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ORIGINAL ARTICLE

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Impact of pregnancy on autograft dilatation and aortic valve function following the Ross procedure

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Abstract

Objective: The effects of pregnancy on autograft dilatation and neoaortic valve function in patients with a Ross procedure have not been studied. We sought to evaluate the effect of pregnancy on autograft dilatation and valve function in these patients with the goal of determining whether pregnancy is safe after the Ross procedure.

Design: A retrospective chart review of female patients who underwent a Ross procedure was conducted.

Patients: Medical records for 51 patients were reviewed. Among the 33 patients who met inclusion criteria, 11 became pregnant after surgery and 22 did not.

Outcome Measures: Echocardiographic reports were used to record aortic root diameter and aortic insufficiency before, during, and after pregnancy. Patient's charts were reviewed for reinterventions and complications. Primary endpoints included reinterventions, aortic root dilation of $\geq$5 cm, aortic insufficiency degree $\geq$ moderate, and death.

Results: There were 18 pregnancies carried beyond 20 weeks in 11 patients. There was no significant difference in aortic root diameter between nulliparous patients and parous patients prior to their first pregnancy (3.53 ± 0.44 vs 3.57 ± 0.69 cm, $P = .74$). There was no significant change in aortic root diameter after first pregnancy (3.7 ± 0.4 cm, $P = .056$) although there was significant dilatation after the second (4.3 ± 0.7 cm, $P = .009$) and third (4.5 ± 0.7 cm, $P = .009$) pregnancies. Freedom from combined endpoints was significantly higher for patients in the pregnancy group than those in the nonpregnancy group ($P = .002$).

Conclusions: Pregnancy was not associated with significantly increased adverse events in patients following the Ross procedure. Special care should be taken after the first pregnancy, as multiparity may lead to increased neoaortic dilatation.

KEYWORDS
aortic valve disease, neoaortic dilatation, pregnancy, pulmonary autograft, reintervention, Ross procedure

1 | INTRODUCTION

Introduced in 1967, the Ross procedure has been an integral option in the management of aortic valve disease over the past 50 years. As originally described by Dr. Donald Ross, the procedure involves replacing the diseased aortic valve with the patient's native pulmonary valve, and placing a cadaveric homograft in the pulmonary position.[1] Despite well-documented drawbacks, such as the surgery turning a 1-valve disease into a 2-valve disease and the increased risk of autograft dilation, the Ross procedure has some clear advantages over other aortic

TABLE 1 Patient demographics and operative characteristics[a]

Demographics for female patients after Ross procedure			
	Pregnancy (n = 11)	No pregnancy (n = 22)	*P* value
Indication for Ross procedure			
Bicuspid aortic valve	6	14	1.0
Endocarditis	2	2	.6
Others	4	6	.7
Median age at time of Ross procedure	12.9 (4.5–33.8)	17.3 (0.8–36.4)	.4
Surgical technique			
Ross	11	18	.1
Ross–Konno	0	4	.3
Length of time between surgery and latest visit	15.9 (9.9–21.1)	16.6 (1.3–23.3)	1.0
Median age at latest follow-up	26.8 (17.9–50.9)	30.5 (17.8–59.3)	.7
Additional risk factors			
Hypertension	1	2	1.0
Tobacco	2	5	1.0
Race			
Caucasian	9	20	1.0
African-American	2	2	.6

[a]Indications for Ross are not mutually exclusive. Data are expressed as absolute values or median (range) in years.

valve substitutes, such as mechanical prostheses, xenografts, and homografts.[2–5] Key among these are the possibility of somatic growth of the autograft in young patients, freedom from anticoagulation, and improved hemodynamics.[6,7] Similarly, comparison between different aortic valve replacements has shown greater event-free survival among children and young adults who receive a pulmonary autograft than those who receive homografts, bioprostheses, and mechanical valves.[8]

The preceding advantages have led to the Ross procedure being recommended in patients with aortic valve disease who wish to become pregnant.[9,10] However, there is still debate on the long-term outcomes, valvular function, and complications requiring reinterventions (RI). Studies have shown conflicting data on RI rates, thus complicating the clinical decision-making process.[2] Information concerning the effect of physiological changes during pregnancy on cardiovascular function in these patients is limited, and the few studies addressing pregnancy following a Ross procedure have either included short follow-up times or limited population sizes.[10–14] In addition, common indications for aortic valve replacement, such as bicuspid aortic valve (BAV), have been suggested to increase the risk of maternal morbidity and mortality, although the risk for aortic root dissection has not been established.[1] To date, no studies have evaluated the effect of pregnancy on aortic root dilatation in patients with a Ross procedure. In this study, we sought to elucidate how pregnancy affects aortic root dilation, autograft valve function, and the RI rate in patients following a Ross procedure, as well as the safety of pregnancy in patients who undergo this surgery, featuring the largest study population, to date, with a longer follow-up period than the previous studies.

