Prosthetic valves during pregnancy

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Pregnancy and Heart Valve Prosthesis

• Good haemodynamics

• The problem is related to anticoagulant therapy for mechanical prosthesis
  – Hypercoagulable state
  – Each antithrombotic regimen has drawbacks
    • unfractionated heparin
    • low-molecular weight heparins
    • vitamin K blockers

  – Limited information from clinical studies

➤ No consensus in clinical practice
Hypercoagulable state of pregnancy

- Increased coagulation factors
- Decreased anticoagulant factors
- Increased activated protein C resistance
- Decreased fibrinolysis
- Increased PAI


Background

- Changes toward hypercoagulability
  - ↑ coagulation factors
  - ↑ thrombin-ATIII complex
  - ↓ protein S
  - impaired fibrinolysis
    (Hellgren Semin Thromb Hemost 2003;29:125-30)

- Risk of venous thromboembolism x 2-4
  (Ginsberg et al. J Thromb Haemost 2003;1:1435-42)

- Anticoagulant therapy is an independent adverse predictor of fetal outcome
  (Siu et al. Circulation 2001;104:515-21)
Unfractionated Heparin

- No placenta crossing: no embryopathy
- Modified activity because of changes in haemostasis:
  - need for increased doses
- Concerns on the reliability of aPTT
  - target aPTT ≥ 2
  - anti-Xa activity 0.3 to 0.5 U/ml
    (Ginsberg et al. Arch Intern Med 2003;163:394-8)
- Short half-life: problems of stability, feasibility
- Risks of osteoporosis and thrombocytopenia

Low Molecular Weight Heparin

- No placenta crossing: no embryopathy
- Better stability and predictability of the antithrombotic effect
- Need for increased and adapted doses during pregnancy
  (enoxaparin 1 mg/kg every 12 hours),
- Lower risks of osteoporosis and thrombocytopenia
- Concerns regarding clinical efficacy in pregnant patients with mechanical prosthesis
Vitamin K Blockers

• Placenta crossing: risk of embryopathy
  – ≈ 5-10%, mainly during the 1st trimester (6-12 wks)
  – Nasal hypoplasia, epiphyseal stippling
  – Dose dependant
  – Few or no consequences on further growth and cognitive development
    (Wesseling et al. Thromb Hemostasis 2001;85:609-13)

• Long half-life (fetus > mother)
  – Fetal bleeding risk on delivery

![Pie chart showing risks associated with Vitamin K Blockers]

- CNS abnormality
- Pregnancy loss (30%) and fetal hemorrhage (10%)
- Warfarin embryopathy (5-10%)
Mechanical prosthesis and pregnancy

1234 pregnancies in 976 women (2/3 mitral prostheses)

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>Embryopathy (%)</th>
<th>Spontaneous Abortion (%)</th>
<th>Thrombo-Embolism (%)</th>
<th>Maternal Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin throughout pregnancy</td>
<td>6.4</td>
<td>25</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Heparin throughout pregnancy</td>
<td>0</td>
<td>24</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>- low-dose</td>
<td>0</td>
<td>20</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>- adjusted-dose</td>
<td>0</td>
<td>25</td>
<td>25</td>
<td>6.7</td>
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<tr>
<td>Heparin during the first trimester, then warfarin</td>
<td>3.4</td>
<td>25</td>
<td>9.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>


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Mechanical prosthesis and pregnancy

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>Embryopathy (%)</th>
<th>Spontaneous Abortion (%)</th>
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<th>Maternal Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillesen et al. (70 pregnancies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin throughout pregnancy</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UFH throughout pregnancy</td>
<td>0</td>
<td>0</td>
<td>3 (38%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>UFH during the first trimester, then warfarin</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Basude et al. (32 pregnancies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin throughout pregnancy</td>
<td>0</td>
<td>17 (77%)</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>LMWH (anti-Xa monitoring)</td>
<td>0</td>
<td>1 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LMWH during the first trimester, then warfarin</td>
<td>0</td>
<td>3 (50%)</td>
<td>1 (25%)</td>
<td>0</td>
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</tbody>
</table>

