Pregnancy outcome and follow-up cardiac outcome in women with aortic valve replacement

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Abstract

Objectives: To compare the maternal, fetal and cardiac outcomes in women who have undergone aortic valve replacement.

Method: Retrospective observational study of all women with aortic valve replacement, who underwent a pregnancy (1998–2012). Maternal-, fetal- and valve-related cardiac outcomes were assessed.

Results: Thirty-two pregnancies in 16 women with aortic valve replacement (nine bioprosthetic, six Ross and 17 mechanical) were evaluated. There were no adverse maternal events in the bioprosthetic and Ross groups but three in the mechanical group. Fetal loss rate was highest in the mechanical valve pregnancies (53%). One woman in the bioprosthetic group needed valve re-operation, and one woman in the mechanical valve group died. There was no difference in the change of V_{max} over the follow-up between the valves ($p = 0.25$).

Conclusions: There was no difference in deterioration between aortic valve replacements during and after pregnancy. The highest risk of maternal and fetal complications occurred in the mechanical valve group.

Keywords

Bioprosthetic heart valve, mechanical heart valve, Ross operation, pulmonary autograft, aortic valve, pregnancy

Introduction

The most appropriate valve substitute for women of reproductive age requiring aortic valve replacement (AVR) is unclear. The choice is between a mechanical valve, a bioprosthetic valve and a pulmonary autograft (Ross operation). There is undisputable evidence that the need for anticoagulation in pregnant women with mechanical valves results in increased maternal and fetal morbidity and mortality.^{1–5} However, most patients only require one operation in their lifetime and the risks in pregnancy may be offset by a reduction in surgical complications over their lifetime. Furthermore, most studies on mechanical valves include prostheses in various positions in the heart.⁶ There are less data on the risks to women who have AVR alone.

Although use of bioprosthetic valves eliminates the need for anticoagulation, these valves are prone to structural valve deterioration in young people, with a resultant need for re-operation and its associated risk.⁷ There is some evidence that pregnancy accelerates this deterioration, but this finding has not been replicated in more recent studies and there is therefore still uncertainty as to whether this occurs.^{8–11}

In the Ross operation, the patient's own pulmonary valve is used for the AVR and a prosthetic pulmonary valve is implanted, with the aim of preventing AVR deterioration and avoiding the need for anticoagulation. However, there are concerns regarding aortic regurgitation and structural valve deterioration of the pulmonary prosthesis, requiring reoperation,^{12,13} with associated morbidity and mortality of 3–13%.^{14,15} There is emerging evidence that pregnancy is well-tolerated following Ross operation with the data suggesting good haemodynamic profiles and limited cardiac complications.^{16–18}

Our cardiac obstetric service has been the regional referral centre for pregnant women with heart disease in the South West of England for 25 years. Our aim was to study our patient cohort to compare the maternal, fetal and cardiac outcomes in addition to valve-related complications in women with bioprosthetic valve, Ross operation and mechanical AVR, over the period of follow-up, to investigate which AVR was optimal for women of child-bearing age in terms of risks of adverse events during the pregnancy and over their lifetime.

Methods

The study was conducted at our regional cardiac obstetric unit. All the pregnancies in women with AVR that were managed at our centre between January 1998 and December 2012 were identified using patient databases. Women who had more than one heart valve replacement (other than Ross procedure) were excluded. Data were obtained retrospectively from the case notes and database. This included the original aortic valve pathology (aortic stenosis, aortic regurgitation or both aortic stenosis and regurgitation), age at surgery, total number and types of cardiac surgeries and surgical complications (cardiac failure, thromboembolism, bleeding, endocarditis and arrhythmia).

Pregnancy-related data included age at conception (conception confirmed by positive urine human chorionic gonadotropin test or ultrasound), body mass index (BMI; raised BMI defined as more than 30), smoking during pregnancy, duration between AVR and conception in years, type of anticoagulation as detailed in our previous paper,² need for planned delivery (induction of labour or caesarean section), indication for planned delivery (cardiac or obstetric), mode of delivery (normal vaginal delivery, operative delivery or caesarean section) and gestation at delivery (preterm delivery defined as before 37 completed weeks of gestation). Obstetric complications included haemorrhage (defined as over 1000 ml), pregnancy induced hypertension (new hypertension after 20 weeks of gestation: systolic blood pressure of 140 mmHg or more and diastolic of 90 mmHg or more), preeclampsia (pregnancy-induced hypertension and proteinuria of more than 0.3 g over 24 h) and fetal growth restriction (defined as less than 10th centile for the gestation). Fetal loss was defined as miscarriage,

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stillbirth (fetal demise after 24 weeks gestation), neonatal death (death before the age of 28 completed days following live birth) and termination of pregnancy (TOP) for medical reasons.

