Pregnancy in patients after valve replacement

Celia Oakley and P. Doherty

From the Division of Cardiovascular Disease (Clinical Cardiology), Hammersmith Hospital, Department of Medicine, Royal Postgraduate Medical School, London W12 0HS

This report is based on information obtained from a questionnaire sent to major cardiac centres in the United Kingdom. This produced details of 39 pregnancies in 34 patients after valve replacement. The 39 pregnancies gave rise to 30 healthy babies. The small size of the series probably reflects both the increasing rarity of young women with rheumatic heart disease in this country and the cautious attitude of their cardiologists. This makes it likely that these women represented the best end of the spectrum of cardiac function after valve replacement.

Twenty-four pregnancies in 20 women who were not given anticoagulants produced 23 healthy babies and 1 spontaneous abortion. This group comprised 6 patients with free aortic homografts, 1 patient with a free fascia lata aortic valve, 2 with a Starr Edwards aortic valve, 7 with mounted mitral homografts, 1 with a fascia lata mitral valve, 1 with a Beall tricuspid prosthesis, 1 with a combined mitral homograft and Starr Edwards aortic prosthesis, and 1 with mitral and aortic frame-mounted fascia lata valves. There were no maternal deaths or thromboembolic complications in this group which included 5 patients who were in atrial fibrillation.

Fifteen pregnancies in 14 women who received anticoagulants gave rise to 7 healthy babies. The fetal losses were one stillbirth, one intrauterine death at 34 weeks, and 3 spontaneous abortions; one surviving child has hydrocephalus as a result of blood clot and there were 2 maternal deaths. This group included 13 patients with Starr Edwards valves, 11 mitral and 2 aortic. A patient with a Hammersmith mitral valve was the only one to have been treated with heparin and her valve thrombosed. One patient with a mounted mitral homograft had a cerebral embolus. Nine of these patients were in atrial fibrillation.

In 3 additional patients the valve replacement was carried out during pregnancy. Two of the patients survived operation. In one of these who was treated with warfarin the pregnancy gave rise to a congenitally malformed baby who died in the neonatal period. The baby born to the mother who did not receive anticoagulants had a hare-lip and talipes.

Women with artificial valves can tolerate the haemodynamic load of pregnancy well, but there is an increased fetal wastage in patients taking oral anticoagulants. This is probably largely attributable to fetal haemorrhage but there is also a risk of malformation caused by a teratogenic effect of warfarin. Experience gained in non-pregnant patients suggests that withholding anticoagulants in pregnant patients with prosthetic valves would usually be undesirable but warfarin should be avoided. The advantages of biological valves were apparent in this series.

Although rheumatic heart disease has become rare among our indigenous youth, its prevalence in many parts of the world remains unchanged and the increasing frequency with which artificial valves are being used in the management of congenital and postinfective as well as rheumatic heart disease means that there is a growing population of women of child-bearing age who have had valve replacements. These women need to know the risks of pregnancy and the chances of having a healthy baby, but physicians and cardiologists cannot yet advise them honestly because of the limitations of individual experience.

A survey was undertaken to find out what the overall experience in the United Kingdom has been. Though there is a growing number of published reports they are mainly case reports, and we felt

Received 23 April 1976.

1Present address: Division of Medicine, Stanford University, Palo Alto, California, U.S.A.
that many of the publications may have been inspired either by the success or by the failure of the pregnancy or pregnancies described and might not be true indicators of overall practice and experience.

Patients

The questionnaire was sent to cardiologists in the United Kingdom and sought the following information.

(1) The patient's age, diagnosis, date of operation, and the interval between it and subsequent pregnancy; (2) the sites, models, and sizes of the artificial valves used; (3) the anticoagulant regimen adopted; (4) the use of other drugs including agents inhibiting platelet aggregation; (5) the course of the pregnancy with particular reference to the development of heart failure, valve dysfunction, embolism, or deep venous thrombosis; (6) the management of labour and the puerperium.

The section of the questionnaire which dealt with the baby inquired about (1) gestational age; (2) the general health at delivery; (3) the presence of congenital abnormalities, and (4) cerebral damage or jaundice.

