

Pregnancy Has No Effect on the Rate of Structural Deterioration of Bioprosthetic Valves: Long-term 18-year Follow Up Results

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Background and aim of the study: Should cardiac valve replacement be required, a bioprosthetic valve (BPV) is generally recommended for female patients of childbearing age to avoid anticoagulation hazards. Whether pregnancy accelerates BPV degeneration, or not, remains the subject of debate. The study aim was to determine the long-term effects of repeat pregnancy on the rate of structural deterioration of BPVs.

Methods: Eighty-five female patients of childbearing age who underwent BPV replacement between 1986 and 2000 were allocated to two groups: group P (n = 49; mean age 25 ± 6 years) who became pregnant (144 pregnancies), and group NP (n = 36; mean age 27 ± 7 years) who never became pregnant. The general characteristics of both groups were comparable. Clinical and echocardiographic data were obtained annually for all subjects; the mean follow up for all patients was 8.5 ± 3.8 years (range: 4.6-18.4 years). Group P received 59 (68% mitral) BPVs, while group NP received 45 (60% mitral). The majority of BPVs were Hancock II® porcine bioprostheses. The end-point

was freedom from redo valve replacement due to structural valve deterioration (SVD).

Results: No major maternal complications were encountered. A total of 144 pregnancies resulted in 114 live deliveries (79%). During the follow up period, 30 patients required reoperation for SVD (23 (46.9%) in group P; seven (19.4%) in group NP). The mean valve survival time for groups P and NP was 11.5 ± 7 years and 13 ± 9 years, respectively. A test of freedom from redo surgery for SVD in both groups demonstrated no significant differences between the P and NP groups (RR 1.8; 95% CI = 0.761-4.256; p = 0.18). Further analysis testing the potential effect of increased number of pregnancies on the duration to redo surgery among P group showed no effect.

Conclusion: Up to 18 years' follow up of patients with a BPV and repeated pregnancy showed there to be no pregnancy-related accelerated degeneration of BPVs. In addition, fetal loss rates were most likely lower with the use of BPVs.

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In theory, an ideal prosthetic heart valve should have the following characteristics: (i) normal hemodynamics similar to a normal valve in the same position; (ii) silent operation; (iii) non-thrombogenicity; (iv) potential for growth; (v) infection resistance; (vi) ready availability and ease of implantation; and (vii) durability, lasting a lifetime free of structural dysfunction and requiring no special medications such as anticoagulation. Clearly, such an ideal valve is yet to be developed.

This lack of an ideal cardiac valve substitute is especially apparent in the young and in women of childbearing age (1,2). Whilst patients with mechanical

prostheses require long-term anticoagulation during gestation, it must be borne in mind that no method of anticoagulation is risk-free. The administration of warfarin is associated with an increased risk of fetal wastage and birth defects (3-6), while different heparin regimens used in these cases have resulted in greater risks of maternal thromboembolism, valve thrombosis, bleeding and death (2,7-9). The use of valves that do not require anticoagulation should eliminate these complications. Therefore, women of childbearing age who require valve replacement are better offered a valve that may obviate anticoagulation and is safe during pregnancy (10,11). Previous reports have indicated that when warfarin or heparin were not required, there was no difference in fetal or maternal mortality and morbidity in women with biological valves when compared with the general population (12,13). Biological valves are prone to structural valve deterioration

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(SVD), and therefore their long-term durability is affected - hence a higher rate of valve reoperation (14,15). Although it has been suggested that pregnancy may accelerate the structural degeneration of bioprostheses (10,16-18), most of these reports have certain limitations. For example, they included non-homogeneous populations, and also disregarded the age of patients, the time from prosthesis implantation to gestation, and prosthesis baseline structural status prior to gestation. These limitations preclude adequate interpretation of the data, and consequently the studies have reached conflicting conclusions. There is also limited information available regarding long-term follow up, especially with repeated pregnancies.

Clinical material and methods

Patients

The incidence of bioprosthetic dysfunction requiring redo surgery was evaluated retrospectively in 85 female patients of childbearing age who underwent BPV replacement at the authors' hospital between 1986 and 2000. The patients were allocated to two groups. Group P patients (n = 49; mean age 25 ± 6 years; range: 15 to 38 years) became pregnant one or more times; the total number of pregnancies was 144, including 30 abortions and no still-births. Group NP patients (n = 36; mean age 27 ± 7 years; range: 17 to 36 years) never became pregnant after BPV implantation. In terms of clinical characteristics, both groups were comparable (Table I).

A total of 59 bioprostheses (80% Hancock II®; Medtronic- Minneapolis, MN, USA) had been inserted in group P, in the mitral position, and 45 (76% Hancock II®) in group NP, in the mitral position (p = 0.411).

The mean follow up of group P was 8.8 ± 3.4 years (range: 3.6 to 18.5 years), while that of the NP group was 8.2 ± 3.0 years (range: 4.2 to 15.7 years) (p = 0.363) (Table I). Group P patients were followed up during their gestation at the authors' high-risk pregnancy clinic. The study end-point was freedom from redo valve replacement for SVD.

