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Outcomes of Pregnancy in Women With Bioprosthetic Heart Valves With or Without Valve Dysfunction

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ABSTRACT

BACKGROUND Although pregnancy outcomes in women with normally functioning bioprosthetic valves (BPVs) are often good, structural valve dysfunction (SVD) may adversely affect pregnancy outcomes, but this has not been studied.

OBJECTIVES The aim of this study was to examine outcomes in pregnant women with BPVs and the association with SVD.

METHODS Pregnancy outcomes in women with BPVs were prospectively collected. Adverse maternal cardiac events (CEs) included cardiac death or arrest, sustained arrhythmia, heart failure, thromboembolism, and stroke. Adverse fetal events were also studied. Determinants of adverse events were examined using logistic regression.

RESULTS Overall, 125 pregnancies in women with BPVs were included, 27% with left-sided and 73% with right-sided BPV. SVD was present in 27% of the pregnancies (44% with left-sided BPVs vs 21% with right-sided BPVs; $P = 0.009$). CEs occurred in 13% of pregnancies and were more frequent in women with SVD compared with those with normally functioning BPVs (26% vs 8%; $P = 0.005$). CEs were more common in women with left-sided BPVs with SVD vs normally functioning BPVs (47% vs 5%; $P = 0.01$) but not in women with right-sided BPVs (11% in those with SVD vs 8% in those without SVD; $P = 0.67$). Left-sided SVD ($P = 0.007$), maternal age >35 years ($P = 0.001$), and a composite variable of "high-risk" features ($P = 0.006$) were predictors of CEs. Fetal events occurred in 28% of pregnancies.

CONCLUSIONS In this cohort of young women with BPVs, SVD was present in 27% at the first antenatal visit and negatively affected pregnancy outcomes. In particular, SVD of left-sided BPVs was associated with high rates of adverse outcomes. (J Am Coll Cardiol 2022;80:2014–2024) © 2022 by the American College of Cardiology Foundation.

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For women of childbearing age with severe valve disease, valve replacement choice is complex. Bioprosthetic valves (BPV) are typically considered a good option because they are associated with lower rates of complications during pregnancy compared with mechanical valves.[1-3] However, structural valve deterioration limits the life span of BPVs and necessitates reoperation.[4-7] In contrast, mechanical valves have better longevity but are associated with the need for anticoagulation and risk for valve thrombosis during pregnancy.[8,9] Although guidelines recommend that women of childbearing age should be offered BPVs,[3,10,11] information on pregnancy outcomes in women with BPVs is based on older studies that did not always discriminate among different BPV types, valve positions, or valve function.[1,8,12-16] Therefore, we sought to assess pregnancy outcomes in a large contemporary cohort of women with BPVs and to examine differences in outcomes according to valve position and valve function.

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METHODS

The outcomes of women with preexisting heart disease enrolled in a subset of the multicenter prospective CARPREG (Canadian Cardiac Disease in Pregnancy) study between 1994 and 2019, who had undergone implantation of BPVs prior to pregnancy, and whose obstetrical and cardiac care was provided at 2 large tertiary care hospitals (in Toronto and Vancouver) were examined, and women were followed until 6 months postpartum. Women with miscarriages at <20 weeks' gestation or termination of pregnancy were excluded. The study was approved by the local research ethics boards.

BASELINE CHARACTERISTICS. Clinical baseline data were recorded at the first antenatal visit, including maternal age, gestational age, parity status, cardiac diagnosis, valve lesion, prior valve interventions, New York Heart Association functional class, prior cardiac events (CEs) (heart failure, stroke, and arrhythmia), comorbid conditions, cardiac medications, body mass index (BMI), and smoking history.[17,18] BPVs were defined according to their position (aortic, mitral, pulmonary, or tricuspid), and BPVs in the aortic position were subclassified according to the type of the aortic prosthesis: pulmonary autograft (after Ross operation) or bioprosthesis (pericardial and porcine xenografts and homografts). Women were classified as having left-sided vs right-sided BPVs. Women who underwent the Ross operation were included in the group with right-sided BPVs, as the BPVs were in the pulmonary position.[19] The time (years) between the most recent valve replacement surgery and the index pregnancy was recorded.