The response to the questionnaire produced the details of 32 patients to which we added 5 of our own (Cases 5, 6, 7, 8, and 30—Table). The patients fell into 3 groups. The first group (Cases 1 to 30) consisted of patients who completed their pregnancies, 3 of whom have already been reported: Case 1 (Littler, 1970); Case 23 (Szekely and Snaith, 1969), and Case 30 (Bennett and Oakley, 1968). Nineteen patients were not given anticoagulants (Cases 1 to 19). Of these patients, 13 had homograft valves (6 aortic; 7 mitral), 1 an aortic fascia lata valve, 2 aortic Starr Edwards valves, 1 a Beall valve in the tricuspid position for Ebstein's disease, 1 a mitral homograft and a Starr Edwards aortic prosthesis, and 1 both mitral and aortic frame-mounted fascia lata valves. Eleven patients were treated with anticoagulants (Cases 20 to 30).

These included 9 patients with Starr Edwards prostheses (7 mitral; 2 aortic), 1 with an Alvarez Hammersmith mitral valve, and 1 with a mounted mitral homograft who was started on anticoagulants after an embolus at 34 weeks. Warfarin was used in 5 patients, 5 received phenindione, and 1 (Case 20) received subcutaneous heparin in full anticoagulant doses.

In the second group, pregnancy was not completed (Cases 31 to 34). Two of these patients had Starr Edwards prostheses and received warfarin. The other had a fascia lata mitral valve and was not given anticoagulants.

The third group consisted of 3 patients who had a valve replacement performed during pregnancy (Cases 35 to 37). Two survived operation, 1 with a Starr Edwards mitral valve who received warfarin and 1 with a free aortic homograft to whom no anticoagulants were given.

The 11 patients in the first and second groups with aortic valve replacement alone were all in sinus rhythm. Seven had free aortic homografts or a fascia lata valve and did not receive anticoagulants. Only 2 of the 4 patients with a Starr aortic valve received anticoagulants. Of the 26 patients who had mitral, mitral plus aortic, or tricuspid valve replacement, 14 were in atrial fibrillation and 13 received anticoagulants. All the patients with Starr Edwards mitral valves received anticoagulants but only one of those with a mitral homograft did so; she was in sinus rhythm but had a cerebral embolus and anticoagulants were started at 34 weeks' gestation.

The intervals between cardiac operation and conception varied between 3 months and 5 years and the ages of the patients ranged from 18 to 38 years.

Results

Babies

Thirty-nine pregnancies in 34 women who conceived after valve replacement gave rise to 30 healthy babies. There were 3 spontaneous early abortions in women taking warfarin and 1 abortion occurring at 24 weeks in a patient who was not on anticoagulants (Cases 31 to 33). There were 2 late intrauterine deaths (Cases 26 and 27); both of these fetal deaths occurred in women who were receiving phenindione. One baby (Case 22) developed hydrocephalus secondary to a blood clot obstructing the third ventricle. As his birth had been by caesarean section at 38 weeks the cerebral bleed can almost certainly be attributed to the warfarin which his mother had received. This child has now had a shunt performed but is retarded and blind. The other two fetal deaths were the result of death of the mother.

Both of the women who survived valve replacement during pregnancy had malformed babies (Cases 35 and 37). The baby born to the patient who received warfarin (Case 35) had multiple congenital malformations and died in the neonatal period; this may have been chondrodysplasia punctata but not recognized as such. The hare-lip and talipes of the baby born to Case 37 must have been determined well before the time of cardiopulmonary bypass in mid-pregnancy, possibly during infective endocarditis.

The only fetal complications in the 20 women who did not receive anticoagulants were a spontaneous abortion at 24 weeks (plus the hare lip and
## Table 1: Anticoagulant therapy in patients with congenital heart disease who underwent cardiac surgery