Cardiac data included valve thrombosis (as diagnosed by echocardiography), deterioration of left ventricular function (assessed by reduction in left ventricular ejection fraction on echocardiography) and structural valve deterioration (diagnosed on echocardiography with increase in the measurement of maximum trans-prosthetic jet velocity ($V_{\max}$) in m/s). Change in $V_{\max}$ was calculated from pre-pregnancy to last follow-up. The immediate post-pregnancy measurements were deliberately excluded to eliminate the influence of transient pregnancy-related increased measurements. Cardiac follow-up data included valve-related morbidity (valve thrombosis and structural valve deterioration), valve-related reoperation and mortality.

Data are described as absolute numbers and percentages. Medians and ranges were computed for non-parametric continuous variables. We used repeated measures analysis of variance to test within-subject effects and between-subject effects on changes in $V_{\max}$. Sphericity criteria were not met and hence Greenhouse-Geisser test of significance was used. Paired sample 't' tests were used to determine the significance between measurements at pre-pregnancy and last follow-up visits. Statistical significance was declared when the p value was <0.05 . All statistical analysis was carried out using SPSS 20.0 (USA).

Results

Sixteen women with AVR underwent 32 pregnancies. Five women with bioprosthetic valves underwent nine pregnancies, three women with the Ross procedure underwent six pregnancies and eight women with mechanical valves underwent 17 pregnancies. The original diagnosis was bicuspid aortic valve in 12 pregnancies, aortic regurgitation in eight pregnancies, aortic stenosis in 13 pregnancies and both aortic stenosis and regurgitation in seven pregnancies (Table 1).

There were no post-operative complications in any of the women following bioprosthetic AVR. Post-operative complications were encountered in one of the three women undergoing the Ross procedure (heart block requiring pacemaker insertion). Atrial fibrillation occurred post-operatively in two of the eight women undergoing mechanical AVR.

Anticoagulation during pregnancy in women with mechanical valves included low-molecular-weight heparin (LMWH) with low-dose aspirin in two pregnancies; a combination regimen of LMWH for the first trimester, warfarin until 36 weeks gestation and then LMWH until delivery in two pregnancies, and warfarin throughout in 13 pregnancies. The dose of warfarin ranged from 8 to 10 mg in the combination regimen group and 4 to 10 mg in the warfarin group.

Pregnancy outcome

Maternal outcome. There were no adverse maternal events in the bioprosthetic or the Ross group. There were three adverse maternal

events in the mechanical valve group including a transient ischemic attack, deterioration of left ventricular function and secondary post-partum haemorrhage. One woman (with Carbomedics 21 mm valve) had a transient ischemic attack at nine weeks gestation, whilst on the combination anticoagulation regimen. Due to concerns regarding compliance and difficulty in monitoring, she was recommenced on warfarin. She miscarried two weeks after re-starting warfarin. Deterioration of left ventricular function was noticed in one woman who had AVR (St Jude 21 mm) aged seven, and who chose the combination anticoagulation regimen during pregnancy but was non-compliant with LMWH administration. She had patient-prosthesis mismatch and a very high trans-prosthetic pressure gradient when first assessed in pregnancy. She suffered a deterioration of left ventricular function and reduction in peak pressure gradient across the prosthetic valve (from 130 mmHg to 80 mmHg), with no evidence of valve thrombosis as assessed by trans-thoracic echocardiography at 35 weeks gestation. Delivery was expedited by inducing labour. A cardio-stable combined spinal-epidural approach was used with a passive second stage of labour, and a forceps-assisted delivery was achieved. Following delivery, the left ventricular function improved with supportive management. The post-partum haemorrhage occurred in another woman six days following delivery, two days after warfarin was recommenced. No obstetric cause for bleeding was found. There was no objective evidence of valve thrombosis in any of the groups.

