Prosthetic Heart Valves and Pregnancy

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In patients with prosthetic heart valves (PHV), pregnancy is associated with the risks of warfarin embryopathy in patients with mechanical PHV and of structural valve deterioration (SVD), both early and late, in patients with biological PHV.

**Mechanical Valves**

**Warfarin**
The use of warfarin, particularly between the 6th and 12th weeks of pregnancy, is associated with an embryopathy, "warfarin embryopathy,“ which is characterized by nasal hypoplasia and/or stippled epiphyses. Uncommon features, including central nervous system and eye abnormalities, may be due to warfarin exposure during the second and third trimester.

There is a wide range of the reported incidence of warfarin embryopathy (Table 1). Ten studies comprising 427 pregnancies reported the incidence was zero (Table 1). From the patient’s point of view, the incidence per live birth may be more important; four recent (between 1994 and 99) studies reported an incidence of 3/189 (1.6%) live births (Table 1). One group has shown that the risk of warfarin embryopathy was extremely low in the 33 women who needed warfarin to maintain an adequate INR. The incidence of warfarin embryopathy will be lower with use of IV unfractionated heparin in the first 3 months (especially between the 6th to 12th weeks) of pregnancy; one review concluded that this strategy “eliminated the risk.” IV unfractionated heparin use in the last 2 weeks of pregnancy is associated with a reduced risk of hemorrhage during delivery and the neonatal period in the mother, as well as in the baby, because warfarin crosses the placenta, and therefore, the fetus/baby is anticoagulated. To reduce the latter complication, some have suggested elective caesarian section in the 38th week of pregnancy.

An earlier study reported the incidence of abortion and stillbirths in these patients was higher than in the population; in a subsequent study the incidence was similar.

**Subcutaneous Heparin**
The recommendation for use of subcutaneous heparin in pregnancy by Ginsberg et al is based on: (1) its value in patients with angina and myocardial infarction; and (2) a study of 100 pregnancies in 77 women. In 98 of the 100 pregnancies, heparin therapy was continued.

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was given for prevention or treatment of thromboembolism, and in 2/100 pregnancies it was given for women with PHV. Oakley has criticized this recommendation. The incidence of thromboembolism on heparin therapy during pregnancy in patients with a mechanical prosthesis is 4 times greater than in those treated with oral anticoagulants. Two studies from the same institution documented mechanical PHV thrombosis with subcutaneous heparin. In one study, 2/23 (8.7%) patients had massive valve thrombosis. In the other study, in 22 pregnant patients with mechanical valves, one had a cerebral embolus and 3 (14%) died, one from gastrointestinal bleeding and 2 with thrombosed PHV. Subcutaneous heparin does not improve fetal outcome and increases maternal mortality.

Low-Molecular-Weight Heparin

There are no good data at the present time documenting the benefits for the use of low-molecular-weight heparin in patients with PHV. Case reports of thrombosed PHV with the use of low-molecular-weight heparin have been reported. The FDA has issued additions to the warnings and precautions sections of the Lovenox (enoxaparin sodium) product labeling. These warnings point out:

- This product (a low-molecular-weight heparin) is not recommended for thrombotic prophylaxis in patients with PHV;
- Cases of PHV thrombosis and of maternal and fetal deaths have been reported with use of this drug;
- Furthermore, in pregnant women who received this drug, both teratogenic and nonteratogenic effects have been reported.

Biological Valves

Bioprostheses (Heterografts)

Operative mortality at initial PHV insertion was 4.3%. Pregnancy in women with a bioprosthesis is associated with SVD; the incidence may average 24% during or shortly after pregnancy. After bioprosthetic PHV valve replacement, the incidence of SVD at 10 years was 55 to 76%; the incidence of PHV-related re-operation was 60 to 80% (Table 3). The incidence of SVD in those who were subsequently pregnant versus those who were not was 76.7 ± 14% versus 25.8 ± 8.5% (P < 0.05) in one study and 55.3 ± 8.2% versus 45.7 ± 4.8% (P = NS) in another. The issue is not similar rates of SVD in women with or without subsequent pregnancy. An important issue is the very high rate of bioprosthetic SVD in people aged 16 to 40 years at the time of PHV implantation: ~50% at 10 years and

### Table 1. Incidence of Warfarin Embryopathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Pregnancies</th>
<th>No. of Live Babies</th>
<th>No. of Pregnancies</th>
<th>% of Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Ismail et al</td>
<td>53</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chen et al</td>
<td>45</td>
<td>...</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Larrea et al (group III)</td>
<td>21</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salazar et al</td>
<td>40</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Iturbe-Alessio et al (group II)</td>
<td>23</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sbarouni and Oakley</td>
<td>64</td>
<td>62</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 1. Incidence of Warfarin Embryopathy**

*Review of the literature.
†Same medical center.
‡Same medical center.
§Thirty-eight of 80 live births were examined.
¶Excluding 128 patients in Salazar study because only 38 of 80 live births were examined, as well as all in the study by Wong et al because the number of pregnancies is not known.
#Excluding 80 live births in the study by Salazar et al because only 38 live births were examined.
**Excluding 3 in the study by Salazar et al and 18 in the study by Wong et al.
"Excluding 3 in the study by Salazar et al.
90% at 15 years (Figure). Furthermore, SVD begins 2 to 3 years after PHV implantation in this age group (Figure). The mortality of re-operation is 3.8% to 8.7%. At 9 years, the rate of SVD of newer porcine valves and the stentless porcine valve is within the expected range of SVD earlier stented porcine valves, indicating that at present all porcine valves have similar rates of SVD; however, data are not available for pregnant women.