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Site</th>
<th>Type</th>
<th>Anticoagulant Type</th>
<th>Stopped before term</th>
<th>Replaced with heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>Aortic</td>
<td>Fascia lata</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>Tricuspid</td>
<td>Beall</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>Mitral aortic</td>
<td>Homograft SE Frame-mounted fascia lata</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>33</td>
<td>Mitral aortic</td>
<td>Homograft SE Frame-mounted fascia lata</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>33</td>
<td>Aortic</td>
<td>SE</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>28</td>
<td>Aortic</td>
<td>SE</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>Aortic</td>
<td>SE</td>
<td>Phenindione</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>29</td>
<td>Aortic</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>22</td>
<td>35</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>23</td>
<td>38</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes 24 hr before induction</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>25</td>
<td>28</td>
<td>Mitral</td>
<td>SE</td>
<td>Phenindione</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>26</td>
<td>28</td>
<td>Mitral</td>
<td>SE</td>
<td>Phenindione</td>
<td>No continued until delivery</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>27</td>
<td>Mitral</td>
<td>SE</td>
<td>Phenindione</td>
<td>Yes at 34/52</td>
<td>Yes</td>
</tr>
<tr>
<td>28</td>
<td>21</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>29</td>
<td>33</td>
<td>Mitral</td>
<td>Mounted homograft</td>
<td>Warfarin from 34/52</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>30</td>
<td>36</td>
<td>Mitral</td>
<td>Hammersmith Alvarez</td>
<td>Subcutaneous heparin Continued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>31</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>24</td>
<td>Mitral</td>
<td>Fascia lata</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>?</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>28</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>28</td>
<td>Mitral</td>
<td>SE</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>36</td>
<td>Mitral tricuspid</td>
<td>SE</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>23</td>
<td>Aortic</td>
<td>Homograft</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** SE = Starr Edwards; CCF = congestive cardiac failure; SBE = subacute bacterial endocarditis; PET = pre-eclamptic
Pregnancy in patients after valve replacement

Course of pregnancy | Fetal complications
--- | ---
Mild PET, vaginal delivery at term | Normal baby
Uncomplicated vaginal delivery, vaginal delivery at term | Normal baby
Normal vaginal delivery | Normal baby
Normal vaginal delivery | Normal baby
Uncomplicated Caesarian section 39/52 | Normal baby
2 normal pregnancies | 2 healthy babies
Forceps delivery 39/52, uncomplicated | Normal baby
Uncomplicated, vaginal delivery at term | Normal baby
Mild CCF, vaginal delivery by forceps at term | Normal baby
Normal vaginal delivery | Normal baby
Normal vaginal delivery | Normal baby
2 normal pregnancies | 2 healthy babies
Uncomplicated 2 pregnancies, both uncomplicated | Healthy baby
2 pregnancies | 2 healthy babies
CCF at 33 weeks, back to grade II by delivery | Normal baby
Uncomplicated | Normal baby
Uncomplicated | Normal baby
Uncomplicated, postpartum haemorrhage | Normal baby
Uncomplicated, postpartum haemorrhage | Normal baby
Uncomplicated, small haematoma of abdominal wall after caesarian section 38/52 | Hydrocephalus with organized clot obstructing 3rd ventricle, shunt performed, retarded and blind
Uncomplicated, normal vaginal delivery | Healthy baby, 2 mg vit. K₁ given at birth
Uncomplicated, normal vaginal delivery | Normal baby
Uncomplicated, caesarian section 37/52 | Normal baby
*Started on diuretics at 20/52, reason not specified
Induced at 34/52 because of intrauterine death | Necropsy: no cause for death
Uncomplicated, low forceps Cerebral embolus 34/52 | Normal baby
Caesarian hysterectomy 33/52, thrombosed prostatic valve, died 6 days postpartum | Neonatal death at 9 hours
2 pregnancies, spontaneous abortions at 8 and 11 weeks | 
Spontaneous abortion at 24/52 | 
Missed abortion at 15 weeks, warfarin changed to heparin before D and C | 
Patient died at 32/52 of ruptured common iliac aneurysm, complication of previous SBE | 
 Valve replaced during pregnancy at 20/52, caesarian section 38/52 | Neonatal death, congenital malformations
Valves replaced during pregnancy, patient died of post-op complications | Hare-lip and talipes
Developed SBE, valve replaced during pregnancy, normal vaginal delivery | 

Toxaemia; D and C = dilatation and curettage

talipes in Case 37 already discussed). The other 19 patients enjoyed 23 successful pregnancies.

