Women with mechanical heart valves: management in pregnancy

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No Disclosures
Thank God for James Young Simpson's discovery of chloroform anaesthesia in 1847
Original Simpson’s Hospital
Our team

- Obstetric anaesthetists
- Obstetricians
- Haematologists with an interest in haemostasis & thrombosis
- Administrative & clerical support
- Midwife
- Coagulation laboratory
- Specialists of the future Trainees
- Thrombosis nurse
- Paediatric haematologist
Aims of this talk

- Understanding of the handling of different anticoagulants in pregnancy and the puerperium
- Understanding of the reversibility of different anticoagulants
- Close work within a multidisciplinary team
- Paucity of evidence on which to base best practice
- Only a few options, lots of guidelines!
Lots of guidelines

**Major Society Guidelines**

2014 American Heart Association/ American College of Cardiology (AHA/ACC) valvular heart disease guidelines

Nichimura RA et al. J Am Coll Cardiol 2014 63 e57

2012 American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy

Bates SM et al. Chest 2012 141 e6915

2011 European Society of Cardiology (ESC) Guidelines

Vahanian A et al. Eur Ht J 2012 33 2451
Pre-conception: evaluation & counselling

Mechanical heart valves –
◦ Increased incidence of thrombo-embolic complications during pregnancy
◦ Therapeutic anticoagulation required throughout pregnancy
◦ Various anticoagulant options

◦ Patients will be on warfarin (or VKA) pre-conceptually
  ◦ How compliant?
  ◦ What is target INR?
  ◦ What is TTR (time within therapeutic range)?
  ◦ How does INR get checked? Warfarin clinic/GP/pharmacy-led clinic? POCT vs venous INR

◦ Paucity of evidence to guide us about the optimum anticoagulant regimen

Bioprosthetic valves – do not require anticoagulation (some exceptions)
Balance of risks

The risk of developing thrombo-embolic complications should be **balanced** against the risk of maternal and foetal complications of anticoagulation.

These risks change in the different trimesters.
Risk of development of thromboembolic complications

Risk is based on:
- Number – multiple valves
- Type – old style valve
- Site – mitral
- Previous thromboembolic complications
- Atrial fibrillation or atrial flutter

Pre-operative CXR with Starr-Edwards caged ball valve
Mechanical prosthetic heart valves

Ball and Cage: Starr-Edwards

Single Disc: Medtronic-Hall, Bjork-Shiley

Bileaflet: St Jude Medical, Carbo Medics, Sorin bicarbon

Development of the original ball and cage valve design attributed to the bottle stopper in 1858;
In the early 1950’s it led to the idea of a prosthetic heart valve consisting of a cage with a mobile spherical poppet
## Handling of anticoagulants in pregnancy

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
<th>Breast-feeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Avoid weeks 5-12; risk of embryopathy</td>
<td>Can be given</td>
<td>Consider switch from 36 weeks</td>
<td>safe</td>
<td>Reversible with vit K and PCCs</td>
</tr>
<tr>
<td>Low molecular-weight heparin (LMWH)</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>Partially reversible with protamine</td>
</tr>
<tr>
<td>Unfractionated heparin (UFH)</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>s/e: osteoporosis, HIT(T); reversible</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>safe</td>
<td>Not much experience in general; would not be appropriate for use in mechanical valves outwith or in pregnancy</td>
</tr>
<tr>
<td>Direct oral anticoagulants (DOACs)</td>
<td>uncertain risk: avoid</td>
<td>avoid</td>
<td>avoid</td>
<td>Uncertain - avoid</td>
<td>Risk unclear; would not be appropriate for use in mechanical valves outwith or in pregnancy</td>
</tr>
</tbody>
</table>
Warfarin freely crosses the placental barrier and can adversely affect foetal development.

Associated with a high incidence of spontaneous abortion, prematurity, still birth, and foetal bleeding.

Can cause neonatal intracranial haemorrhage or a retroplacental haematoma.

