferior vena cava and iliac veins by the pregnant uterus and resulting stasis or during vaginal or abdominal delivery.
THROMBOEMBOLISM IN O&G

- VTE risks is 5-6 X higher in pregnant women compared to non pregnant women
- PE in 24% of untreated VTE and 15% of PE fatal
- Major cause of marternal morbidity and mortality
- 17% maternal deaths in western world
VTE in Pregnancy

- 2/3 of VTEs occurred in the antepartum period and distributed equally among 3 trimesters
- Risk of postpartum VTE is about 3X that of antenatal VTE
- 43 - 60% of PE appear to occur in the puerperium.

Almost 90% of DVTs occur on the **LEFT** side in pregnant women compared with 55% among women who are not pregnant.

*R Iliac artery compressing on L Iliac Vein*

*Lancet 1999;353:1258–65*

*Thromb Haemost 1992;67:519–20*
Incidence of VTE in Pregnancy

- Estimated at 0.76 to 1.72 per 1000 pregnancies
- 4X the risk in the non-pregnant population
- Incidence in Asia Unknown


Venous Thromboembolism in ASIA

- Perceived as rare in Orientals / Asians

- Perception re-inforced
  - Absence of Factor V leiden in Orientals
  - Absence of Prothrombin 20210 in Orientals

- Increasing trend in DVT prevalence among hospitalised patients noted
  - 0.453% (2002-2003)
  - 0.158% (1996–1997)
  - 0.079% (1989–1990)

Absence of Pulmonary Embolism in Asians Br Med J 1964
Trends in prevalence of VTE.... Ng HJ, Lee LH. Thromb Haemost 2009; 101: 1095–1099
Maternal VTE- Hong Kong

January 1998 to December 2000

- 32 women diagnosed with VTE (80% calf DVT, 2 PE, 1 died)
- Incidence of 1.88 per 1000 deliveries (total 16,993 deliveries)
- Western incidence of VTE ranges from 0.6 to 1.3 episodes per 1,000 deliveries

Increase in U/S request and VTE diagnosed

- Doppler US requests for suspected DVT before and after the event of maternal death were 1.62 and 10.7 per 1000 deliveries (P <.001);
- Corresponding cases of deep venous thrombosis diagnosed were 0.29 and 2.94 per 1000 deliveries, respectively (P <0.001)

8th ACCP, Chest June 2008
Maternal Mortality - Singapore

- **Chen LH 1997 - maternal deaths (92-95)**
  - 3/7 die from PE.
  - 4.9 per 100 000 maternities

- **Maternal Mortality 1990 to 1999 (Lau G 2002)**
  - 51 cases of maternal deaths
  - Amniotic fluid embolism -16 deaths (rate 3.3 per 10,000 life births)
  - Massive Pulmonary embolism - 10 deaths (2.1 per 10,000 life births)

Reduction of Maternal mortality from PE

- Prophylaxis of those with increased risks for VTE
- Aggressive investigations in those with suspected VTE to facilitate early treatment

Evidence for VTE prevention strategies and anticoagulant regimes based limited data from pregnant subjects and often extrapolated from non-pregnant subjects
VTE Prophylaxis – Risk Stratified Approach

AETIOLOGICAL RISK FACTORS

- Age >38 years,
- Para 4 or more
- Obesity
- Pre-eclampsia
- Hospitalization and restricted activity
- Method of delivery - emergency LSCS
- Extended major surgery - Caesarean hysterectomy, LSCS plus ovarian cystectomy
- Past history of deep vein thrombosis or pulmonary embolism
- Lupus-anticoagulant-associated thrombotic disease
- Hereditary thrombotic diseases
  - PC, PS, AT deficiencies
  - Hyperhomocysteinaemia from MTHFR mutation
  - Prothrombin G20210A, Factor V Leiden
Antenatal assessment and management (to be assessed at booking and repeated if admitted)

**Obstetric thromboprophylaxis risk assessment and management**

**High risk**
Requires antenatal prophylaxis with LMWH
Refer trust-nominated thrombosis in pregnancy expert/team

**Intermediate risk**
Consider antenatal prophylaxis with LMWH
Seek trust-nominated thrombosis in pregnancy expert/team advice

**Lower risk**
Mobilisation and avoidance of dehydration

- Single previous VTE+
  - Thrombophilia or family history
  - Unprovoked/oestrogen-related
  - Previous recurrent VTE (>1)

- Single previous VTE without family history or thrombophilia
- Thrombophilia + no VTE
  - Medical comorbidities, e.g. heart or lung disease, SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, intravenous drug use
  - Surgical procedure, e.g. appendectomy

- Age > 35 years
- Obesity (BMI > 30 kg/m²)
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, SPD, long-distance travel
- Pre-eclampsia
- Dehydration/hyperemesis/OHSS
- Multiple pregnancy or ART