Mothers

The maternal complications were few. The only patient who was treated with heparin throughout pregnancy rather than oral anticoagulants died. She was the only patient with a Hammersmith (Alvarez) prosthesis (Case 30); she received full anticoagulant doses of heparin subcutaneously throughout pregnancy and though she had enjoyed 3 years of good health since her valve replacement the valve became encapsulated by thrombus and fibrin when she was 33 weeks' pregnant (Bennett and Oakley, 1968). In the second group, one patient who was on warfarin died at 32 weeks after rupture of a common iliac aneurysm; this was thought to be a complication of previous infective endocarditis (Case 34). There was one maternal death in the third group and this resulted from postoperative complications following double valve replacement during the second trimester of pregnancy (Case 36). None of these major maternal complications can be attributed to the use of anticoagulants, though warfarin may have contributed to the fatal bleeding from the common iliac artery. There were 3 other minor complications attributable to anticoagulants: Cases 20 and 21 had postpartum haemorrhages and Case 22 developed a small haematoma of her abdominal wall after caesarian section. Apart from Case 30 there was only one thromboembolic complication in either group: Case 29 was in sinus rhythm with a mounted mitral homograft but had a cerebral embolus at 34 weeks; she was started on anticoagulants and the outcome was good. The patients seemed to deal easily with the haemodynamic stresses of pregnancy and congestive failure was noted in only 2 patients. In neither case was it a worry and both recovered well after a period of bed rest and diuretics. One was 35 years old with a mounted mitral valve prosthesis and atrial fibrillation (Case 10) and the other was a 33-year-old in sinus rhythm who was one of the only two patients in whom both mitral and aortic valves had been replaced, one of which was subsequently found to be leaking slightly (Case 17).

Discussion

An increase in cardiac output of up to 50 per cent above the non-pregnant level is achieved in pregnancy by an increase in stroke volume without an increase in rate. Provided the left atrium can empty freely even the disabled heart can adapt satisfactorily to pregnancy by an increase in rate to
compensate for any inability to increase stroke volume.

While many patients who have had aortic valve replacement for congenital or postinfective aortic valve disease have nearly normal cardiac function most patients with rheumatic mitral or multivalvular disease still have considerably impaired cardiac performance after operation and many are in atrial fibrillation. Despite this, it has become apparent that many patients can easily cope with the demands of pregnancy after valve replacement (Ueland, Tatum, and Metcalfe, 1966; Barnard and Heydernych, 1969; Radnich and Jacobs, 1970; Jenkins and Braimbridge, 1971; Ibarra-Pérez and Del Bosque-Ruiz, 1972). Only 1 maternal death occurred among 95 completed pregnancies reported up to the end of 1975 (Mahairas and Weinhold, 1963; Palacios-Macedo, Díaz-Devis, and Escudero, 1969; Laros, Hage, and Hayashi, 1970; Macdonald, 1970; Buxbaum et al., 1971; Jenkins and Braimbridge, 1971; Hirsh, Cade, and Gallus, 1972; Casanegra et al., 1975; Chew and Ratnam, 1975).

This was our Case 30, previously reported (Bennett and Oakley, 1968) and her death was caused by thrombosis of her mitral valve and not by any haemodynamic inadequacy existing before this complication. Even triple valve replacement can allow safe and successful pregnancy, yet accompanying their replies to the questionnaire a number of cardiologists spontaneously referred to their ‘vigorous sterilization policy’ or volunteered that they ‘would never permit a patient with an artificial valve to undertake pregnancy’. Few of our patients became pregnant against the advice of their cardiologists and their cautious attitude indicates the selected nature of our material. We see a predominance of single valve replacements, of biological valves, and of sinus rhythm in this series.

The general care of these patients during pregnancy does not differ in principle from that of pregnant patients with valvular heart disease who have not had valve replacements. Current practice has been well reviewed by Szekely, Turner, and Snaith (1973) and by Conradsson and Werkö (1974). There are, however, some aspects of management which take on special importance and warrant further discussion.

In contrast to the good experience of the mothers the fetal mortality is high. That this is not a necessary consequence of the maternal disease is shown by the experience of Szekely and his colleagues (1973) in Newcastle who reported a perinatal mortality of under 5 per cent in over 200 patients with rheumatic heart disease between 1961 and 1969 (with no maternal mortality). This high fetal mortality is intimately connected with the use of oral anticoagulants. All 23 completed pregnancies in women who were not receiving anticoagulants produced healthy babies in this series. There was no fetal or neonatal mortality or morbidity and the only congenital malformations were in Cases 35 and 37 who had a valve replaced during pregnancy. Buxbaum et al. (1971) reported a similar experience in 6 patients.

