ANTITHROMBOTIC THERAPY IN PREGNANCY AND PUERPERIUM

Freek W.A. Verheugt

Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG)

Amsterdam, The Netherlands
Freek W.A. Verheugt

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2. received speaker fees and honoraria for consultancy from Sanofi-Aventis, Bayer Healthcare, Boehringer Ingelheim, Merck and Eli Lilly
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 (AEPC), and the German Society for Gender Medicine (DGesGM)

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 Gohlke-Baerwolf (Germany), Bulent Gorenek (Turkey), Bernard Iung (France), Mike Kirby (UK), Angela H.E.M. Maas (The Netherlands), Joao Morais (Portugal), Petros Nihoyannopoulos (UK), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Jolien W. Roos-Hesselink (The Netherlands), Maria Schaufelberger (Sweden), Ute Seeland (Germany), Lucia Torracca (Italy).

Overall death rates per million maternities

- Cardiac
- VTE
- Suicide
- CNS Haemorrhage
- Sepsis
- Pre-eclampsia
- AFE
- Haemorrhage
- Infections

Roos-Hesselink Heart 2009;95:680-6

Evolution of Maternal Mortality from Heart Disease in the UK

Cardiac


*ESC Guidelines Pregnancy. Eur Heart J* 2011;32:3147-3197
# Aetiology of Cardiac Diseases in Pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rheumatic</th>
<th>Cong.</th>
<th>Other</th>
<th>Mortality</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siu 2001, 2002, Canada</td>
<td>562</td>
<td>Acquir. VD14 - 22%</td>
<td>74%</td>
<td>12%</td>
<td>1%</td>
<td>13%</td>
</tr>
<tr>
<td>Lesniak Sobelga 2004, Poland</td>
<td>259</td>
<td>62% Rheum 20% MVP</td>
<td>-</td>
<td>18% VR</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>Madazli 2010, Turkey</td>
<td>144</td>
<td>88% Rheum</td>
<td>12%</td>
<td>-</td>
<td>0%</td>
<td>6% - 66%</td>
</tr>
</tbody>
</table>
Haemodynamic Changes During Pregnancy

- ↑ blood volume ≈ 50%.
- ↑ cardiac output 30-50% maximum between, 5th and 8th months.
- ↓ systolic and diastolic blood pressure.
- ↓ systemic arterial resistance (hormones, placenta).

Thorne Heart 2004;90:450-6
Haemodynamic Changes During Delivery

- Labour:
  - ↑ O$_2$ consumption,
  - ↑ baseline cardiac output,
  - ↑ cardiac output and blood pressure during uterine contractions, depending on modalities of delivery (epidural analgesia, Cesarean section)

- Post-partum:
  - ↑ blood shift from placenta,
  - ↑ preload and cardiac output.


HEMOSTATIC CHANGES IN PREGNANCY

**Table 1** Haemostatic changes during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Increased</th>
<th>Decreased</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic changes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procoagulant factors</td>
<td>I, V, VII, VIII, IX, X</td>
<td>XI</td>
<td>PC</td>
</tr>
<tr>
<td>Anticoagulant factors</td>
<td>Soluble TM</td>
<td>PS</td>
<td>PC</td>
</tr>
<tr>
<td>Adhesive proteins</td>
<td>vWF</td>
<td></td>
<td>TAFI</td>
</tr>
<tr>
<td>Fibrinolytic proteins</td>
<td>PAI-1, PAI-2</td>
<td>t-PA</td>
<td>APLA</td>
</tr>
<tr>
<td>Microparticles and</td>
<td>MP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiphospholipid antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local placental changes</td>
<td>TF</td>
<td>TFPI</td>
<td></td>
</tr>
</tbody>
</table>

*Brenner B. Thrombos Res 2004;114:409-414*
MECHANIC CHANGES IN PREGNANCY

Venous Stasis
12-36 weeks
Increased venous distensibility
Increased plasma volume
IVC compression

Endothelial Damage
Compression of IVC and iliac veins on the uterus
Vaginal or Abdominal delivery

