Pharmacology Thromboprophylaxis for Obstetrics VTE

Carol KK Lim
MFM, HoSHAS
13 May 2017
HoSHAS
Thromboprophylaxis

• Thromboprophylaxis – any measure taken to prevent formation of thrombi
  ➢ Non-Pharmacological
  ➢ Pharmacological
Thromboprophylaxis

- Risk identification
- General measures
- Non-pharmacological measures
- Thromboprophylaxis agents
- Intervention / Thromboprophylaxis - appropriate & timely
Risk Identification

• Look for risk factors – use antenatal & postnatal assessment checklists

• Important to counsel at risk woman before embarking on pregnancy (pre-pregnancy clinic)
Non Pharmacological Measures

• Encourage ambulation as soon as possible
• Avoid dehydration
• Full length graduated elastic compression stockings (GCS)
• Thrombo-embolism deterrent (TED) stockings
• Intermittent pneumatic compression (IPC)
• Inferior vena caval (IVC) filter
Compression Stocking

• To help prevent formation of Deep Vein Thrombosis.

• To promote increased blood flow velocity in the legs by compression of the deep venous system.
Compression Stocking

DONNING GUIDE

1. Insert hand & grab stocking at top of heel pocket.

2. While still holding heel pocket, turn stocking inside out down towards toe.

3. Open stocking & slide foot in until toe & heel are positioned in place.

4. Knee-high: Grasp top of stocking and pull up over ankle and calf. Position tops approximately 1" below bend of knee.

Thigh-high: Grasp top of stocking and pull up over ankle and calf. Position top of stocking at mid-thigh.

Pantyhose: With crotch in a snug, comfortable position, stretch panty high with both hands. Adjust waist band to normal position.
Intermittent Pneumatic Compression (IPC)
Antithrombotics (1)

1. Anticoagulants

A. Factor Xa Inhibitors:
   ✓ Heparin group / glycosamioglycans – eg UH, LMWH, Fondaparinux;
   ✓ Direct Xa – eg Rivaroxaban

B. Direct thrombin (II) Inhibitors eg Dabigatran

C. Vit K Antagonist (VKA) eg Warfarin
Antithrombotics (2)

2. Antiplatelets eg Aspirin
3. Thrombolytics / fibrinolytics eg Streptokinase

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Antiplatelets</th>
<th>Thrombolytics / Fibrinolytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FXa inhibitors,</td>
<td>- aspirin</td>
<td></td>
</tr>
<tr>
<td>- Direct Thrombin inhibitors,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VKA.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thromboprophylaxis Agents

- Examples of available agents in O&G setting in MOH are:
  a) LMWH
  b) Unfractionated heparin (UFH)
  c) Warfarin
Low Molecular Weight Heparin (LMWH)

- Agents of choice for antenatal thromboprophylaxis for their efficacy and safety profile (safer than UFH)

- Examples of LMWH:
  a) Enoxaparin
  b) Tinzaparin

- Doses based on weight
Low Molecular Weight Heparin (LMWH)

• Comparing to unfractionated heparin, LMWH has lower risks of:
  a) Heparin-induced thrombocytopenia
  b) Osteoporosis & fractures
  c) Bleeding

• Monitoring of platelets & AntiXa levels are not required during thromboprophylaxis

• Caution in patients with impaired renal function – need to reduce LMWH dosage

• Safe during breastfeeding
## Low Molecular Weight Heparin (LMWH)

### Prophylaxis Dosage

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Enoxaparin</th>
<th>Tinzaparin (75u/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>20 mg daily</td>
<td>3500 units daily</td>
</tr>
<tr>
<td>50-90</td>
<td>40 mg daily</td>
<td>4500 units daily</td>
</tr>
<tr>
<td>91-130</td>
<td>60 mg daily*</td>
<td>7000 units daily*</td>
</tr>
<tr>
<td>131-170</td>
<td>80 mg daily*</td>
<td>9000 units daily*</td>
</tr>
<tr>
<td>&gt;170</td>
<td>0.6 mg/kg/day*</td>
<td>75 u/kg/day*</td>
</tr>
</tbody>
</table>

- High prophylactic for women 50-90 kg (intermediate risk)

* May be given in two divided doses
Tinzaparin: Pharmacokinetics

- Bioavailability following s.c. injection: 90%
- Peak plasma activity (Cmax) reached between 4-6 hrs
- Elimination half-life: 1-2 hrs (80 mins)
- Absorption half-life: 3-4 hrs (200 mins)
- Routes of elimination: Renal & reticulo-endothelial system
- Eliminated primarily with urine as unchanged drug
Tinzaparin: FDA approved indications

1- Prophylaxis of DVT in medically ill and elderly patient.
2- Total hip & knee replacement
3- Extended hip-replacement
4- Abdominal surgery
5- Treatment of DVT with or without PE
6- Prophylaxis and treatment of DVT in pregnant women.
Tinzaparin