Four important issues to consider before bioprosthetic PHV is implanted in young women before pregnancy are:

- Some may suffer SVD even before their first pregnancy
- Some may suffer SVD during pregnancy or soon after delivery
- If women have babies before SVD and die at re-operation, the babies/children will be without a biological mother
- With mitral bioprosthesis, the rate of SVD will be higher than that cited above for aortic valve replacement with a bioprosthesis.

Sbarouni and Oakley have asked, "Why should young women be singled out?"

### Table 2. Bioprostheses and Pregnancy: Early SVD

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Early SVD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born et al</td>
<td>20</td>
<td>4</td>
<td>20† Needed re-operation during pregnancy or in puerperium</td>
</tr>
<tr>
<td>Bartolotti et al</td>
<td>7</td>
<td>2</td>
<td>29* &lt;3 months after delivery</td>
</tr>
<tr>
<td>Salazar et al</td>
<td>5</td>
<td>3</td>
<td>60* During pregnancy and 7 to 12 months after pregnancy</td>
</tr>
<tr>
<td>Badduke et al</td>
<td>17</td>
<td>2</td>
<td>12 Re-operation 3 to 10 months after pregnancy</td>
</tr>
<tr>
<td>Hanania et al</td>
<td>42</td>
<td>5</td>
<td>12* 4 to 36 months after delivery</td>
</tr>
<tr>
<td>Sbarouni and Oakley</td>
<td>49</td>
<td>17</td>
<td>35† During pregnancy or soon after delivery</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>33</td>
<td>24</td>
</tr>
</tbody>
</table>

*Porcine valves.
†Mainly porcine and few other biological valves.

### Table 3. Bioprostheses and Pregnancy: Late Complications (10 y)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Badduke et al</th>
<th>Jamieson et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVD</td>
<td>76.7±14%</td>
<td>55.3±8.2%</td>
</tr>
<tr>
<td>Valve related complication</td>
<td>78.3±12.7%</td>
<td>...</td>
</tr>
<tr>
<td>Valve related re-operation</td>
<td>79.7±12.4%</td>
<td>59.8±7.8%</td>
</tr>
<tr>
<td>PHV endocarditis</td>
<td>47.1%</td>
<td>50.9%</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>5.9%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Non-SVD</td>
<td>...</td>
<td>1.9%</td>
</tr>
<tr>
<td>Sudden death</td>
<td>...</td>
<td>1.9%</td>
</tr>
<tr>
<td>Total</td>
<td>70.6%</td>
<td>66.1%</td>
</tr>
</tbody>
</table>

Percent freedom from structural valve deterioration in 1408 patients who received the Hancock MO, Hancock standard, and Carpentier-Edwards porcine bioprosthesis by age of patients at time of PHV implantation at Stanford University. Note: in patients aged 16 to 49 at time of PHV implantation, SVD began at years 2 to 3 after PHV implantation and is about 50% at 10 years and 90% at 15 years. Reprinted with permission from reference 28.

Percent freedom from structural valve deterioration in 1408 patients who received the Hancock MO, Hancock standard, and Carpentier-Edwards porcine bioprosthesis by age of patients at time of PHV implantation at Stanford University. Note: in patients aged 16 to 49 at time of PHV implantation, SVD began at years 2 to 3 after PHV implantation and is about 50% at 10 years and 90% at 15 years. Reprinted with permission from reference 28.
out for obligatory re-operation with its attendant risks?"9

Homografts (Allografts)

Homografts (allografts) have the same rate of SVD as porcine bioprostheses29,30; data are not available for pregnant women with long-term follow-up.

Autografts (Pulmonary Autograft for Aortic Valve Replacement [Ross Principle])

The Ross31 principle is a more complex and more difficult procedure, but has at least some advantages. For example, when inserted in children, the valve increases in size as the child grows. Of 8 women who had 14 pregnancies after receiving a pulmonary autograft, one woman developed dilated cardiomyopathy (peripartum cardiomyopathy)? 6 months after delivery, one developed obstruction of the unsupported fascial pulmonary valve, and one developed acute endocarditis of the freeze-dried aortic homograft that had been inserted in the pulmonary position. The remaining 5 patients were well at last follow-up.