When considering whether or not to continue oral anticoagulants the risk to the fetus if they are used has to be weighed against the risk of thromboembolism in the mother if they are stopped. Experience in non-pregnant patients indicates that anticoagulants are effective in reducing the incidence of thromboembolic complications after valve replacement (Akbarian et al., 1968). During pregnancy the concentration of most coagulation factors in the blood is increased and fibrinolysis is decreased (Hedstrand and Cullhed, 1968), but despite this there is little evidence of increased risk of pulmonary thromboembolism during normal pregnancy (Villasanta, 1965; Bonner, 1975) probably because of the increased cardiac output. There is a real risk of embolism in patients with prosthetic valves whose anticoagulants are stopped or interrupted during pregnancy (Akbarian et al., 1968; Jenkins and Braimbridge, 1971) and in the cases reviewed by Buxbaum et al. (1971) there were 4 embolic episodes in 8 patients compared with only 3 in 29 pregnancies covered with anticoagulants throughout. However, Sowinsky, Zdebski, and Haduch-Kowalczyk (1972), reviewing 15 cases who had not received anticoagulants in pregnancy, found only 1 who had suffered a thromboembolic episode. Experience with the newer cloth-covered Starr Edwards valves shows that there has been a decrease in the incidence of embolic episodes (Isom al., 1972). The trend, which applies particularly to aortic prostheses, becomes more obvious the longer the valve is in situ and is attributed to endothelialization of the supporting structures of the prosthesis. Unfortunately, the protection from thromboembolic risk conferred by any of the newer artificial valves is not absolute. There is a higher incidence of embolism in patients with mitral than with aortic prostheses because these patients more frequently have atrial fibrillation and large atrial cavities and appendages. Anticoagulants are mandatory in such patients but are still recommended in patients with aortic prostheses. Anti-coagulants are usually not needed after tissue valve replacement. Thromboembolism is virtually unknown after free aortic homograft insertion and seems to be rare after replacement of the mitral valve with stented aortic homografts despite the frequency of atrial fibrillation. The only
embolic episode in the series was in such a patient (Case 29) despite sinus rhythm when seen. The advantages of a biological valve in a young woman who may wish to have a family are apparent even though these valves may show less long-term durability than the artificial valves.

The formation of thrombus in relation to prostheses has been shown to be the result of the build-up of adherent platelet aggregates and the deposition of fibrin (Mustard et al., 1966). This has led to the use of 'antiplatelet aggregating' agents, of which dipyridamole (Sullivan, Harken, and Gorlin, 1971) and aspirin (Stuart et al., 1974) have proved to be effective when combined with warfarin, but whether they will be safe in pregnancy or effective when used on their own has yet to be shown. There is one case report (Ben Ismail et al., 1975) of a woman with 3 prosthetic valves in whom warfarin was replaced by 1·5 g aspirin and 225 mg dipyridamole daily at 2 months’ gestation and who continued to term with a successful outcome.

Oral anticoagulants of the coumarin and indanedione groups cross the placental barrier and reach the fetus whose state of anticoagulation is likely to be different from that of the mother as well as unmeasurable. Because of immature fetal liver enzyme systems the baby is likely to grow in a continuing state of anticoagulant overdose if the mother’s state of anticoagulation is within the therapeutic range. It is probably more dangerous to give oral anticoagulants early in pregnancy because the fetus is then at its most vulnerable both from bleeding and from the teratogenic effects of these drugs (vide infra). A small haemorrhage can at this time produce severe damage because of the close proximity of the developing structures.