- Effective and safe in the treatment of DVT and PE in pregnant and non-pregnant patients
- Does not cross the placenta
- Convenient once-daily dosage: better compliance, better outcome
- Dual elimination – by renal system and reticulo-endothelial system: safe in renal impairment
- Highest neutralization by protamine sulphate compared to other LMWHs
Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

The National Institute for Health and Care Excellence (NICE) estimates that low-molecular-weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively. Therefore it is reasonable to assume that it may substantially reduce the risk of VTE in obstetric patients. A Scandinavian study found a relative risk reduction of VTE of 88% in obstetric patients with one previous VTE given LMWH.
Unfractionated Heparin (UFH)

• Shorter half-life compared to LMWH
• Can be reversed by protamine sulphate
• Interval between prophylactic dose and regional analgesia/ anesthesia is less ie 4 hours (interval is 12 hours for LMWH)
• Subcutaneous 5,000 to 7,500 units 12-hourly
Fondaparinux

- Synthetic pentasaccharide
- Specific inhibition of factor Xa via antithrombin
- No placental passage? but anti Xa activity was found in cord blood of some newborns
- Premature to conclude its safety and role in pregnancy
- Reserved for women intolerant of heparin compounds
- Prophylactic dose subcutaneous 2.5mg daily
- Unknown if excreted in breast milk, thus to avoid in lactating women
Warfarin

• Restricted to situation where heparin is unsuitable eg women with mechanical heart valves
• 5% risk of warfarin embryopathy when exposed between 6-12 weeks gestation
• Other risks: spontaneous miscarriage, stillbirth, fetal / maternal hemorrhage
• Safe during breastfeeding
• Conversion from LMWH should be delayed for 5-7 days after delivery to minimise hemorrhage risk
## Comparison between agents

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (LMWH)</th>
<th>Tinzaparin (LMWH)</th>
<th>Unfractionated Heparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
</table>
| **Mechanism**          | ↑ AT effects, more selectively on Factor Xa  
Less binding to plasma protein  
→ More predictable dose response | ↑ AT effects on Factor Xa & thrombin  
Bonds non-specifically to plasma protein  
→ Unpredictable dose response | ↑ anti-Xa activity of AT  
Specifically for AT  
No binding to other plasma protein, good predictability | |
| **Mean molecular weight (Da)** | 4500 | 6500 | 15000 | 2000 |
| **Half-life**          | 4.5 hr | 3.4 hr | 45min (IV)  
1-2 hr (SC) | 17-21 hr |
<p>| <strong>Bioavailability</strong>    | 90-92% | 90% | Low (after SC) erratic | Excellent |</p>
<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (LMWH)</th>
<th>Tinzaparin (LMWH)</th>
<th>Unfractionated Heparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>None</td>
<td>None</td>
<td>aPTT</td>
<td>None</td>
</tr>
<tr>
<td>Last Rx dose before</td>
<td>24 hr</td>
<td>24 hr</td>
<td>4 hr</td>
<td>4-5 days</td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
<td>Unknown. Suggest alternative agent</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Protamine sulfate neutralizes 60% activity, based on time since LMWH was dosed. &lt;8hr: 1 mg/1 mg LMWH 8-12 hr: 0.5mg/1 mg LMWH &gt;12hr: not recommended</td>
<td>Protamine sulfate 1 mg neutralizes 100 units UH (based on UH given last 3-4 hr)</td>
<td>Not reversible</td>
<td></td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal Adjust for CrCl &lt;30ml/min</td>
<td>Hepatic</td>
<td>Renal Contraindicated in CrCl&lt;30</td>
<td></td>
</tr>
</tbody>
</table>
# Timing of Procedures

<table>
<thead>
<tr>
<th>Timing for epidural anaesthesia (setting block or removal) in relation to prophylaxis dose</th>
<th>Enoxaparin (LMWH)</th>
<th>Tinzaparin (LMWH)</th>
<th>Unfractionated Heparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure 12 hr after last dose</td>
<td>Procedure 12 hr after last dose</td>
<td>Procedure 4 hr after last dose</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Next dose &gt;6 hr after procedure</td>
<td>Next dose &gt;6 hr after procedure</td>
<td>Next dose &gt;2 hr after procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last Rx dose before procedure</td>
<td>24 hr</td>
<td>24 hr</td>
<td>4 hr</td>
<td>4-5 days</td>
</tr>
</tbody>
</table>
Bioavailability following subcutaneous injection

Bioavailability of UF Heparin 5000 u, Low MW heparin (LMWH) 10,000 u, 5000 u, 2500 u following subcutaneous injection.