MECHANICAL VALVE THROMBOSIS IN PREGNANCY (n=65)
Figure 2  Comparison of the incidence of prosthetic valve thrombosis (PVT) in mitral, aortic and tricuspid position for prostheses of prior generations (old=Starr-Edwards, Smeloff-Cutter, Lillelei-Kaster), various tilting disc prostheses (TD), Carbomedics (CM), St. Jude Medical (SJM), and bioprostheses (bio) is shown in 67 patients.
### Fetal consequences

<table>
<thead>
<tr>
<th>28 studies</th>
<th>W alone (n = 792)</th>
<th>H 12w, then W (n = 230)</th>
<th>H alone (n = 21)</th>
<th>none (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abortion</td>
<td>25%</td>
<td>25%</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>malformations</td>
<td>6%</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>fetal wastage</td>
<td>34%</td>
<td>27%</td>
<td>43%</td>
<td>20%</td>
</tr>
</tbody>
</table>

W = warfarin  
H = heparin

* Chan WS. Arch Intern Med 2000;160:191-196*
## Fetal consequences

<table>
<thead>
<tr>
<th>prospective studies only</th>
<th>W alone (n = 247)</th>
<th>H 12w, then W (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abortion</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>malformations</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>fetal wastage</td>
<td>30%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*W = warfarin  H = heparin*

*Chan WS. Arch Intern Med 2000;160:191-196*
## ANTICOAGULATION IN PREGNANT WOMEN WITH PROSTHETIC HEART VALVES

### Maternal consequences

<table>
<thead>
<tr>
<th></th>
<th>all 28 studies</th>
<th>W alone (n = 788)</th>
<th>H 12w, then W (n = 229)</th>
<th>H alone (n = 20)</th>
<th>none (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>embolism</td>
<td></td>
<td>4%</td>
<td>9%</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>death</td>
<td></td>
<td>2%</td>
<td>4%</td>
<td>15%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Chan WS. Arch Intern Med 2000;160:191-196
# Properties of Parenteral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>LMWH</th>
<th>Penta-saccharide</th>
</tr>
</thead>
<tbody>
<tr>
<td>KiloDaltons</td>
<td>12.0 - 15.0</td>
<td>4.0 - 6.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Saccharide units</td>
<td>40 - 50</td>
<td>13 - 22</td>
<td>5</td>
</tr>
<tr>
<td>Anti Xa/IIa ratio</td>
<td>1 : 1</td>
<td>2:1 - 4:1</td>
<td>∞</td>
</tr>
</tbody>
</table>
LMWHs IN PREGNANCY

Yinon Y. Am J Cardiol 2009;104:1259-1263
Valvular Heart Disease (II)

- Oral anticoagulation (OAC) with vitamin K antagonists are the safest therapy to prevent valve thrombosis and are therapy of choice during the second and third trimester (IC).

- During the first trimester continuation of OAC should be considered when warfarin daily dose is < 5 mg (IIaC).

- With higher dose requirements, unfractionated or low-molecular weight heparin should be considered with strict dose adjustment according to APTT or anti-Xa levels (weekly control) (IIaC).

- At the 36th week, OAC should be discontinued and replaced by dose-adjusted heparin (IC).
12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A):

(a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer’s peak anti-Xa LMWH 4 h postsubcutaneous-injection or

(b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or

(c) UFH or LMWH (as above) until the 13th week, with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed.
12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older generation prosthesis in the mitral position or history of thromboembolism), we suggest vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C).

Remarks: Women who place a higher value on avoiding fetal risk than on avoiding maternal complications (eg, catastrophic valve thrombosis) are likely to choose LMWH or UFH over vitamin K antagonists.

12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C).
4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A).

4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B).

4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).

4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin and factor Xa inhibitors (Grade 1C).

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breast-feed, we suggest continuing this medication (Grade 2C).
Pregnancy induces a hypercoagulable state

**Conclusions**

1. Pregnancy induces a hypercoagulable state

2. Warfarin, though most effective, is probably teratogenic when used in a daily dose > 5 mg

3. Low molecular weight heparin (LMWH) does not cross the placenta and, thus, is safer, but seems less effective than warfarin
Conclusions

4. Optimal LMWH dosing is twice daily at pre-dosing anti-Xa levels of at least 0.6 U/ml or 1.0 U/ml 4h post dosing

5. The most recommended strategy is: LMWH till 12th week, then warfarin until the 35-36th week, and then LMWH close to delivery. Restart warfarin thereafter (lactation allowed)