3 or more risk factors
2 or more if admitted
< 3 risk factors

RCOG Green-top Guideline No. 37 2009
Postnatal assessment and management (to be assessed on delivery suite)

Obstetric thromboprophylaxis risk assessment and management

Any previous VTE+ Anyone requiring antenatal LMWH

Caesarean section in labour Asymptomatic thrombophilia (inherited or acquired) BMI > 40 kg/m² Prolonged hospital admission MEDICAL COMORBIDITIES, e.g. heart or lung disease, SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, intravenous drug user

Age > 35 years Obesity (BMI >30kg/m²) Parity ≥ 3 Smoker Elective caesarian section Any surgical procedure in the puerperium Gross varicose veins Current systemic infection Immobility, e.g. paraplegia, SPD, long distance travel Pre-ecampsia Mid-cavity rotational operative delivery Prolonged labour (> 24 hours) PPH >1 litre or blood transfusion

High risk At least 6 weeks postnatal prophylactic LMWH

Intermediate risk At least 7 days postnatal prophylactic LMWH Note: if persisting or > 3 risk factors, consider extending thromboprophylaxis with LMWH

Lower risk Mobilisation and avoidance of dehydration

RCOG Green-top Guideline No. 37 2009
# VTE Prophylaxis – Previous VTE and Thrombophilia

<table>
<thead>
<tr>
<th>Risk</th>
<th>History</th>
<th>Prophylaxis</th>
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</thead>
<tbody>
<tr>
<td>Very high</td>
<td>Previous VTE on long-term warfarin</td>
<td>Recommend antenatal high-dose LMWH and at least 6 weeks postnatal LMWH/warfarin</td>
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<tr>
<td></td>
<td>Antithrombin deficiency</td>
<td>Requires specialist management by experts in haemostasis and pregnancy</td>
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<td></td>
<td>Antiphospholipid syndrome with previous VTE</td>
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<tr>
<td>High</td>
<td>Previous recurrent or unprovoked VTE</td>
<td>Recommend antenatal and 6 weeks postnatal prophylactic LMWH</td>
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<tr>
<td></td>
<td>Previous estrogen-provoked (pill or pregnancy) VTE</td>
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<tr>
<td></td>
<td>Previous VTE + thrombophilia</td>
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</tr>
<tr>
<td></td>
<td>Previous VTE + family history of VTE</td>
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<td></td>
<td>Asymptomatic thrombophilia (combined defects, homozygous FVL)</td>
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<tr>
<td>Intermediate</td>
<td>Single previous VTE associated with transient risk factor no longer present without thrombophilia, family history or other risk factors</td>
<td>Consider antenatal LMWH (but not routinely recommended)</td>
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<td></td>
<td>Recommend 6 weeks postnatal prophylactic LMWH</td>
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<td></td>
<td></td>
<td>Recommend 7 days (or 6 weeks if family history or other risk factors)</td>
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<td>postnatal prophylactic LMWH</td>
</tr>
</tbody>
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FVL = factor V Leiden; LMWH = low-molecular-weight heparin

*RCOG Green-top Guideline No. 37 2009*
Thrombophilia and VTE in Pregnancy

Presence of thrombophilia in pregnancy (a hypercoagulable state) does not always result in VTE

• About 50% of cases of VTE in pregnancy assoc with thrombophilia
• Inherited thrombophilias are common, affecting 15% of Western populations
• VTE occurs in only 0.1% of pregnancies
• Routine screening of pregnant women is not cost-effective

Thromboembolism Prophylaxis

- Thrombotic risk assessment
- Thromboprophylaxis initiated according to risk stratification
- Each patient considered individually
Guidelines on Treatment and Prophylaxis

Clinical Practice Guideline on DVT Prophylaxis in Obstetrics and Gynaecology

Statement of Intent

The clinical practice guideline is not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

These parameters of practice are based on the best available evidence at the time and reflect a consensus of experts in the field.

Reducing the Risk of Thrombosis and Embolism During Pregnancy and the Puerperium

This is the second edition of this guideline, which was published in 2004 under the title 'Thromboprophylaxis During Pregnancy, Labour and after Vaginal Delivery.'

Executive summary of recommendations

Recommendations for thromboprophylaxis during pregnancy

The College of Obstetricians and Gynaecologists,

November 2009

Anticoagulation - Warfarin

Mar 2006
Diagnosis of VTE in Pregnancy

• Very challenging

• Classic s/s of VTE e.g. Leg swelling, tachycardia, tachypnea, and dyspnea, may be associated with a normal pregnancy.

• Common strategies and clinical score systems for DVT pulmonary embolus have not been validated in pregnancy.

• Sudden death can occur in pregnant patients with VTE.