Considered safe in breast feeding.
Warfarin: emergency reversal

1. Stop warfarin

2. Intravenous vitamin K 5mg

3. Prothrombin complex concentrate e.g. Beriplex, Octaplex
Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves
Nicola Vitale, Marisa De Feo, Luca Salvatore De Santo, Alessio Pollice, Nicola Tedesco and Maurizio Cotrufo
J Am Coll Cardiol Vol 33 Issue 6 May 1999

<table>
<thead>
<tr>
<th>Warfarin Dose (mg)</th>
<th>Healthy Fetuses</th>
<th>Fetal Complications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>28</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>27 FT</td>
<td>4 SA</td>
<td>1 PR</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3 FT</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>2 WE</td>
<td>18 SA</td>
<td>1 SB</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>27</td>
<td>58</td>
</tr>
</tbody>
</table>

legend FT = full term; GR = growth retardation; PR = premature; SA = spontaneous abortion; SB = stillbirth; VSD = ventricular septal defect; WE = warfarin embryopathy.
Warfarin-induced embryopathy

Also known as “foetal warfarin syndrome”; “Di Saia syndrome”

Warfarin prevents the normal formation of the vitamin K-dependent matrix gla-protein in the embryo

Howe A M Teratology Vol 46 (4) 1992 379-390
Warfarin-induced embryopathy

Facial dysmorphism – reduced growth of embryonic nasal septum
Hypoplasia of nasal ridge
Laryngomalacia
Pectus carinatum
Congenital heart defects (ASD, PDA)
ventriculomegaly

Stippled epiphyses
Telebrachydactyly
Growth retardation
Agenesis of corpus callosum
Optic atrophy
Low birth weight
Seizures
Reduced muscle tone
Intellectual disability
Deafness
Feeding difficulty
Warfarin Embryopathy Syndrome

- Fetal bone and cartilage formation abnormalities
- Facial abnormalities, optic atrophy, digital abnormalities, epithelial changes, and mental impairment.
- Incidence: 4% to 10%
- The risk is highest when warfarin is administered during the 6th - 12th week of gestation.
- The risks are dose-dependent, a dose of < 5 mg daily have the lowest risks (3%).
DOACs

Direct oral anticoagulants (or new oral anticoagulants) include:

DABIGATRAN – direct thrombin inhibitor

APIXABAN, RIVAROXABAN, EDOXABAN, BATRIRXABAN – direct factor Xa inhibitor

Should NOT be considered as alternatives for use in mechanical heart valves during or outwith pregnancy

Safety data in pregnant and breast-feeding women are lacking
How to manage: Options: first trimester

Mechanical heart valve, no associated risk factors
Warfarin maintenance dose <5mg daily

1. Continue warfarin with close INR monitoring during the first trimester

OR

1. Dose-adjusted SC LMWH from weeks 5-12; twice daily dosing advised
Options: first trimester

If warfarin maintenance dose is >5mg daily

Switch to SC LMWH throughout the first trimester

Target peak LMWH-anti-Xa level: 1.0-1.2 iu/ml for mitral valve; 0.8-1.0 iu/ml for aortic valve

Suggested checking of trough levels aiming for a minimum level of 0.6 iu/ml (safety and efficacy of this approach uncertain)
Second trimester, and up to 36 weeks

Least maternal risk:
VKA, adjusted to target INR, + aspirin 75-100mg/d until 36 weeks
(timing of anticoagulant switch may depend on risk of pre-term delivery)
OR,

Least foetal risk:
Therapeutic LMWH SC twice daily, with monitoring of trough and peak levels, + aspirin 75-100mg/d

In countries where LMWH is unavailable/low resource settings, VKA is preferred anticoagulant. Dose-adjusted SC UFH is a “last resort” option when LMWH is unavailable; regular monitoring to ensure 6 hour post dose APTT is at least twice baseline
Peripartum management

Planned delivery best

Multidisciplinary approach

Preference for vaginal delivery; reserve Caesarian section for obstetric indications