One woman in the bioprosthetic group had pregnancy-induced hypertension in the late third trimester. None of the women in Ross or mechanical valve group had pregnancy-induced hypertension and none had preeclampsia.

None of the women in the bioprosthetic group required obstetric intervention for cardiac reasons, although all five had planned deliveries due to obstetric indications. Of these, two had planned caesarean section (one previous caesarean section and another for maternal request) and three had induction of labour (one for fetal growth restriction and two for post-maturity). None of the women in the Ross group needed planned delivery; therefore, spontaneous labour was awaited. All the women in the mechanical valve group needed planned delivery in order to manage anticoagulation, of which one woman required induction of labour due to deterioration of left ventricular function as described above. Four of these women had obstetric indications for which elective caesarean section were planned; this included placenta praevia in one woman and three women had previous caesarean sections. All the women undergoing induction of labour had vaginal deliveries, five normal and one operative delivery. Two of the three women undergoing spontaneous labour had normal delivery and one had operative delivery (Table 2). None of the women in any of the groups required an emergency caesarean section. A total of six out of 15 (40%) babies were delivered by elective caesarean section, two out of 15 (13%) by operative vaginal delivery and seven out of 15 (47%) had a normal vaginal delivery.

Table 1. Demographic and descriptive data in the three groups.

	Bioprosthesis	Ross	Mechanical
Number of pregnancies (women)	9 (5)	6 (3)	17 (8)
Age in years at AVR: median (range)	31 (24–39)	20 (14–32)	25 (7–33)
Post-operative complications (number of women)	0	2 (3)	2 (8)
Duration between AVR and pregnancy: median (range)	2 (1–5)	7 (3–12)	9 (2–18)
Age at pregnancy: median (range)	33 (26–42)	22 (18–32)	30 (20–38)
High body mass index (>30)	0	0	1
Smoking: women (pregnancies)	0 (0)	1 (1)	4 (5)
Follow-up after pregnancy in years: median (range)	3 (1–6)	3 (1–5)	3 (1–5)

AVR: aortic valve replacement.

Fetal outcome. Within the bioprosthetic group, four of nine pregnancies ended in first trimester miscarriage. There was fetal loss in two of six pregnancies in the Ross group. One woman with the diagnosis of bicuspid aortic valve and aortopathy underwent TOP due to progressive aortic root dilatation at 18 weeks of gestation. There was an intra-uterine fetal demise at 37 weeks gestation in another pregnancy (birth weight on 30th centile), with no identifiable cause. In the mechanical group, fetal loss occurred in nine of 17 pregnancies. This included eight miscarriages and an intrauterine fetal death at 17 weeks gestation. The latter was diagnosed in a woman on the combination regimen, following recommencement of warfarin. The post mortem showed intra-ventricular haemorrhage and multiple periventricular haemorrhages (Table 2).

One woman was delivered at 37 weeks due to intrauterine fetal growth restriction, in the bioprosthetic group. The neonate weighed 2040 g (2nd centile for the gestation) and had an uneventful course following birth. No other fetus in any of the groups had growth restriction. The median birth weight centile in the bioprosthetic group was 30 (range: 2–80), in the Ross group was 45 (range: 18–60) and in the mechanical group was 25 (range: 20–40). All but two fetuses were delivered after 37 completed weeks of gestation. Both these women were delivered at 36 weeks, both in the mechanical group, one due to deterioration of cardiac function as described above and the other due to placenta praevia.

Table 2. Pregnancy outcome in the three groups.

	Bioprosthetic (n = 9)	Ross (n = 6)	Mechanical (n = 17)
Miscarriage	4	0	9
Medically indicated TOP	0	1	0
TOP for personal reasons	0	1	1
Stillbirth	0	1	0
Total fetal loss ^a	4/9	2/6	9/17
Intrauterine growth restriction	1	0	0
Preterm delivery	0	0	2
Livebirth	5	3	7
Total planned delivery	5	0	7
Cardiac indication	0	0	7 ^b
Obstetric indication	5	0	4 ^c
Mode of delivery			
Normal vaginal	3	2	2
Instrumental delivery	0	1	1
Caesarean section	2	0	4

TOP: termination of pregnancy.

^aTotal foetal loss excluding terminations for personal reasons.