2 | MATERIALS AND METHODS

To identify women who underwent a Ross procedure at the study institution or had surgery performed elsewhere and subsequently been monitored by cardiologists at the study institution between 1989 and 2017, we conducted a retrospective review. Patients were included in the pregnancy group if they carried a pregnancy beyond 20 weeks, whereas the patients were included in the nonpregnancy group if they were below 40 years old at the time of surgery, and if they were currently 17 years of age or older at their most recent follow-up. The patients who were not within the specified age range or who had been lost to follow-up immediately after surgery were excluded. Available data were collected, including demographics, initial procedure type, RI, and pregnancy outcomes (Table 1).

Aortic root diameters and valve function data were gathered from echocardiogram or magnetic resonance imaging reports immediately after the Ross procedure, at each follow-up visit before, during, and after pregnancy, immediately before RI, and at the most recent patient visit. Ascending aorta diameters were considered only in patients who underwent RI owing to aortic aneurysms, with aortic diameter at the sinus of Valsalva used to compare the aortic measurements in all other patients. All available aortic diameter measurements were compared before and after each pregnancy for primigravida patients and subsequent pregnancy measurements were compared to the measurements taken before the first pregnancy for multiparous patients unless stated otherwise. Severity of aortic insufficiency (AI) was measured to assess valve function. Primary endpoints measured included aortic root diameter of $\geq$5 cm, moderate or greater AI, left ventricular outflow tract (LVOT) RI, right ventricular outflow tract (RVOT) RI, and death.

This study was approved by the Washington University in St. Louis Institutional Review Board, and a waiver of consent was obtained. The patients were contacted by telephone to inquire about any data not found in their medical records.

Statistical analyses employed were Kaplan–Meier survival curves, log-rank test for curve comparison, Mann-Whitney *U* test for

TABLE 2 Pregnancy patient characteristics[a]

Pregnancy patient characteristics				
Parity	**1**	**2**	**3**	***P* value**
Number of patients	7	1	3	.2
Age at time of pregnancy	24.4 ± 6.5	26.4 ± 7.8	27.6 ± 0.9	.7
Time between surgery and pregnancy	9.5 ± 5.6	8.2 ± 2.5	13.4 ± 3.9	.4
Time between pregnancy and last follow-up	7.4 ± 7.6	10.2 ± 7.0	7.9 ± 6.3	.8
Patients with a sustained increase of ≥1° of AI after pregnancy	2	0	0	.8
Mean aortic root diameter (cm)	3.7 ± 0.4	4.3 ± 0.7	4.5 ± 0.7	.07

[a]Number of pregnancies refers only to the pregnancies with available records after their Ross procedure. Data are presented as mean ± SD.

comparison between 2 groups, Kruskal–Wallis test for continuous variables with Dunn's multiple comparisons test, Holm–Sidak multiple comparison test for post hoc testing, and Wilcoxon signed-rank test for ordinal variables, calculated with GraphPad Prism 7.03 (GraphPad Software, Inc, La Jolla, California), with an α level of .05 for determining statistical significance.

3 | RESULTS

Of the 51 females who had a Ross procedure, 8 were lost to follow-up immediately after discharge. Twenty-three pregnancies were identified in 11 patients. Of these, 18 pregnancies were carried to a gestational age of >20 weeks and were included in the study. There were 3 spontaneous and 2 induced abortions. The nonpregnancy group was composed of 22 nulliparous patients who met inclusion criteria. The most common indication for surgery was congenital aortic stenosis owing to BAV (Table 1). Demographic data for all patients are summarized in Table 1, whereas pregnancy characteristics are summarized in Table 2, and can be found individually in Supporting Information Annex 1.

Primary endpoints, including aortic diameter of ≥5 cm, moderate or greater AI, RI, and death, were combined among each group to compare the freedom from complications between nulliparous and pregnant patients (Table 3). In case a patient experienced more than 1 endpoint, only the first event to occur was taken into consideration when comparing combined endpoints (Figure 1). The difference in freedom from combined endpoints was significantly lower for the nonpregnancy group when compared to the pregnancy group at latest follow-up ($P = .002$).