Investigations

Clinical and echocardiographic data were obtained annually for all subjects. The clinical conditions investigated included congestive heart failure (characterized by pulmonary congestion or low cardiac output), atrial fibrillation and other symptomatic arrhythmias, thromboembolic episodes categorized as valve thrombosis, cerebrovascular accident or systemic embolism, infective endocarditis and valve reoperation. The echocardiographic analysis of bioprosthetic valves included thickening, calcification, tear, stenosis, thrombosis and vegetation.

The guidelines for reporting morbidity and mortality complication after valve replacement were used for the definition of valve-related complications, categorization and statistical methods (19).

Statistical analysis

Patient characteristics were summarized as frequencies and percentages for categorical variables and as mean (± SD) for continuous variables.

A chi-square test, Fisher's exact test and Student's *t*-test were used as appropriate to make between-group comparisons for age, prosthesis position, clinical complications and structural prosthetic changes. Kaplan-Meier and log-rank tests were used to compare time from valve operation to redo surgery (freedom from valve dysfunction) of the two groups, and Cox regression analysis to adjust for confounding factors. Statistical analyses were carried out using the SPSS 10.0 program. A p-value <0.05 was considered to be statistically significant.

Results

The total number of pregnancies was 144, ranging from one pregnancy to nine pregnancies per patient (Table II). Among the 144 pregnancies there were 30 abortions and no still-births; 114 pregnancies resulted in live deliveries (79%). There were no mortalities in either group during the entire follow up period. Among patients, 76% of group P and 70% of group NP

Table I: Clinical characteristics of both groups.

Characteristic	Pregnant (n = 49)	Never pregnant (n = 36)	p-value
Age (years)*	24.6 ± 5.8	26.8 ± 6.5	0.118
Follow up (years)*	8.8 ± 3.4	8.2 ± 3.0	0.363
No. of bioprostheses	59	45	0.411
No. of pregnancies	144	-	-
SVD (%)	14.3	11.1	0.753

*Values are mean ± SD.

Table II: Number of pregnancies per patient in group P.

No. of Patients	Pregnancies per patient	Total no. of pregnancies
11	1	11
12	2	24
12	3	36
8	4	32
1	5	5
3	6	18
2	9	18

were in sinus rhythm. There were no episodes of thromboembolism or infective endocarditis. A total of 30 patients required reoperation for SVD (23 in group P, seven in group NP). The rate of SVD was 5.3% per patient-year (pt-yr) for group P, and 2.4% per pt-yr for group NP. The mean valve survival time (the time between the first and second operations) was 11.5 ± 7 years for group P and 13 ± 9 years for group NP ($p = 0.175$). None of the reoperations was performed while the patient was pregnant.

A test of freedom from redo surgery due to SVD in both groups using Cox regression analysis was performed, but demonstrated no significant inter-group differences (relative risk (RR) 1.8, 95% CI = 0.761-4.256, $p = 0.18$) (Fig. 1). A further analysis failed to identify any potential adverse effect of repeated pregnancy on the duration to SVD and redo surgery.

Discussion

Rheumatic heart disease remains a problem in Saudi Arabia, with an annual prevalence of 2.4-6.4 per 1000

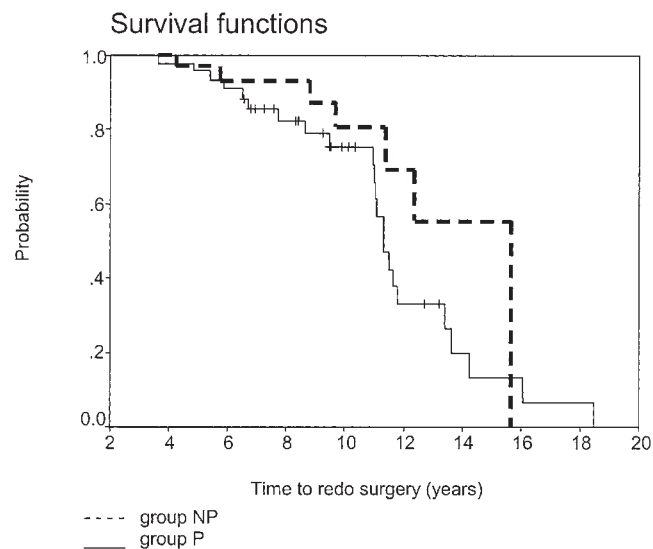


Figure 1: Valve survival time shown as interval from valve implantation (OR_1) to valve explantation due to structural valve degeneration (OR_2).

population. This results in a high number of patients who are relatively young but require surgical intervention for valvular heart disease. Although valve repair is the best option in these cases, it is not always feasible and valve replacement becomes necessary. Valve replacement in the young remains problematic with regard to the choice of a bioprosthesis versus a mechanical valve (1). This problem is further aggravated in young females of childbearing age who wish to become pregnant (20). With mechanical valves, the risk of valve thrombosis and thromboembolic events increases as pregnancy induces physiological changes favoring thromboembolic complications (21). Coumarins are usually effective in preventing thromboembolic events (21), but fetal exposure to these compounds is associated with an increased incidence of fetal wastage and a greater probability of embryopathy, with a reported fetal loss rate of 30-60%, irrespective of the regimen used in managing anticoagulation during pregnancy (3,4,6,22,23).