(Basude et al. BJOG 2012;119:1008-13)
Warfarin Throughout Pregnancy

Outcome of Pregnancy

71 pregnancies in 52 patients with mechanical prosthesis

Warfarin throughout pregnancy
(Target INR 2.25-4.0)
Elective cesarean section at 37th week

- 23 spontaneous abortions (32%)
- 4 cases of embryopathy (5.6%) (2/4 alive)
- No thromboembolism
- No bleeding
- No maternal mortality

(Cotrufo et al. Obstet Gynecol 2002;99:35-40)

Outcome of Pregnancy

Influence of Warfarin Dose

58 pregnancies in 43 women with warfarin throughout pregnancy

<table>
<thead>
<tr>
<th>Warfarin dose (mg)</th>
<th>Warfarin ≤ 5 mg</th>
<th>Warfarin &gt; 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy babies</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>1st trimester</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stillbirth (3rd trimester)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fetal growth retardation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Embryopathy</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>Prosthetic thrombosis</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*: abortion at 6 months

(Vitale et al. J Am Coll Cardiol 1999;33:1637-41)
PRECONCEPTION EVALUATION AND COUNSELING

Women of childbearing age who have prosthetic heart valves should receive preconception evaluation and counseling regarding risks associated with prosthetic valves and the risks and benefits of antithrombotic therapy.

APPROACH DURING PREGNANCY
• **For bioprosthetic valves** — Bioprosthetic valves typically do not require anticoagulation (except anticoagulation for the first three to six months after surgical implantation) unless the patient has other thromboembolic risk factors (such as atrial fibrillation).

• For patients with a bioprosthetic valve, continuing low-dose aspirin (75 to 100 mg/day) during pregnancy.

• **For mechanical valves** — Pregnant women with mechanical valves should be fully informed about the importance of therapeutic anticoagulation throughout pregnancy and the maternal risks and fetal risks associated with each anticoagulant regimen.

• The patient should participate in and agree with the decision about the treatment regimen.

• For pregnant women with mechanical prosthetic valves, we recommend low-dose aspirin (75 to 100 mg/day) in addition to anticoagulation throughout pregnancy.
Major society Guidelines
Class I recommendations

- For all patients taking a VKA, such as warfarin, a therapeutic INR of 2-3 (INR of 2.5–3.5 for mitral valves) is recommended.

- In pregnant patients, warfarin may be used to achieve therapeutic INR in second and third trimesters.
Class I recommendations

- It is also recommended to discontinue warfarin and initiate IV UFH with aPTT greater than two times the control before planned vaginal delivery.
- Low-dose aspirin (75mg to 100 mg) is also recommended during second and third trimesters
  - **No Class I recommendations are available for anticoagulation during the first trimester.**
ESC Guidelines on the management of cardiovascular diseases during pregnancy

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPedC), and the German Society for Gender Medicine (DGezGM)

Authors/Task Force Members Vera Regitz-Zagrosek (Chairperson) (Germany), Carina Blomstrom Lundqvist (Sweden), Claudio Borghi (Italy), Renata Cifkova (Czech Republic), Rafael Ferreira (Portugal), Jean-Michel Foidart (Belgium), J. Simon R. Gibbs (UK), Christa Gohlicte-Baerwolf (Germany), Bulent Gorenek (Turkey), Bernard Hung (France), Mike Kirby (UK), Angela H. E. M. Maas (The Netherlands), Joao Morais (Portugal), Petros Niohannopoulos (UK), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Jolien W. Roos-Hesselink (The Netherlands), Maria Schaufelberger (Sweden), Ute Seeland (Germany), Lucia Torracca (Italy).