A baseline transthoracic echocardiogram was obtained and interpreted by an experienced echocardiographer at the first antenatal visit.[20] Measurement of left ventricular systolic function was performed using standardized echocardiographic methods.[21] Left ventricular systolic function <55% was considered abnormal. Right ventricular function was determined by visual assessment. Valvular area, gradients, and regurgitation of the native valves were calculated according to standard echocardiographic guidelines,[22,23] and a native valvular lesion was considered significant if moderate or greater stenosis or regurgitation was present.

BPV DYSFUNCTION. BPV function was assessed according to current recommendations with 2-dimensional imaging and Doppler echocardiography.[24] Significant structural valve dysfunction (SVD) was determined by integrating morphologic and Doppler parameters. Morphologic features included the presence of thickening and/or calcifications of the leaflets with restriction of leaflet mobility. Doppler parameters included: 1) increased transprosthetic peak and mean gradients; 2) a reduced calculated effective orifice area (in aortic and mitral BPVs); and/or 3) the presence of moderate to severe intravalvular prosthetic valve regurgitation.[24] Aortic prosthesis stenosis was defined as an effective orifice area <0.8 cm^2, a mean gradient >35 mm Hg, and/or a peak velocity >4 m/s. Mitral prosthesis stenosis was defined as an effective orifice area <1.0 cm^2, a mean gradient >10 mm Hg, and/or a peak velocity ≥2.5 m/s. Pulmonary prosthesis stenosis was defined as a peak velocity ≥3.2 m/s and/or a mean gradient >20 mm Hg and tricuspid prosthesis stenosis as a mean gradient ≥6 mm Hg and/or a peak velocity >1.7 m/s.[24] All echocardiograms with reported dysfunction of the BPV were reviewed by one of the study investigators to confirm SVD.

ADVERSE OUTCOMES. Adverse maternal CEs, fetal and neonatal events (FEs), and obstetrical events were recorded from the first antenatal visit up to 6 months after delivery. The primary CE of interest was a composite of any of the following: maternal cardiac death, cardiac arrest, left- or right-sided heart failure, supraventricular or ventricular arrhythmia requiring treatment, cardiac thromboembolism, and

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
BPV = bioprosthetic valve
CE = cardiac events
FE = fetal and neonatal events
SVD = structural valve dysfunction

TABLE 1 Baseline Characteristics

	All Bioprosthetic Valves (N = 125)	Left-Sided Valves[a] (n = 34)	Right-Sided Valves[b] (n = 91)	*P* Value
Maternal characteristics				
No. of women	101	30	71	
Maternal age, y	31 ± 5	32 ± 5	31 ± 5	0.19
Maternal age >35 y	23 (18)	9 (27)	14 (15)	0.16
Years since valve implantation	6 ± 3	5 ± 3	6 ± 6	0.23
Nulliparity	56 (45)	19 (55)	37 (41)	0.13
Twin pregnancy	3 (2)	0 (0)	3 (3)	0.28
Late pregnancy assessment (>20 wk gestation)	25 (20)	8 (24)	17 (17)	0.55
Prior cardiac events[c]	30 (24)	9 (27)	21 (23)	0.69
Any comorbidities (diabetes, hypertension)	9 (7)	4 (12)	5 (5)	0.25
History of smoking	13 (10)	3 (9)	10 (11)	1.00
Body mass index ≥30 kg/m^2 [d]	17/122 (14)	4/32 (13)	13/90 (14)	0.72
New York Heart Association functional class III or IV	4 (3)	3 (9)	1 (1)	0.03
Cardiac medications				
Cardiac medication except anticoagulation or aspirin at first visit	14 (11)	6 (18)	8 (9)	0.16
Anticoagulation (warfarin)	1 (1)	0 (0)	1 (1)	1.00
Low-molecular-weight heparin	2 (2)	2 (6)	0 (0)	0.12
Aspirin	27 (22)	11 (32)	16 (18)	0.07
Cardiac diagnosis[e]				
Congenital heart disease	112 (90)	22 (65)	90 (99)	<0.001
Bicuspid aortic valve	37 (30)	18 (53)	19 (21)	<0.001
Pulmonary stenosis	5 (4)	0 (0)	5 (5)	0.16
Complex congenital heart disease[f]	64 (51)	0 (0)	64 (70)	<0.001
Tetralogy of Fallot	55 (44)	0 (0)	55 (60)	0.001
Ebstein anomaly	4 (3)	0 (0)	4 (4)	0.21
Acquired heart disease	13 (10)	12 (35)	1 (1)	<0.001
Rheumatic heart disease	12 (10)	11 (32)	1 (1)	<0.001
Echocardiographic features				
Prosthetic valve dysfunction	34 (27)	15 (44)	19 (21)	0.009
Subaortic ventricular dysfunction[g]	14 (11)	4 (12)	10 (11)	1.00
Subpulmonic ventricular dysfunction	37 (29)	2 (6)	35 (38)	<0.001
Dysfunction of any native left-sided valve[h]	3 (2)	2 (6)	1 (1)	0.18
Dysfunction of any native right-sided valve[h]	18 (14)	6 (18)	12 (13)	0.57