There are several schools of thought to overcome this problem. The first approach is not to allow women with mechanical valves, or those who need anticoagulation for one reason or another, to become pregnant. Those women willing to accept this solution to the problem can undergo tubal ligation. The second approach is to allow women with mechanical valves to become pregnant under very close medical supervision. The management of anticoagulation during pregnancy remains a controversial issue (24). Some regimens suggest the use of heparin (either unfractionated or low molecular-weight) during the first trimester, and oral anticoagulants for the remainder of the pregnancy until close to delivery, at which time the patient is switched back to heparin. Reported doses and routes of administration of heparin vary widely (25). Many studies, however, from various regions of the world have shown that such regimens carry considerable risk to the mother's life as there is increased incidence of valve thrombosis and bleeding (7-9,20,25). Other regimens recommend the use of oral anticoagulants throughout the pregnancy, stating that warfarin embryopathy has been overstated and the risk is minimal, particularly if the dose does not exceed 5 mg (22,23,26,27). Nevertheless, certain medico-legal issues may exist regarding these regimens, as there is still a restrictive labeling recommendation against the use of enoxaparin and warfarin during pregnancy (28). The third approach to the problem is to use a bioprosthesis in those women who wish to become pregnant but who need cardiac valve replacement. These patients will definitely require a reoperation, as experience shows that bioprostheses ultimately fail (14,15). This third option has been the policy followed by the present authors. However, the major drawback to BPV use

is susceptibility to SVD. A direct correlation between patient age and SVD has been established, in that the younger the patient the more rapidly the bioprosthesis degenerates. Bioprostheses are therefore generally recommended for older age groups (>65 years), and the durability of BPVs in these older patients has been documented (29,30). The use of bioprostheses in patient aged <40 years is generally rare, is performed only under certain indications, and has generally been discouraged - particularly for pregnant women (31). In the present authors' region of Saudi Arabia, bioprostheses have been implanted in young patients, mainly because of the difficulties encountered in controlling anticoagulation and because of pregnancy in young females.

Several previous reports have suggested that pregnancy accelerates SVD (10,17,18,31). In the present study, the aim was to evaluate the effects of pregnancy on bioprosthesis degeneration. Consequently, among two groups of young women with a bioprosthesis (mostly Hancock II®) implanted mainly in the mitral position there were no mortalities over the entire follow up period, despite the pregnancies and need for reoperation. Moreover, there were no episodes of endocarditis or thromboembolism, even in patients with atrial fibrillation.

It has been reported that when warfarin or heparin were not used during pregnancy, there was no difference in fetal or maternal morbidity and mortality between women with biological valves and women without structural valve disease (12,13). This finding was confirmed in the present study. There was a fetal loss rate of 21%, though this was better the value of up to 45% reported previously in pregnant women with mechanical valves and receiving heparin or warfarin (23).

During the follow up period, 30 of the present patients required reoperation for SVD (23 in group P (5.3%/pt-yr) and seven in group NP (2.4%/pt-yr). The mean time from implantation to SVD was 11.5 ± 7 years for group P, and 13 ± 9 years for group NP. There were more reoperations in group P, but more patients were followed for longer in this group (mean follow up for group P was 8.8 years compared to 8.2 years for group NP), and therefore no statistically significant difference was detected between the two groups regarding SVD. This led to the conclusion that pregnancy did not accelerate the degeneration process of the bioprosthesis. The actuarial freedom for SVD at 10 years was $75 \pm 7\%$ for group P and $80 \pm 1\%$ for group NP. This finding was also supported by the comparable incidence of specific structural changes detected on echocardiography, such as leaflet thickening, calcification and stenosis in both groups. The results of the present study are in agreement with those of other reports suggesting that pregnancy does not accelerate

bioprosthesis structural degeneration (20,32). Although retrospective in nature, the present study was unique as it compared two groups of women with similar clinical characteristics who had a bioprosthesis implanted at the same institution and were followed for up to 18 years.

In conclusion, the results of this retrospective study showed that pregnancy had no effect on the rate of bioprosthesis structural deterioration, but a lower rate of fetal wastage was observed. These findings, together with the fact that reoperation was associated with no mortality and low morbidity, justify the continued approach of bioprosthesis use in young women who wish to conceive. During the life of the bioprosthesis, these women can have as many pregnancies as they can afford. Moreover, when they come to reoperation their situation can be reassessed in terms of the appropriate replacement prosthesis to be used. It is understood that this approach might be considered provocative, but unless a prospective study is conducted to compare maternal and fetal outcomes of pregnancy in women with mechanical versus biological valves, the approaches and study results may always be biased.

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