There was no significant difference in aortic root diameter between the 2 groups at baseline (3.53 ± 0.44 vs 3.57 ± 0.69 cm, $P = .74$). In the pregnant group, there was no statistically significant change between mean aortic root diameters before and after the first pregnancy ($P = .056$), although multiparous patients showed significant changes after their second ($P = .009$) and third ($P = .009$) pregnancies when compared to the baseline measurements.

At latest follow-up, 9/22 (40.9%) nulliparous versus 4/11 (36.4%) parous patients had developed moderate or greater AI ($P = .39$). Within the pregnancy group, 3 patients experienced an increase of 1.0° in AI during their first pregnancy, and 1 patient had a progression of 0.5° (from mild-to-moderate AI to moderate AI) during her first pregnancy. Of these, 2 patients returned to baseline parameters after pregnancy and 2 maintained increased AI. Subsequent pregnancies in multiparous patients found an increase in AI in 1 patient during her third pregnancy, with a return to baseline parameters after delivery. Within the nonpregnancy group, 4 patients developed severe AI at an average of 9.8 ± 7.6 years after their Ross, whereas no patients in the pregnancy group developed severe AI.

There were no statistically significant differences in RVOT ($P = .52$) or LVOT ($P = .57$) RI procedures between the 2 groups. A total

TABLE 3 Comparison of endpoints between pregnancy and nonpregnancy groups[a]

Combined endpoints			
	Pregnant	**Nonpregnant**	***P* value**
RVOT RI	4	6	.5
LVOT RI	3	7	.6
AI ≥ moderate	4	9	.4
Aortic diameter ≥5 cm	2	2	.5
Death	0	3	.4
Combined	6	16	.3

[a]Endpoints are not mutually exclusive. For combined endpoints, only the first event to occur was taken into account. There was no significant difference between groups for any of the endpoints analyzed.

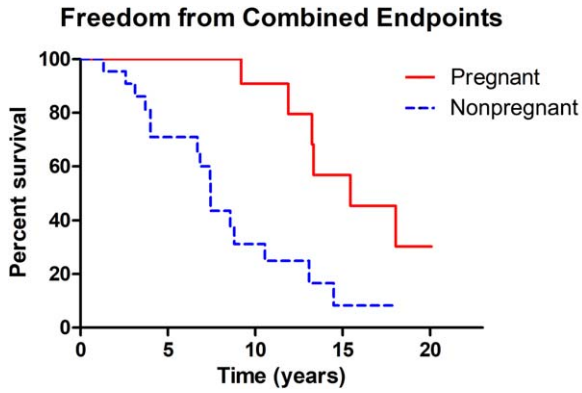

FIGURE 1 Freedom from combined endpoints (LVOT RI, RVOT RI, AI ≥ moderate degree, aortic root diameter ≥ 5cm, death) for patients in the pregnancy and nonpregnancy groups ($P = .002$)

of 7 RI were performed on patients in the pregnancy group, with 4 RVOT RI and 3 LVOT RI. All patients in this group who required LVOT RI did so due to aortic dilatation after pregnancy (Annex 2). It is worth noting that 1 patient who underwent valve-sparing aortic root dissection repair initially had progressive aortic root dilation noted during routine echocardiographic follow-up in her third trimester. After delivery, the diagnosis of type A aortic dissection was established via computed tomography angiography. During surgical repair, it was noted that the aortic dissection involved the pulmonary autograft exclusively, with the native ascending aorta remaining unaffected. Among patients in the nulliparous group, a total of 13 RI were carried out among 12 patients, with 7 taking place in the LVOT and 6 in the RVOT.

There were 3 mortalities among patients in the nonpregnant group: 1 patient died from hemorrhage after an aortic valve replacement owing to severe AI, 1 died from complications after an orthopedic procedure, and 1 died of liver failure owing to a hemangioendothelioma. No patients died in the pregnancy group ($P = .37$). Survival rates at 5-year intervals were 95.2% (5 and 10 years) and 82.1% (15 and 20 years).

