Anticoagulation in pregnant women with mechanical heart valve prostheses

S S Meschengieser, C G Fondevila, M T Santarelli, M A Lazzari

Abstract
Objective—To evaluate the outcome of pregnancy in women with mechanical heart valve prostheses in relation to the anticoagulant treatment used in the first trimester and the incidence of thrombotic and bleeding complications.

Methods—92 pregnancies in 59 women were followed between 1986 and 1997. In 31 pregnancies, oral anticoagulants were discontinued when pregnancy was diagnosed and subcutaneous heparin was started (12 500 U every 12 hours) adjusted to prolong the adjusted partial thromboplastin time to twice the control level. In the second trimester oral anticoagulants were resumed but changed to heparin again 15 days before the expected delivery date. In 61 pregnancies oral anticoagulants were continued during the first trimester. The same regimen of heparin was used for delivery.

Results—Abortion or fetal losses were similar (p = 0.5717) in women exposed to oral anticoagulants in the first trimester (13/61; 25%) compared with those who received adjusted subcutaneous heparin (6/31; 19%). Embolic episodes were more common (p = 0.0029) in women who received heparin (4.92%) compared with those on oral anticoagulants (0.33%). Embolic episodes were cerebral and transient. No valve thromboses were observed. No malformations appeared in the 71 newborns, except for one case of hydrocephalus. There were no maternal deaths secondary to thrombotic complications. The only death was the result of major bleeding after the delivery of a premature stillborn.

Conclusions—Oral anticoagulants seem to be safer for the mother than adjusted subcutaneous heparin. Heparin does not offer a clear advantage over oral anticoagulation in the pregnancy outcome.

Keywords: pregnancy; oral anticoagulants; heparin; prosthetic valves

The use of oral anticoagulants during pregnancy is controversial and there is no agreement on the most suitable treatment for patients with mechanical prosthetic heart valves, who have a high risk of thromboembolism. Comma

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BLEEDING
Bleeding was classified as major when it was fatal or required transfusions.

FETAL OUTCOME
Newborn infants were examined by trained neonatologists aware of the changes induced by oral anticoagulants, to determine whether malformations were present.

STATISTICAL ANALYSIS
Data are presented as means and 95% confidence intervals. Where appropriate, Fisher’s exact test or the χ² test was used. A p value less than 0.05 was considered significant.

Results
In the group of women who continued with oral anticoagulation in the first trimester, pregnancy resulted in 46 liveborn infants (75%, 95% CI 62.4 to 85.1; 34 vaginal deliveries and 12 caesarean sections). In the group who received adjusted subcutaneous heparin in the first trimester, there were 25 liveborn infants (81%, 95% CI 61.9 to 91.2; 11 vaginal deliveries and 14 caesarean sections) (table 2).

Fetal loss predominated in the first trimester in the women receiving heparin (5/6; 95% CI 6.1 to 34.5). In women receiving oral anticoagulants the frequency of fetal loss was similar in the first and second trimester (6/15; 95% CI 4.06 to 20.8) and lower in the third trimester (3/15; 95% CI 1.3 to 14.6) (table 3). Although the rate of fetal loss was higher in the group of women who continued on oral anticoagulation, the difference was not significant (p = 0.5717) (table 3).

FETAL OUTCOME
The weight of the newborn infants ranged from 1850 g to 4000 g (median weight 3000 g). Thirteen of the 71 neonates were of low birth weight (below 2500 g). There were no neonatal deaths. One baby developed a hydrocephalus. The mother of that baby received oral anticoagulants during the first trimester and she went into premature labour while she was still orally anticoagulated. She had a vaginal delivery of a low birth weight baby, although we would have preferred a caesarean section. The mother received fresh frozen plasma to prevent bleeding. We are not certain about the origin of the hydrocephalus but we cannot rule out intracranial bleeding as a cause.