**Figure 2**

- UF Heparin 5000 u
- Low MW heparin (LMWH)
  - 10,000 u
  - 5000 u
  - 2500 u

**Graph Parameters**

- X-axis: Hours
- Y-axis: Xa I activity (IU/ml)
New MOH Obst VTE Checklist


• The difference:
  1) Weightage / Risk score
  2) Risk factors – some were taken off
  3) Duration of postnatal thromboprophylaxis
Risk Factors - removed

- Age
- Parity
- Varicose vein
- Multiple pregnancy
- Preterm delivery
Risk Factors - modified

• Smoker - >10/day

• All LSCS – same score of 2*

*start thromboprophylaxis the evening before scheduled ELLSCS (at least 12hr from LSCS)
## Duration

<table>
<thead>
<tr>
<th>Period</th>
<th>Score</th>
<th>Duration of thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal</td>
<td>≥ 4</td>
<td>Consider giving from 1&lt;sup&gt;st&lt;/sup&gt; trimester up to 6 weeks postnatal (up to 6 weeks postnatal if there is a single risk with a score of 4. If a combination score of ≥ 4, then give up to 3 weeks postnatal then to be reviewed by an O&amp;G specialist to decide if a further 3 weeks of prophylaxis is warranted)</td>
</tr>
<tr>
<td>Antenatal</td>
<td>3</td>
<td>Consider prophylaxis from 28 weeks till 3 weeks postnatal</td>
</tr>
<tr>
<td>Postnatal</td>
<td>2</td>
<td>Consider prophylaxis for 10 days</td>
</tr>
<tr>
<td>Postnatal</td>
<td>&gt; 2</td>
<td>Consider prophylaxis for 10 days or longer, specialist to decide</td>
</tr>
</tbody>
</table>

All antenatal and postnatal patients, even those considered low risk should be counselled on VTE prevention and recognition of VTE signs & symptoms.
Does guidelines work?

• There has been a significant decline in deaths from PE following the publication and implementation of guidelines that were recommended in previous confidential enquiry reports. (Confidential Enquiry into Maternal Deaths, UK)

• The number of deaths in the UK attributed to PE were 18 between 2006-2008 compared to 41 in 2003-2005.

• Evidence that clinical guidelines works.....
Direct Deaths from VTE in UK: 1985-2008

Thromboprophylaxis in O&G, RCOG-PACE, 1995

Thromboprophylaxis During Pregnancy, Labour & after Vaginal Delivery, RCOG, 2004

Reducing the risk of Thrombosis and Embolism during Pregnancy & the puerperium, RCOG, 2009

CMACE 2011
Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

Pulmonary embolism (PE) remains a leading direct cause of maternal death in the UK. There was a significant fall in the maternal mortality rate from PE (from 1.56 [95% CI 1.43-2.63] per 100,000 maternities in 2003-2005 [33 deaths] to 0.70 [95% CI 0.49-1.25] per 100,000 maternities in 2006-2008 [16 deaths] due largely to reductions in deaths from antenatal VTE (which fell from 11 to 3) and deaths from VTE after vaginal delivery (which fell from 8 to 2) and attributed to the first version of this guideline published in 2004.
MOH CPG on VTE

• Published in August 2013

• “All women should be assessed at booking and after delivery or if they are admitted to the hospital for any reason or develops other problems”

• “All should be stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate”
Other Local Guidelines

Training Manual
Prevention & Treatment of Thromboembolism in Pregnancy & Puerperium

GARIS PANDUAN MENERUSKAN PROFILAKSIS HEPARIN / LOW MOLECULAR WEIGHT HEPARIN (LMWH) DI KLINIK KESIHATAN

BAHAGIAN PEMBANGUNAN KESIHATAN KELUARGA
&
LEMBAGA BIDAN MALAYSIA

KEMENTERIAN KESIHATAN MALAYSIA

APRIL 2013
Other Local Guidelines

2nd Edition due out soon !!!
Obstetric VTE:

What’s next?

- Improve public awareness on VTE / PE and the risk factors
- Capacity building and improve knowledge among health care providers – including AMO
- Early referral, appropriate management and risk modification via pre-pregnancy clinic before embarking pregnancy, for high risk women
- Review color coding check list to include history of VTE
- Antenatal Risk Assessment and appropriate management based on VTE risk stratification -
- Increase awareness on importance of postmortem
The way forward

Root Cause Analysis
Key Performance Index
- Assessment
- Prophylaxis
Hosp accreditation program
Clinical Pathway
Include in color coding
Checklist in home based antenatal book (red card)
Summary (1)

Obstetric thromboprophylaxis:

• essential
• do-able
• comprehensive
• consistent

→ Because Maternal VTE Deaths are often preventable
Summary (2)

• LMWH is agent of choice

• Once antenatal thromboprophylaxis is started, need to continue for 3-6 weeks postnatal or until conversion to warfarin

• Don’t forget to look out for bleeding risks

Bleeding risk?  Clotting risk?
Key Message

Pregnancy is an independent risk factor for VTE

When pregnant, think VTE!!
Thank you for your attention

Know the risk factors of VTE

- Advancing age
- Temporary immobilisation e.g. travel
- Major surgery or trauma
- Pregnancy
- Specific medical conditions e.g. cancer
- Oestrogen use
- Being overweight/obese
- Long periods of inactivity
- Family history

What Everyone Should Know About Blood Clots
Because knowing could save your life.

SPOT THE CLOTS

carolkklim@yahoo.com

vte Asses. Prevent.