• Clinical suspicion is critical for the diagnosis of VTE - All pregnant women with signs and symptoms suggestive of VTE should be investigated quickly.
DIAGNOSIS OF DVT

- Clinical
- Venography
  - Radiation hazard, can shield fetus with abdominal apron
  - Invasive
- Doppler U/S - 95% sensitive in proximal DVT
  - Obesity, severe edema can limit the examination
- MRI (Magnetic resonance imaging)
  - Does not involve radiation exposure
  - Is Gadolinium harmful to the fetus?
  - High sensitivity and specificity for diagnosis of iliac-vein thrombosis
DIAGNOSIS OF PULMONARY EMBOLISM

- Clinical, ECG, CXR - Unreliable
- VQ lung scan, Spiral CT Pulmonary angiography a/w radiation hazards

◆ Fetal dose of radiation
  - VQ lung scan higher (640 - 800 μGy) than CT (3 - 131 μGy)
  - perfusion scanning alone will reduce the radiation exposure
  - VQ scan carries a slightly higher risk of childhood cancer in offspring than does CTPA (1 case in 280,000 vs <1 in 1 million)

◆ Maternal Radiation
  - higher with CT than with VQ (2.2 to 6.0 mSv vs. 1.4 mSv)
  - CT has greater risk of maternal breast cancer (the lifetime risk is up to 13% greater with CTPA than with VQ scans)
Radiation Risks and Pregnancy

- Radiation exposure to the fetus from CTPA and lung ventilation–perfusion scanning is negligible.

- Reaching the exposure limit of 50,000 μGy, acceptable by National Council on Radiation Protection and Measurements in pregnancy, would require 100 ventilation–perfusion scans or nearly 400 CTPAs.

- PE during pregnancy is a serious condition and the risk of not diagnosing a PE is much greater than the radiation risks.

D- Dimer

Degradation product of cross linked fibrin blood clot

- Elisa method more sensitive than latex agglutination
- Elevated in acute DVT
- Also elevated in DIVC, trauma, malignancy, liver disease
  - Low positive predictive value - non specific
  - Used as a tool for exclusion.
  - Negative predictive values > 95%
D-Dimers in Pregnancy

• Levels of d-dimer increase with the progression of a normal pregnancy.
• A study using a highly sensitive assay, (SimpliRED assay)
  • Negative test in 1st and 2nd trimesters had a negative predictive value of 100% (sensitivity and specificity of a +ve test were 100% and 60%.)
  • Useful in pregnancy because a normal result excludes DVT and occurs frequently enough to be clinically helpful.
  • BUT not validated in larger cohorts of pregnant patients
• Has been shown that negative d-dimer test may not necessarily rule out VTE
• D-dimer test should be used in combination with other tests

Diagnosis of VTE in Pregnancy

Figure 1. Diagnostic Algorithm for Suspected Deep-Vein Thrombosis and Pulmonary Embolism during Pregnancy.
If compression ultrasonography was negative, low-molecular-weight heparin was discontinued. MRDTI denotes magnetic resonance direct thrombus imaging.
TREATMENT of VTE

- Objectives
  - Prevent local extension of thrombus
  - Prevent embolisation
  - Prevent recurrent thrombosis

- DVT and PE are different ends of spectrum of a single disorder. Similar Pharmacologic Treatment
TREATMENT of VTE

- Anticoagulation is the cornerstone of treatment
- Anti-thrombin replacement
  - In anti-thrombin deficiency, if levels <50% of normal
  - Replace with anti-thrombin concentrate at 50-70 iu/kg eod for 1 week after delivery
- IVC filter - not recommended in pregnancy
- Thrombolytic therapy - not recommended in pregnancy
- Emergency embolectomy - for massive PE
Anticoagulation for new DVT

- Immediate heparinisation at therapeutic dose
  - UFH to maintain PTT at 2X normal
  - LMWH to achieve anti-Xa levels of 0.6 to 1.2 U/ml

- Importance of adequate anticoagulation
  - 24% Untreated DVT develop PE
  - 10-15 X increase in recurrences if inadequately treated
Duration of Anticoagulation for new DVT

- Maintain at therapeutic dose for at least 6 months after VTE
- If patient is still pregnant after 6 months of therapeutic anticoagulation, the doses may be decreased to prophylactic doses
- Warfarin may be used in the 2nd trimester if unable to continue injections
  - Risks of CNS defects and intrauterine bleed bleeding
- Prophylaxis till 6 weeks post partum
Complications of Anticoagulants during Pregnancy

- Fetal Complications
  - Teratogenicity
  - Bleeding

- Maternal Complications
  - HIT
  - Heparin Induced Osteoporosis
  - Bleeding
Anticoagulation drugs

- Standard Heparin
- Low Molecular Weight Heparin
- Warfarin
Warfarin

- Vitamin K antagonist
- Oral preparation
- Unpredictable absorption
- Multiple drug interactions
- Require frequent blood tests
Challenges in Warfarin Management during Pregnancy

- Crosses the placenta
- Increased foetal loss
- Teratogenic in 1st trimester
- Neurological malformations in any trimester
  - nasal hypoplasia
  - stippled epiphyses
  - CNS - ageneisi of corpus callosum, ventral midline dysplasia, optic atrophy
- Fetal bleeding and retroplacental haemorrhage in last trimester
- Post partum haemorrhage
Warfarin safe for foetus?