No malformations were diagnosed in the remaining 45 newborn infants who were exposed to oral anticoagulants during the first trimester (table 3). The mean (SD) daily dose of acenocoumarol at the beginning of pregnancy was 3.23 (1.30) mg, range 0.71 to 7.0. In 10 cases the daily dose was 5 mg or more. Abortions or fetal loss in the women exposed to higher doses of acenocoumarol were not significantly more common than in the group receiving less than 5 mg (30% vs 23%, p = 0.968).

EMBOLIC COMPLICATIONS
Four cerebral embolic episodes were observed (4.92/100 patient-months) while the patients...
Table 2  Outcome of pregnancies, by treatment in the first trimester

<table>
<thead>
<tr>
<th></th>
<th>Oral anticoagulant</th>
<th></th>
<th>Adjusted heparin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>61</td>
<td>31</td>
<td>25</td>
<td>81 (61.9 to 91.2)</td>
</tr>
<tr>
<td>Liveborn infants</td>
<td>45</td>
<td>74 (60.7 to 83.8)</td>
<td>25</td>
<td>81 (61.9 to 91.2)</td>
</tr>
<tr>
<td>Healthy babies</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>19 (8.12 to 38)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>7</td>
<td>11 (5.1 to 23)</td>
<td>6</td>
<td>19 (8.12 to 38)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>34</td>
<td>56 (42.5 to 68)</td>
<td>11</td>
<td>35 (20 to 55)</td>
</tr>
<tr>
<td>Deliveries</td>
<td>12</td>
<td>20 (11 to 32)</td>
<td>14</td>
<td>45 (27.8 to 64)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 3  Abortions or fetal wastage, by anticoagulant treatment during the first trimester

<table>
<thead>
<tr>
<th></th>
<th>Oral anticoagulant (n = 61)</th>
<th></th>
<th>Adjusted heparin (n = 31)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>First trimester</td>
<td>6</td>
<td>10 (4.06 to 20.8)</td>
<td>5</td>
<td>16 (6.1 to 34.5)</td>
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<tr>
<td>Second trimester</td>
<td>6</td>
<td>10 (4.06 to 20.8)</td>
<td>5</td>
<td>16 (6.1 to 34.5)</td>
</tr>
<tr>
<td>Third trimester</td>
<td>3</td>
<td>5 (1.3 to 14.6)</td>
<td>1</td>
<td>3 (0.17 to 18.5)</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>25 (14.8 to 37.6)</td>
<td>6</td>
<td>19 (8.12 to 38)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 4  Embolic complications

<table>
<thead>
<tr>
<th></th>
<th>Oral anticoagulant</th>
<th></th>
<th>Adjusted heparin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow up (months)</td>
<td>588.3</td>
<td>81.2</td>
<td>0.0029</td>
</tr>
<tr>
<td>Embolic episodes (n)</td>
<td>Minor</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incidence (episodes/100 patient-months)</td>
<td>0.33 (CI 0.06 to 1.36)</td>
<td>4.92 (CI 1.58 to 12.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of valve</td>
<td>Mitral</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Aortic</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Discussion
The management of anticoagulation during pregnancy is controversial and there is no ideal treatment. Patients with prosthetic heart valves have the highest thromboembolic risk, and pregnancy itself is a thrombogenic situation owing to physiological hypercoagulation. Modern valves have fewer thromboembolic complications because of better design and materials, but there are many women with earlier models of prosthetic valve attending our anticoagulation clinic who become pregnant.