The evidence that these are real hazards comes from Mahairas and Weingold (1963) and the review by Villasanta (1965) later supported by Fillmore and McDevitt (1970). Villasanta related the experience of 93 women who were treated with oral anticoagulants during their pregnancies, resulting in 14 stillbirths, 3 neonatal deaths, and 2 congenital malformations. He concluded that oral anticoagulant drugs should not be prescribed during pregnancy. Villasanta’s experience that 16 per cent of the babies suffered brain damage attributable to haemorrhage in utero was particularly alarming as most of the mothers studied by him had received anticoagulants for venous thrombosis and so had only been treated for a few weeks rather than throughout pregnancy. The risk of intrauterine death was reported also by Palacios-Macedo et al. (1969) who described 3 stillbirths occurring in 6 patients with prosthetic valves, in 1 of whom multiple haemorrhages were found at necropsy and in another the fetus had probably died at a time when there was excessive anticoagulant effect in the mother. Poor anticoagulant control is likely to compound the risks. The case reported by Kenmure (1968) was an example of the kind of patient who fortunately does not appear in our series; in her 40s and diabetic with an accidental pregnancy, she had a mitral Starr valve and was in atrial fibrillation, with a history of postoperative cerebral embolism: the baby was stillborn at 33 weeks.

Mahairas and Weingold showed a connexion between depression of prothrombin activity and perinatal haemorrhage if oral anticoagulants were continued during delivery. Experimental evidence that the trauma of vaginal delivery is also a major risk factor in the production of perinatal cerebral haemorrhage is available from the work of Hirsh, Cade, and O’Sullivan (1970) who showed that widespread haemorrhage occurred in the fetuses of rabbits who were given warfarin until term; all were stillborn. In those cases reviewed by Villasanta (1965) who were receiving oral anticoagulants up to term there were 5 cases of perinatal haemorrhage, 4 of which proved fatal. Hirsh’s group showed that no perinatal haemorrhage occurred if fetal clotting factors were allowed to return to normal by stopping warfarin a few days before delivery, or even in the presence of depressed fetal coagulation factors if delivery were by caesarian section. The usual practice now is for patients to have their oral anticoagulant changed to heparin, which does not cross the placenta, at least two weeks before term. This will not always be possible if labour starts prematurely, and vitamin K₁ or fresh frozen plasma given to the mother may not have time to correct the depressed fetal clotting state before delivery. Premature labour may be an indication for caesarian section when the mother is on oral anticoagulant treatment.

Maternal bleeding requiring transfusion during labour is rare. There are 3 cases reported by Buxbaum et al. (1971) in association with the use of heparin. Haematomas in episiotomy sites or in caesarian scars (Case 22) do occur and show the need for scrupulous haemostasis (Hirsh et al., 1970, 1972).

Anticoagulants need to be used, so what is the best regimen to adopt? Heparin throughout pregnancy would be expected to remove the fetal hazards but is not always a practical possibility. The use of self-administered subcutaneous injections of heparin have recently been shown (Bonner, 1975) to produce effective blood levels. Though its successful use in pregnancy has been reported (Otterson, McGranahan, and Freeman, 1968) and subcutaneous heparin has the advantage

Pregnancy in patients after valve replacement 1145
of allowing therapy to be controlled on an outpatient basis, its effectiveness during pregnancy is still unknown. Even though it was used in full anticoagulant dosage in Case 30 the results were disastrous. The lack of standardization of available heparin preparations is another problem (Jaques, 1975). A compromise would be to use heparin in the first trimester, then to substitute oral anticoagulants until 2 to 3 weeks before term, when heparin is reintroduced. Hirsh *et al.* (1970) used this regimen in 15 pregnancies and had no fetal or neonatal complications. The obvious difficulty about this counsel of perfection would be the accurate prediction of the future conception in order to change the regimen in time.

Oral anticoagulant treatment is re-established after delivery. The presence of anticoagulant in the breast milk is not a significant problem compared with the higher concentration to which the baby had been exposed *in utero*. All babies should routinely be given vitamin K₁ at birth.