^bPlanned delivery to manage anticoagulation in all, one needed delivery due to worsening left ventricular function.

^cAdditional obstetric indications.

Follow-up cardiac outcome

All women were followed up by the adult congenital heart disease team throughout the duration of this study; one woman in the mechanical group was lost to follow-up post-pregnancy. The total duration of follow-up since AVR was a median of five years (range: 4–10 years) in the bioprosthetic group, nine years (range: 9–16 years) in the Ross group and 13 years (range: 6–20 years) in the mechanical group.

The $V_{\max}$ measurements at the pre-pregnancy and last follow-up are shown in Table 3. The last documented $V_{\max}$ before conception was used as the pre-pregnancy value. The changes in $V_{\max}$ from the pre-pregnancy assessment to the assessment at the last follow-up showed a borderline significance in all the three groups. There was no significant interaction between the changes of $V_{\max}$ from pre-pregnancy to last follow-up visit to the type of AVR ($p = 0.25$).

In their lifetime, until the end of the follow-up period, the women had a median of 1 (range: 1–2) valve-related operation in the bioprosthetic group, 2 (range: 1–2) in the Ross group and 1 (range: 1–4) in the mechanical group. The valve-related operations included AVR, valve repair or valvuloplasty. Two women had two AVR operations. Both of these women had initial bioprosthetic AVR followed by mechanical AVR. One of these women had developed mild stenosis of her xenograft ($V_{\max}$ 3.0 m/s) with evidence of calcification on echocardiographic assessment before conception, which ended in a first trimester miscarriage. The stenosis worsened over the following two years ($V_{\max}$ 5.6 m/s), necessitating repeat AVR five years after her initial bioprosthetic valve. The second woman moved to our catchment area and was followed up after her mechanical AVR in 2002. None of the women in Ross or the mechanical groups needed repeat valve replacement during the period of follow-up.

There was one death over the duration of this study, which occurred in a woman with a mechanical valve. She suffered deterioration of left ventricular function during pregnancy, which recovered with supportive management as described above. She was itinerant and had been poorly compliant with warfarin. She was lost to follow-up and died two years after delivery, of an unknown cause.

Discussion

In keeping with previous studies, we found no maternal complications and a relatively low incidence of fetal adverse events in women who had undergone a bioprosthetic AVR or a Ross operation;^{16,19,20} although one woman with a bioprosthesis underwent repeat AVR two years after the pregnancy. Conversely, women in the mechanical valve group had a high rate of maternal adverse events, including a death and a 53% fetal loss rate, consistent with current evidence.^{3,4} A recent study comparing pregnancy outcomes in women with AVR described maternal cardiac complications in 14% women with bioprostheses, 5% with a pulmonary autograft and 29% with mechanical AVRs. The fetal loss rate including miscarriage, TOP for cardiac reasons and fetal death was 0%, 9% and 56% in the bioprosthetic group, Ross and the mechanical group, respectively.²⁰ Our study follows this trend in terms of our complication rate in women with mechanical valves but our numbers are smaller. It is interesting to note that, compared to this study, we found relatively lower rates of obstetric

Table 3. $V_{\max}$ measurements at pre-pregnancy and last follow-up and the significance of change (in the three groups).

Trans-aortic $V_{\max}$	Bioprosthetic Median (range)	Ross Median (range)	Mechanical Median (range)
Pre-pregnancy	2.2 (1–3)	1.6 (1–2)	2.4 (1.2–3.5)
Last follow-up	2.4 (2.3–5.6)	2 (1.9–2.2)	2.7 (1.4–3.7)
Change in $V_{\max}$, mean (CI), p^* value	−0.76° (−0.19–1.50), 0.046	−0.51 (−1.01–0.18), 0.045	−0.31 (−0.49–0.07), 0.043

*paired t-test for comparison between visits.

complications (26% as compared to 38%), including intrauterine growth restriction (6% as compared to 15%) and preterm delivery (13% as compared to 24%).²⁰