Values are n, n (%), mean ± SD, or n/N (%). *P* values describe differences between left- and right-sided valves. [a]Left-sided bioprosthetic valves: 17 aortic bioprostheses, 9 mitral valve bioprostheses, and 8 both aortic and mitral bioprostheses. [b]Right-sided bioprosthetic valves: 86 pulmonic bioprostheses and 5 tricuspid bioprostheses. [c]Prior heart failure, arrhythmia, or thromboembolic event. [d]Three values for body mass index were missing (2 from left-sided bioprosthetic valves and 1 from a right-sided bioprosthetic valve). [e]Other underlying diagnoses included congenital aortic stenosis, Marfan syndrome, Shone complex, atrioventricular septal defect, truncus arteriosus, pulmonary atresia with intact ventricular septum, transposition of the great arteries with pulmonary stenosis, unspecified tricuspid stenosis, mitral valve prolapse, and previous endocarditis. [f]Tetralogy of Fallot, transposition of the great arteries, pulmonary atresia with intact ventricular septum, atrioventricular septal defect, Ebstein anomaly, and truncus arteriosus communis. [g]Ejection fraction <55%. [h]Moderate or severe stenosis or regurgitation.

stroke or transient ischemic attack. Secondary CEs included urgent invasive cardiac procedures during pregnancy or within 6 weeks after delivery. Adverse FEs included any of the following: fetal death (>20 weeks of gestation), neonatal death (within 28 days after birth), premature birth (<37 weeks of gestation), small-for-gestational-age birth weight (<10th percentile), respiratory distress syndrome, and intraventricular hemorrhage. Adverse obstetrical events included noncardiac death, postpartum hemorrhage (blood loss >500 mL after vaginal delivery or >1,000 mL after caesarean section), and clinically diagnosed preeclampsia.

STATISTICAL ANALYSIS. SPSS version 26.0 for Mac (IBM) was used for data analysis. Baseline characteristics are presented as mean ± SD or proportions. Differences in baseline characteristics, CE rates, and FE rates between pregnancies in women with left-sided and right-sided BPVs and between women with and without BPV dysfunction were determined using chi-square tests, Fisher exact tests, or Student's *t*-tests as appropriate. Logistic regression was used to identify determinants of CEs and FEs. The variables identified as statistically significant in the univariate analysis ($P < 0.05$) were entered as adjustment covariates into a multivariable logistic regression model. Variables that were significant on univariate analysis and were part of the CARPREG II risk factors were combined into a composite "high-risk" variable that represented the logit calculated using the beta coefficients from the CARPREG II study[17]; this high-risk variable included the following variables: prior CEs or arrhythmias, poor functional class or cyanosis, systemic ventricular dysfunction, pulmonary hypertension, high-risk aortic disease, and late pregnancy assessment. Not included were no prior intervention, mechanical valve, and coronary artery disease, as none of our study cohort had these features. Also not included was the high-risk valve disease variable, as it would be closely correlated with the exposure variable of interest (left-sided prosthetic valve dysfunction). A similar approach was performed to calculate the adjusted risk for adverse FEs related to candidate variables on univariate analysis with *P* values <0.10. To account for multiple pregnancies in some women, secondary analyses were performed with using general estimating equations (Stata version 17.0, StataCorp).[18,25]