Although the high fetal wastage can be attributed largely to the oral anticoagulant treatment it is not wholly consequent upon bleeding. A teratogenic effect of anticoagulants first suggested by Villasanta is now well substantiated. Stippled epiphyses have been reported in 7 babies after warfarin (Fourie and Hay, 1975; Pettifor and Benson, 1975; Becker *et al.*, 1975; Shaul, Emery, and Hall, 1975). This condition, also known as chondrodysplasia punctata or the Conradi-Hunermann syndrome, causes saddle nose deformity, nasal hypoplasia, frontal bossing, and short stature. Inconstant features include optic atrophy, cataracts, mental retardation, and flexion contractures. There was no definite example of this condition in our series except, possibly, for the baby of Case 35. It appears three times in the reports of pregnancy after valve replacement; DiSaia's (1966) patient whose baby had nasal hypoplasia and optic atrophy, Kerber, Warr, and Richardson's (1969) patient whose baby had nasal hypoplasia, and Tejani's (1973) patient whose baby had nasal hypoplasia and multiple neurological abnormalities. All 3 of these patients had received warfarin throughout the pregnancy until the 31st, 35th, or 36th week when heparin was substituted. According to Fourie and Hay (1975), chondrodysplasia punctata is a rare embryopathy whose incidence has been estimated at 1 in 500 000 births and which otherwise is hereditary, occurring in a severe autosomal recessive and a milder autosomal dominant form. It seems unlikely, therefore, that the association with warfarin administration is a chance one. Perhaps an indanedione rather than a coumarin drug should be chosen for anticoagulant management in young women, but this raises the problem of renal and hepatic failure after phenindione. Though this complication rarely occurs without preceding skin eruption many would regard the teratogenic risk of coumarin to the baby as preferable to the probably greater risk of phenindione to the mother.

The subject of family planning should be approached early in patients who are likely to require a valve replacement during their childbearing years. They should be advised when possible to have their children before valve replacement unless they have lone aortic valve disease and homograft aortic valve replacement is available for them. Mounted mitral homograft valves or other forms of tissue mitral valves are less generally available and less favoured but all except one of the patients with such valves in our series did well without anticoagulant treatment. Mitral regurgitation and multivalvar disease is less dangerous than pure mitral stenosis in pregnancy because of a lesser risk of pulmonary oedema. While mitral valvotomy can be carried out safely in pregnancy and should not be delayed when the valve is suitable, vigorous medical management of a woman who will need valve replacement is still worth while in order to take her through pregnancy before cardiac surgery is undertaken. While open heart surgery can be carried out successfully during pregnancy, in most institutions it is not yet as safe for the baby as a closed procedure so that deferral of open heart surgery and choice of closed rather than open mitral valvotomy seems to be wise at the present time. In the 3 cases we report who underwent valve replacement during pregnancy (Cases 35 to 37), there was one maternal and fetal death resulting from postoperative complications and the 2 babies who survived birth had congenital malformations. Zitnik *et al.* (1969) reported 3 patients who underwent valve replacement during pregnancy, all of whom survived. Two of these had normal babies; the other who was operated on at 19 weeks had a spontaneous abortion three days after operation. These were included in a series of 20 patients who had open heart surgery during pregnancy. Among these there was one maternal death in a patient with an atrial septal defect, and a high fetal mortality of 33 per cent. Zitnik recommended that operation should be performed after the 28th week when organogenesis is complete and suggested short bypass times with high flow to provide maximal placental perfusion.

**Conclusion**

A review of previously reported cases in addition to our own series indicates that most patients with
artificial valves can safely undertake pregnancy. If the patient who is taking an anticoagulant understands that there is an increased risk to the baby but is still keen, then future pregnancy need not be discouraged. Patients with tissue valves who do not require an anticoagulant after valve replacement can undertake pregnancy with a normal expectation of achieving a healthy baby. For this reason biological valves maintain an advantage over other types of prostheses in young women. For those patients who need to be on an oral anticoagulant there is an increased risk of abortion, stillbirth, perinatal mortality, and morbidity and, in addition, a risk of fetal malformation caused by warfarin. An alternative anticoagulant should be considered when young women are started on anticoagulants after valve replacement.

We thank the following physicians who sent us details of their patients: Drs. David Boyle, Norman Coulshed, Hewan Dewar, Ronald Gold, Monty Goldberg, Frederic Jackson, William Littler, R. M. Marquis, Martin McNicol, Sam Oram, Michael de Swiet, Paul Szekely, and Malcolm Towers.

References


Requests for reprints to Dr. Celia Oakley, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS.
Pregnancy in patients after valve replacement.

C Oakley and P Doherty

Br Heart J 1976 38: 1140-1148
doi: 10.1136/hrt.38.11.1140

Updated information and services can be found at:
http://heart.bmj.com/content/38/11/1140

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/