- True incidence of teratogenicity adverse affects not known
- Previously reported cases associated with high dose warfarin
- Lower dose in moderate intensity anticoagulation probably safe at 0-6 weeks conception and during second trimester

Sharouni et al; British Heart Journal 1994
Foetal Warfarin Syndrome

- Occurred in 1997, Neonatology SGH
- Mother on warfarin 3.0-3.5 mg daily for mitral valve replacement from conception to 36 weeks

*Singapore Paediatric Journal. March 2000*


**Fetal warfarin syndrome.**

Sathienkijkanchai A, Wasant P.
Division of Medical Genetics, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

**Abstract**
Fetuses exposed to Warfarin in the first trimester of pregnancy have an increased risk of embryopathy which consists of nasal hypoplasia and stippled epiphyses, known as fetal warfarin syndrome or warfarin embryopathy. We herein report a first case of an infant with fetal warfarin syndrome in Thailand. The patient was an offspring of a 34-year-old mother with history of SLE and arterial embolism for several years. She had an unplanned pregnancy while taking warfarin. The patient developed difficulty breathing in the first few hours after birth from severe nasal hypoplasia. He also had short limbs, brachydactyly, nail hypoplasia, and calcifications in the epiphyseal regions of humeri, femora and vertebrae radiographically. The patient eventually died from respiratory failure at 6 months of age.
Standard Heparin

Safe for fetus

Maternal complications

- 2% Bleeding in pregnant patients
- Increased bleeding/thrombotic complications
  - unpredictable bioavailability, unstable anticoagulation profile
- Osteoporosis (heparin >1 month)
  - 30% significant reduction in bone density
  - 2-3% vertebrae fractures
- HIT

Thromb Haemost 1996; 75: 254-257
Low Molecular Weight Heparin

- Predictable bioavailability & long half-life
- Constant and adequate anticoagulation profile
- Convenient & easy administration
- Does not cross the placenta
- No adverse report of its use in pregnancy
- No significant osteoporosis reported in long term use
- Lower incidence of thrombocytopenia

Anticoagulant of choice during pregnancy
Choice of Anticoagulation

- Discuss with patients
  - Indications for treatment
  - Risks of embryopathy
  - Risks of thrombosis
  - Risks of bleeding

- Informed Choice
Intra-partum Management - Patients on therapeutic anticoagulation

- Special caution must be exercised during labour and delivery
- Admit for planned delivery when the cervix is favourable
- Omit LMWH on the day of delivery
- At induction of labour, start i/v unfractionated heparin if the thrombotic risk is high
- Stop i/v heparin once active labour begins
- No active anticoagulation is recommended during delivery
- Resume LMWH within 12 hrs after delivery (NO significant bleed)
- Overlap with warfarin till therapeutic INR achieved
Epidural Anaesthesia

- Decision made on individual basis
- Reports of spinal haematomas
- Successful use in 43 pregnancies without complications
- Safe if PTT normal and no standard heparin for 4-6 hours prior to epidural catheter insertion
- Can be given at least 12 hours after the last prophylactic dose and 24 hours after the last therapeutic dose of LMWH
- LMWH can be re-started 3 hours after removal of epidural catheter
Peri-partum Bleeding

- Exclude obstetric complications predisposing to haemorrhage
- Heparin and LMWH if present can be reversed with protamine sulphate
Caesarian Section

- Indications for Obsteterics Reasons only
- Elective LSCS
  - stop infusional heparin at least 4 hours before surgery
- Emergency LSCS
  - consider protamine sulphate
Post Partum

- Prophylaxis - anticoagulation should remain for at least 6 weeks
- Therapeutic - the patient should continue with therapeutic intensity of anticoagulation until 6 months after the thrombotic event.
- Unfractionated heparin, LMWH and Warfarin are safe for breast feeding mothers
- Warfarin which can be taken orally is usually the preferred anticoagulation drug after delivery
Use of Anticoagulants in Nursing Mothers

- Heparin and LMWH not secreted into breast milk
- Warfarin does not induce an anticoagulant effect in the breast-fed infant while the mother is on warfarin treatment

For lactating women using warfarin or UFH who wish to breastfeed, recommend continuing these medications (Grade 1A) 8th ACCP 2008

Thank You