If on warfarin, switch to LMWH at 36 weeks

Low-dose aspirin continued up until delivery – must discuss with anaesthetist

Last dose of LMWH: 24 hours before induction if renal function normal
Planned Labour - options

1. 12 hours after cessation of LMWH, commence iv heparin at 1000-1200 units/hour, no loading dose and infusion rate adjusted to aim for APTT ratio of 2.0 -3.0 (or 1.5-2.5 dependent on lab range)

- iv heparin should be stopped when in second stage of labour

- iv heparin should be stopped 4-6 hours prior to neuraxial anaesthesia/analgesia, and catheter can be sited if APTT has returned to normal

2. use of intermittent prophylactic doses of LMWH e.g. Enoxaparin 40mg SC OD, Dalteparin 5000 units SC OD

- 12-hour rule for siting of neuraxial anaesthesia/analgesia

3. induction of labour 24 hours after last dose of LMWH, and then an early epidural catheter can be sited; 6-8 hours after non-traumatic siting a prophylactic dose of LMWH can be given if not yet in active labour and repeated every 24 hours until cervix dilated to >6cm
Which vial of heparin would you choose to make up a heparin infusion?
Use of heparin infusion nomogram

NHS Lothian
Adult Heparin Infusion Chart
(for standard bleeding risk)

<table>
<thead>
<tr>
<th>Medicine (Approved Name)</th>
<th>Final Concentration</th>
<th>Total Dose</th>
<th>Volume</th>
<th>Route</th>
<th>Prescribed / Transcribed By Sign &amp; print name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1000 units/ml</td>
<td>40,000 units</td>
<td>40 mls</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

*Please note that in NHS Lothian heparin sodium solution for infusion is available in a ready concentration of 1000 units/ml so further dilution is not required. If in doubt, contact pharmacy for advice.

**Initiation of therapy**
- Check baseline FBC, INR, APTT, urea, creatinine.
- Prescribe loading dose and infusion on the patient Main Prescription Chart.
- Loading dose: 5000 units iv bolus. For patients with a high risk of bleeding eg. elderly >70yrs, creatinine clearance <30ml/min or low body mass index, a loading dose may not be required.
- Immediately start continuous infusion of heparin (1000 units/ml) set at initial rate of 1,200 units (1.2 ml/hr). If actual body weight over 120kg seek advice from haematologist.
- For patients with a high risk of bleeding, a lower starting rate may be required, such as 1,000 units (1.0ml/hr).

**Infusion Rate Instructions**

<table>
<thead>
<tr>
<th>Initial Rate</th>
<th>Date</th>
<th>Time</th>
<th>Rate ml/hr</th>
<th>Prescribed by</th>
<th>Adjusted by</th>
<th>APTT ratio</th>
<th>Reason for Change/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Emergency delivery

Differing opinions regarding when and how aggressively to reverse the anticoagulation

If on LMWH: protamine can be considered, but only gives partial reversal
- baby not at risk of bleeding

If on warfarin: “give vitamin K 2mg (oral/iv) to give partial correction of INR (note will not reverse fetal INR): and stop warfarin, and give 4-factor PCC to a target INR of 2.0” (!)
- baby will be at risk of bleeding
- must receive vitamin K at birth
Emergency delivery

For all above situations, a 24-hour rule applies for the siting of neuraxial anaesthesia/analgesia

Post-delivery neuraxial catheters may be removed no earlier than 10-12 hours after the last dose of prophylactic LMWH and before anticoagulant therapy is resumed
Postpartum

-timing of restarting anticoagulation depends on haemostasis
- one option is to restart iv heparin at usual dose, no loading dose and increase gently to therapeutic dose over 24-48-72 hours
- or restart prophylactic LMWH and then an intermediate dose of LMWH twice daily, incrementing to usual dose after 48-72 hours
- warfarin should not be introduced for 5-7 days
- patient should be aware that she will be an in-patient for over a week post-delivery

- increased risk of wound haematoma, postpartum haemorrhage
- this can be most tricky to manage!
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