4 | DISCUSSION

Our results show that pregnancy was safe in patients who underwent a Ross procedure. Among the 11 patients studied, only 1 patient suffered from complications during pregnancy, presenting with an aortic dissection during her third trimester. This patient was followed carefully during the remainder of her pregnancy, and underwent surgical repair promptly after delivery. Among multiparous patients, a significant increase in aortic root diameter was observed after their second and third pregnancies. There was no difference in risk of moderate or greater AI, LVOT RI, or aortic root diameter of $\geq$5 cm between patients in the pregnancy and nonpregnancy group,

The differences seen in aortic root diameter among multiparous patients suggest that repeat pregnancy may play an important role in promoting autograft dilation. This may be due to the repetition of increased stress on the neoaorta resulting from increased cardiac output and hormonal changes during pregnancy, which can lead to structural instability in the aortic wall.[15,16] In addition, although an even mix of aortic aneurysms and increased AI prompted LVOT RI in patients before pregnancy and in those with no pregnancies, 100% of LVOT RI performed after pregnancy were prompted by autograft dilation. This may be indicative of an increased risk of aortic dilatation requiring RI, although it may also be due to increased echocardiographic vigilance during pregnancy.

The results from the previous studies have shown pregnancy to be safe for patients with a Ross procedure. Among these, several studies showed no cardiac complications during and after pregnancy, and no significant progression of AI.[10,11,13,14] Heuvelman et al.[12] reported that 1 patient with a Ross procedure required termination of pregnancy owing to a dilated aortic root with aortic and pulmonary insufficiency. Similarly, 1 patient in the study by Morimoto et al.[14] had aortic root dilatation although she did not require RI. Interestingly, Basude et al.[13] mentioned 1 patient who terminated pregnancy at 18 weeks of gestation owing to aortic root dilatation. This patient subsequently became pregnant again, with no progression of her root dilatation. However, the increase in cardiac output seen during pregnancy reaches its peak at around 24 weeks of gestation; the gestational age at which she terminated her first pregnancy may explain why she did not experience dilatation in the following pregnancy.[16]

Furthermore, in the studies comparing pregnancy between patients with a Ross procedure and those with a bioprosthetic valve, patients with a pulmonary autograft had lower rates of valvular degeneration, as well as similar or lower rates of RI and mortality than those with a bioprosthetic valve.[8,13,14] These advantages have led some to suggest that the Ross procedure should replace aortic bioprostheses as the standard treatment for aortic valve disease in young patients who desire to avoid anticoagulation.[9] Despite these findings, the 2014 AHA/ACC guidelines for the Management of Patients with Valvular Heart Disease, as well as their 2017 Focused Update, recommend aortic valve replacement with a bioprosthesis for patients who wish to avoid anticoagulation, whereas the Ross procedure is given a Class IIb recommendation in patients with contraindications for anticoagulation and those who desire to avoid it.[17,18]

In accordance with current guidelines, we believe that the patients who undergo a Ross procedure should receive preconceptional guidance by a team of experts regarding potential maternal and fetal complications, modification of risk factors for aortic root dilation, and warning signs for possible complications, as well as regular follow-up by a cardiologist. Special care should be taken when monitoring multiparous patients, due to the increase in aortic diameter observed in these patients.

As in all retrospective studies, we recognize there are some limitations. Among these, the lack of complete follow-up records for patients within our cohort was one of the most important. Some variations in echocardiographic measurements were also unavoidable owing to the study's operator-dependent nature. Another limitation is the small size of our population, which limits the conclusions that can be drawn from our observations. Nevertheless, data obtained from our study, along with the previously published data, support the safety of the Ross procedure in female patients who wish to become pregnant. Further studies are warranted with larger cohorts to properly assess the effect of pregnancy on aortic root dilatation, especially in multiparous patients.

5 | CONCLUSIONS

The Ross procedure, when performed by an experienced cardiothoracic surgical team, is a safe valvular replacement option for patients with a desire for future pregnancy. By avoiding anticoagulation therapy, the Ross procedure minimizes the risk for maternal and fetal complications. Careful monitoring by a team of high-risk obstetricians and adult congenital cardiologists is essential for these patients, and special care should be taken to monitor pulmonary autograft dilatation in multiparous patients.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the manuscript.

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Data analysis/interpretation: Carvajal, Brar, Barger, Billadello, Eghtesady

Article drafting: Carvajal

Statistical analysis: Carvajal

Data analysis: Lindley

Concept/design: Lindley, Barger, Billadello, Eghtesady

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

ANNEX 1. Pregnancy patient characteristics. Number of pregnancies refers only to pregnancies with available records after their Ross procedure

ANNEX 2. LVOT RI indications, surgical technique, and aortic valve function parameters

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