RESULTS

In total, 125 pregnancies occurred in 101 women with 1 or more BPVs. Baseline characteristics are described in **Table 1** and Supplemental Table 1. Thirty-four pregnancies occurred in women with left-sided BPVs, among whom 17 had aortic valves (14 xenograft and 3 homograft valves), 9 had mitral BPVs, and 8 had both aortic and mitral valves. Women with right-sided BPVs (n = 91) primarily had pulmonary valves (n = 86); 5 women had tricuspid valves. Three pregnancies were twin pregnancies. The underlying cardiac diagnoses differed among women with

TABLE 2 Characteristics of Bioprosthetic Valve Dysfunction Stratified According to Valve Position and Type

	Aortic Valves				
	Bioprosthetic Valve	Autograft	Bioprosthetic Mitral Valves	Bioprosthetic Pulmonic Valves	Bioprosthetic Tricuspid Valves
No. of valves	25	20	17	86	5
No. of women[a]	22	16	14	67	5
Years since valve implantation	5 ± 3	7 ± 6	5 ± 3	6 ± 6	5 ± 3
Prosthetic valve dysfunction					
No. of dysfunctional valves (% in each group)	10 (40)	1 (5)	5 (29)	17 (20)	2 (40)
Years since valve implantation	6 ± 3	18	6 ± 4	11 ± 8	8 ± 2
Type of valve dysfunction					
Stenosis	7	0	4	11	0
Regurgitation	1	0	1	0	1
Mixed regurgitant and stenotic lesions	2	1	0	6	1

Values are n, mean ± SD, n (%), or mean. [a]Women and pregnancies are not mutually exclusive in one group, as 18 women had >1 pregnancy, 6 women (8 pregnancies) had aortic and mitral valve prostheses, and 20 pregnancies occurred in 16 women after the Ross procedure with autografts in the aortic position and prosthetic valves in the pulmonary position.

left-sided BPVs and right-sided BPVs. Women with left-sided BPVs had either acquired (most commonly rheumatic) heart disease or simple congenital heart disease, such as bicuspid aortic valve disease. In contrast, 70% of women with right-sided BPVs had complex congenital heart disease, with tetralogy of Fallot accounting for 60% (n = 55) of the cases. Twenty pregnancies occurred in 16 women after the Ross operation, with a pulmonary autograft in the aortic position and a BPV in the pulmonary position.

PREVALENCE OF SVD. In 27% of the pregnancies (n = 34 of 125), SVD of the BPV was present. One woman after the Ross operation had dysfunction of the autograft and the pulmonary BPV; no other woman had dysfunction of 2 BPVs.

Women with left-sided BPVs were more likely to have SVD than those with right-sided BPVs (44% with left-sided BPV vs 21% with right-sided BPV; $P = 0.009$). Notably, only 1 woman (5% [n = 1 of 20]) with a Ross operation had dysfunction of the autograft in the aortic position, whereas 40% (n = 10 of 25) of aortic BPVs were dysfunctional at the first antenatal visit. The time between surgery and pregnancy was comparable in women with left- and right-sided BPVs (5 ± 3 years and 6 ± 6 years; $P = 0.23$); however, it differed between pregnancies with and without SVD (left-sided BPVs [7 ± 3 years in those with SVD vs 4 ± 2 years in those without SVD; $P = 0.001$] and right-sided BPVs [11 ± 7 years in those with SVD vs 5 ± 5 years in those without SVD; $P < 0.001$]). Table 2 shows the prevalence of SVD according to valve type. SVD was most commonly due to stenosis in 63% (n = 22 of 35), 29% (n = 10 of 35) had mixed stenotic and regurgitant BPV dysfunction, and 9% (n = 3 of 35) had significant BPV regurgitation. The peak and mean gradients in patients with SVD and aortic BPV stenosis were 83 ± 19 mm Hg and 48 ± 12 mm Hg, respectively. The mean gradient in patients with SVD and mitral BPV stenosis was 14 ± 6 mm Hg. The peak and mean gradients in patients with SVD and pulmonary BPV stenosis were 49 ± 8 mm Hg and 28 ± 4 mm Hg, respectively. In those with SVD and regurgitant lesions, regurgitation was moderate or severe in all cases.