The only woman who had structural valve deterioration and required a repeat AVR was in the bioprosthetic group. We acknowledge that the median follow-up after delivery in all the groups was only three years. However, it is interesting to note that the change in V_{max} from pre-pregnancy to last follow-up was not significantly different in the bioprosthetic group as compared to the Ross or the mechanical group. There was a trend for the velocity to increase slightly in all groups over the follow-up period. This lack of correlation of pregnancy-related valve deterioration to the valve type is consistent with other studies.^{8,9,11} Similarly, a study of women with bioprosthetic valves, comparing 48 women who underwent pregnancy and 37 who did not, showed no significant difference in the rates of structural valve deterioration at the end of five years.¹⁰ North et al. followed up 164 women who had undergone bioprosthetic, homograft or mechanical single valve replacements over a period of 10 years, of which 71 women underwent 132 pregnancies. They found that pregnancy did not increase structural valve deterioration or decrease survival in women with bioprostheses.¹³ Structural valve deterioration is more common in younger patients^{21,10} and is seven times higher in mitral than in aortic bioprostheses.^{22,7}

Although there are concerns regarding aortic regurgitation and structural valve deterioration of the pulmonary prosthesis requiring reoperation following the Ross operation, there is emerging evidence suggesting low reoperation rates.¹⁷ None of the women in our study with Ross operation required reoperation, over the period of follow-up. In one woman who had undergone a Ross operation and had terminated her pregnancy due to neo-aortic dilatation, the dilatation did not progress and she went on to have another pregnancy, during which the aortic root remained stable. Unfortunately, this ended in stillbirth, of unknown cause.

Mechanical valves are highly durable but require stringent anticoagulation. Due to the thrombogenic state and pharmacokinetic changes, pregnancy further increases the risks of thrombosis and bleeding.³ The use of anticoagulants is complicated by lack of an ideal regimen that is safe for both mother and fetus.² Recent nationwide data from Denmark, over a period of 30 years, showed that women with mechanical AVR generally tolerate pregnancy well, although there remains high risk of mortality related to anticoagulation and thromboembolism,⁶ in keeping with previous studies.^{4,5} The use of bioprosthetic valves or Ross operation eliminates the need for anticoagulation and therefore reduces the maternal and fetal risks. The Practice Guidelines of the American College of Cardiology and the American Heart Association Task Force (Class IIb) and The European Society of Cardiology guidelines on the management of valvular heart disease (Class IIa) recommend that a bioprosthesis should be considered in young women contemplating pregnancy.^{18,23}

The new generation biological prostheses have been shown to have extended durability, reduced reoperation-related mortality and increased life expectancy.^{24,25} The operative risk of a second valve replacement has significantly decreased.²⁶ The risk of re-operation depends on patient's age, number of previous surgeries, pre-operative New York Heart Association (NYHA) class and indication for re-operation.²⁷ Regular evaluation of patients and planned re-operation at relatively lower NYHA functional class can reduce the associated mortality.²⁷ Nevertheless, young patients with bioprosthetic valves will still require re-operation, with an associated mortality rate of up to 5%.²⁸ With advances such as trans-catheter aortic valve implantation, in future, the risk of reoperation may be further reduced.²⁹

This study is limited by its retrospective nature. It is an observational study in a single centre, and our data are limited by the number of women included and the limited duration of follow-up. However, we have compared cases with AVR alone and excluded women with multiple valve replacements, allowing a more valid comparison of biological to mechanical valves in pregnancy. The available data

comparing the pregnancy and cardiac outcomes in women with different types of AVRs are sparse. Our study provides useful information on the relative outcomes in women with bioprosthetic, Ross and mechanical AVR.

Conclusion

We found no difference in valve deterioration during a short period of follow-up between different types of AVRs, but mechanical valves were associated with relatively high maternal and fetal morbidity and mortality when compared to bioprosthetic AVRs and the Ross operation. In spite of improved haemodynamics with new generation valves, anticoagulation is high risk in pregnancy. This information needs to be passed on to women of child-bearing age prior to valve replacement.

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Declaration of conflicting interests

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Ethical approval

This project falls under the definition of 'service evaluation' by NRES standards and therefore is not subject to ethical approval. Ref NRES 'Defining Research' <http://www.nres.npsa.nhs.uk/applications/is-your-project-research/>

Guarantor

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Contributorship

SB was responsible for collecting and assessing data and writing the manuscript; JT was responsible for advising on manuscript preparation and supervising the project; SC and MC were responsible for the initial project idea, advising on the manuscript and supervising the project.

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