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www.escardio.org/guidelines
## Recommendations for the management of valvular heart disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is &lt; 5 mg/day (or phenprocoumon &lt; 3 mg/day or acenocoumarol &lt; 2 mg/day), after patient information and consent.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Discontinuation of OAC between weeks 6 and 12 and replacement by adjusted-dose UFH (a PTT ≥ 2 x control; in high risk patients applied as intravenous infusion) or LMWH twice daily, (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL) should be considered in patients with a warfarin dose required of more than 5 mg/day (or phenprocoumon &gt; 3 mg/day or acenocoumarol &gt; 2 mg/day).</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>LMWH should be avoided, unless anti-Xa levels are monitored.</td>
<td>III</td>
<td>C</td>
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## Recommendations for the management of valvular heart disease

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<tr>
<td>OAC should be discontinued and dose-adjusted UFH (a PTT ≥ 2 x control) or adjusted-dose LMWH (target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL) started at the 36th week of gestation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In pregnant women managed with LMWH, the 4-6 hours post-dose anti-Xa level should be assessed weekly.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>LMWH should be replaced by intravenous UFH at least 36 hours before planned delivery, UFH should be continued until 4-6 hours before planned delivery and restarted 4-6 hours after delivery if there are no bleeding complications.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Diagnosis and management of valve thrombosis

• **Comparable with management in non-pregnant patients** (optimizing anticoagulation with i.v. heparin and resumption of oral anticoagulation for non-critically ill patients and surgery when anticoagulation fails and for critically ill patients with obstructive thrombosis)

• Most fibrinolytic agents do not cross the placenta

• Risk of embolization 10% and subplacental bleeding is a concern

Diagnosis and management of valve thrombosis

• Because fetal loss is high with surgery, fibrinolysis may be considered instead of surgery in non-critically ill patients when anticoagulation fails

• Fibrinolysis is the therapy of choice in right-sided prosthetic valve thrombosis

• Thrombolytic therapy is best reserved for life-threatening maternal thromboembolism
Delivery

• **No delivery under vit K blockers**
  – Fetal risk of cerebral bleeding
    (Sareli et al. Am J Cardiol 1989;63:1462-5)
  – Prolonged anticoagulation in the fetus

• **Substitution by heparin at 36th week**
  – Heparin discontinued at the onset of labour and resumed 4-6 h after delivery

• **Cesarean section**
  – ↓ risk of intracerebral fetal haemorrhage
  – ↑ maternal risk of bleeding and thromboembolism

• **Vaginal delivery**
  – Consider risk of peridural analgesia

Urgent delivery

• **CS is preferred to reduce risks of fetal trauma & hemorrhage**

  ➢ **Warfarin**
    – Fresh frozen plasma (FFP) can be administered (initial dose, 15 to 30 mL/kg).
    – Small doses (eg, 2 mg) of oral or IV vitamin K will reverse the maternal INR in approximately six hours or more (target INR of 2.0)
    – Vitamin K is routinely given to newborns shortly after birth to prevent vitamin K deficiency bleeding

  ➢ If the woman is on therapeutic **LMWH**: protamine

  ➢ If the woman is on **IV UFH**,
    – cessation of the infusion will rapidly reverse the anticoagulant effect.
    – Protamine is only required if the woman has major bleeding complications.
Postpartum management

• The timing of resumption of anticoagulation is selected by balancing the risk of incisional or uterine bleeding Vs the risk of thromboembolic complications including prosthetic valve thrombosis.

• In the absence of significant bleeding, anticoagulation should be resumed shortly after delivery.

Postpartum management

• IV UFH or SQ LMWH: resumed four to six hours after delivery at a prophylactic dose, gradually increasing the dose to achieve therapeutic anticoagulation over 24 to 48 hours.

• After an uncomplicated vaginal delivery, OAC’s can be resumed the same day.

• If caesarean section: OAC’s should be delayed for 5-7 days (postpartum hemorrhag).

• Standard guidelines suggest continuing heparin until the INR has been therapeutic for 24 to 48 hours.
Direct acting oral anticoagulants

- Currently, there is no indication for the use of direct acting oral anticoagulants (DOACs) for anticoagulation in patients who have received a mechanical heart valve.
- Currently DOACs are not recommended for use in pregnant patients as they are able to cross into the placenta.

Conclusion

- Pregnancy with mechanical prosthesis is always at high risk.
- No consensus on the optimal anticoagulant therapy in pregnant women with a mechanical prosthesis
- Multidisciplinary collaboration is mandatory at every stage of pregnancy
- Need for contemporary prospective registries.
Thank you...