A review of this procedure30 showed that:

- Thrombo-emboli was 0% to 1.2% per year
- Infective endocarditis was 0% to 1.2% per year
- Re-operation within the first 6 months was 0%, 1.5%, 3.8%, and 10% in four different studies
- Late re-operation rates ranged from 0.4% to 1.5% per year

There is a risk of rheumatic valvulitis in the autograft in those who have rheumatic heart valve disease.33,34

The only studies with a follow-up of >10 years are from Ross’s group (Table 4).35–38 The freedom from autograft replacement ranged from 48.5±13.7% at 19 years to 85% at 20 years; the most likely explanation for this wide range is selection of patients reported

### Table 4. Ross Procedure by D.N. Ross

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry into studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitals</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1*</td>
</tr>
<tr>
<td>Clinics</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>No. of patients</td>
<td>241</td>
<td>339</td>
<td>339</td>
<td>151</td>
</tr>
<tr>
<td>Age, y, range</td>
<td>9 to 60</td>
<td>3.5 to 60</td>
<td>&lt;10 to &gt;60</td>
<td>11 to 52</td>
</tr>
<tr>
<td>Operative mortality</td>
<td>6.6%</td>
<td>7.4%</td>
<td>7.4%</td>
<td>13%</td>
</tr>
<tr>
<td>Longest follow-up</td>
<td>18y 7m</td>
<td>24 y</td>
<td>24 y</td>
<td>26 y</td>
</tr>
<tr>
<td>Total patient years</td>
<td>1130</td>
<td>3986</td>
<td>3774</td>
<td>2752</td>
</tr>
<tr>
<td>Survival</td>
<td>57.3±9.6% at 19 years</td>
<td>80% at 20 years</td>
<td>80% at 20 years</td>
<td>61% at 20 years†</td>
</tr>
<tr>
<td>Freedom from autograft replacement</td>
<td>48.5±13.7% at 19 years</td>
<td>85% at 20 years</td>
<td>85% at 20 years</td>
<td>75% at 20 years*</td>
</tr>
</tbody>
</table>

Values are expressed as n, range, or mean±SD, as indicated.

*Unique pioneer series from the National Heart Hospital.
†In operative survivors, ie, excluding operative mortality.
in these 4 studies. In the series from only the National Heart Hospital:

- Operative mortality was 13%.
- In operative survivors (ie, excluding operative mortality), late mortality was 40.5% and actuarially determined mortality at 15 and 20 years was 25% and 39%, respectively.

- Actuarially determined freedom from autograft replacement was 75% at 20 years.

**Conclusions**

**Mechanical Valves**

- Patients with mechanical valves need close monitoring of warfarin therapy during pregnancy. Substitution of warfarin with IV unfractionated heparin in the first 6 to 12 weeks and last 2 weeks of pregnancy is associated with a low rate of warfarin embryopathy and of bleeding in the mother and baby. The initiation of heparin therapy is clinically most feasible and practical at 4 to 6 weeks of pregnancy. Women who need ≤5 mg of warfarin are probably at low risk for fetal warfarin embryopathy and may be able to receive warfarin throughout pregnancy, but more data are needed.

- Subcutaneous heparin and low molecular weight heparin cannot be recommended at the present time in such patients.

**Biological Valves**

- Bioprostheses have a risk of early SVD during or shortly after the end of pregnancy. Moreover, at 10 years there is a high rate of SVD (55% to 77%) and of valve-related re-operation (60% to 80%).

- Both men and women aged 16 to 40 years at time of bioprosthetic PHV implantation are at risk of SVD, which begins 2 to 3 years after valve replacement; at 10 to 15 years, the rate of SVD is very high (50% to 90%).

- One has to balance the risks of SVD and its consequences to the mother and family in those who receive a bioprosthetic PHV versus the small risk of warfarin embryopathy in the fetus in those women who receive a mechanical PHV.

- There are no data in patients who had received a homograft.

- More data are needed in patients who have had the pulmonary autograft procedure according to the Ross principle.

- If anticoagulation is needed the use of LMWH is of concern because the FDA has cited the occurrence of both teratogenic and non-teratogenic effects with use of LMWH. More data, including randomized trials, are needed.

**Algorithm 4.**

**Algorithm 5.**
Management Strategies
The management of young women with VHD who are contemplating a future pregnancy, the choice of PHV if one is necessary, and the management of such patients during pregnancy are outlined in algorithms 1 to 6. Patients with aortic or mitral regurgitation (AR and MR, respectively) can cope with the volume load of pregnancy better than patients with severe valve stenosis because the reduction of systemic vascular resistance during pregnancy favors a reduction of aortic or mitral regurgitation. The volume load associated with pregnancy is not well tolerated in the presence of a severe valve stenosis (aortic stenosis as valve area $\leq 1.0 \text{ cm}^2$; $\leq 0.6 \text{ cm}^2/m^2$) or mitral stenosis (mitral valve area $\leq 1.0 \text{ cm}^2$).

References