There is general agreement that, where possible, oral anticoagulants should be discontinued in the first trimester to avoid the warfarin embryopathy. However, there is no agreement on the dose or on the way the heparin should be administered. Low fixed doses of subcutaneous heparin have proven to be insufficient to prevent embolism. Our experience until 1986 was similar to that reported by Lee et al and Chen et al. Our incidence of embolic complications with low dose heparin was higher (11.7 episodes/100 patient-months) than with oral anticoagulation or adjusted heparin. Adjusted subcutaneous heparin decreased the number of embolic episodes to 4.92%, although the lowest incidence (0.33%) is associated with oral anticoagulation. In our experience, however, the administration of adjusted subcutaneous heparin was not as disappointing as reported by Salazar et al and Sbarouni and Oakley. We had no maternal deaths from valve thrombosis or cerebral embolism, and the embolic episodes left no sequelae. The single death in our series was explained by major bleeding after the delivery of a dead fetus. Embolism was more common with mitral valve prostheses and with adjusted heparin. However, the fact that two women each had two embolic episodes with either treatment suggests an individual thrombogenic predisposition or a thrombogenic valve. In Sbarouni’s report, heparin was blamed for the high rate of valve thrombosis and maternal deaths. However, that study was retrospective, different centres were involved, and the adequacy of heparin anticoagulation was not reported in every case where a thrombotic complication was observed. It is difficult to assume that subcutaneous adjusted heparin is unsafe when the level of anticoagulation cannot be established. In Salazar’s report, adjusted heparin again resulted in poor protection from valve thrombosis and embolism, and in that study laboratory control was adequate and heparin was given more frequently to overcome the high rate of thrombotic complications, but without success. We think Salazar’s patients are
comparable with our population, so the reasons for their poor results are not clear. Ginsberg et al concluded that the high frequency of adverse effects with heparin may be associated with maternal comorbidity conditions. Ginsberg and Hirsh also suggested that patients with mechanical heart valves may be resistant to moderate doses of heparin and that an inadequate target therapeutic range can explain the reported failure.

The protection given by subcutaneous unfractionated heparin is certainly not constant and probably there are a few hours each day during which anticoagulation is inadequate. Intravenous heparin is an alternative but requires hospital admission. This may be appropriate before delivery but is not ideal in the first trimester. The use of low molecular weight heparin has been reported in pregnancy, and this may represent the future management of these patients.

The incidence of abortions or fetal wastage is rather high in this population of pregnant patients with prosthetic heart valves. There have been reports of abortion rates as high as 50% but most range between 23% and 33%. Switching to heparin in the first trimester certainly does not dramatically improve the number of successful pregnancies. In our own experience the rate of fetal loss before 1986 was as high as 40%, but it has since fallen to 25%, probably because of better obstetric and cardiological care. The use of oral anticoagulants or heparin might be directly involved in first trimester fetal losses, but it seems more difficult to explain fetal wastage during the second or third trimester, when obstetric conditions are more likely to be responsible.

Cotrufo et al found no abortions or malformations in a group of patients whose warfarin requirement was less than 5 mg/day. There are no reports on acenocoumarol dose and the incidence of abortion or embroyopathy. We did not observe any significant difference in fetal outcome between those women requiring 5 mg or more of acenocoumarol a day and those receiving less than 5 mg.

No malformations were observed either in the neonates exposed to oral anticoagulants in the first trimester or in those receiving heparin. Central nervous system abnormalities resulting from either haemorrhage or malformation have been found to be related to exposure to coumarin derivatives during the second and third trimester of pregnancy, although they are uncommon. We had one case of hydrocephalus in a low birth weight baby born to a woman exposed to oral anticoagulants during her entire pregnancy; her baby was delivered while she was still on coumarins. We cannot be certain about the cause of the hydrocephalus but intratertiary or perinatal intracranial haemorrhage cannot be ruled out. We agree with Salazar et al that a caesarean section is indicated if labour starts while the mother is still on oral anticoagulants, as reversal of the mother’s anticoagulation can be quickly achieved.

There is no ideal method of anticoagulation during pregnancy in women with prosthetic valves, and no definitive recommendations can be made at present. We prefer to avoid oral anticoagulants during the first trimester and before delivery, although they appear to be safer for the mother. The outcome of pregnancy may be slightly improved when heparin is given in the first trimester but this did not reach statistical significance in our study. Low molecular weight heparins may represent the future management of these patients, as they do not cross the placenta, induce less osteoporosis, and offer more consistent protection against thromboembolism.

We are indebted to Olga Suárez and Verónica Rodríguez for their assistance in writing this paper.