ADVERSE EVENTS DURING PREGNANCY. Table 3 shows rates of CEs, FEs, and adverse obstetrical events. Overall, 38% of pregnancies (n = 47 of 125) were complicated by adverse CEs, FEs, or obstetrical events. Adverse maternal CEs occurred in 13% (n = 16 of 125) of all pregnancies. Six pregnancies were complicated by arrhythmias, all in the antepartum period. Five women had supraventricular tachycardia, 1 requiring electric cardioversion, and 1 woman with tetralogy of Fallot had nonsustained ventricular tachycardia. Congestive heart failure occurred in 11 pregnancies, 6 in the antepartum period and 5 in the postpartum period, and 2 of the patients also had arrhythmia.

Two women required valve surgery during pregnancy. One woman with severe stenosis of her mitral BPV presented at 18 weeks' gestation with biventricular heart failure and underwent valve replacement within 1 week after presentation. A second woman presented at 19 weeks' gestation with severe stenosis of her aortic BPV and functional class III symptoms unresponsive to therapy. She underwent valve replacement surgery at 23 weeks' gestation. One woman with severe mitral BPV regurgitation and

TABLE 3 Adverse Cardiac, Fetal, and Obstetrical Events Stratified According to Left-Sided vs Right-Sided BPVs

	All Pregnancies (N = 125)	Left-Sided BPV (n = 34)	Right-Sided BPV (n = 91)	*P* Value
Any primary adverse cardiac event[a]	16 (13)	8 (24)	8 (9)	0.03
Cardiac death	1 (1)	1 (3)	0 (0)	0.27
Cardiac arrest	0 (0)	0 (0)	0 (0)	
Congestive heart failure	9 (7)	4 (12)	5 (5)	0.25
Arrhythmia	6 (5)	3 (9)	3 (3)	0.34
Stroke	0 (0)	0 (0)	0 (0)	
Secondary adverse cardiac event				
Cardiac surgery within 6 wk postpartum	3 (2)	3 (9)	0 (0)	0.019
Any adverse fetal event[a]	35 (28)	12 (35)	23 (25)	0.27
Fetal or neonatal death	2 (2)[b]	2 (6)[b]	0 (0)	0.07
Preterm delivery	15 (12)	5 (15)	10 (11)	0.57
Small for gestational age	19 (15)	7 (21)	12 (13)	0.31
Respiratory distress syndrome	2 (2)	0 (0)	2 (2)	1.00
Intracerebral hemorrhage	0 (0)	0 (0)	0 (0)	
Any adverse obstetrical event[a]	6 (5)	2 (6)	4 (4)	0.66
Preeclampsia	1 (1)	0 (0)	1 (1)	1.00
Postpartum hemorrhage	5 (4)	2 (6)	3 (3)	0.61

Values are n (%). *P* values describe differences between left- and right-sided valves. [a]Events are not mutually exclusive. [b]2 fetal deaths followed maternal cardiac surgery during pregnancy.
BPV = bioprosthetic valve.

mildly reduced left ventricular systolic function developed pulmonary edema in the early postpartum period and underwent valve replacement. All other episodes of heart failure were treated medically. One woman with severe stenosis of the aortic BPV and ventricular dysfunction died suddenly at home in the postpartum period. None of the woman had thromboembolic complications, myocardial infarction, or aortic dissection. Of the 8 women with left-sided BPVs who had CEs, 63% had severe BPV stenosis, and 25% had moderate or severe BPV regurgitation. In contrast, 75% of women with right-sided BPVs who had CEs had normal pulmonary BPV function. The 2 CEs in women with right-sided SVD occurred in a woman after the Ross operation with stenosis of the pulmonary BPV and severe regurgitation of the aortic autograft and in a woman with Ebstein anomaly and mixed stenosis and regurgitation of the tricuspid BPV.

Seventy-five percent of patients who experienced CEs during pregnancy had previous episodes of either arrhythmia (59%) or heart failure (19%) prior to the pregnancy. Supplemental Table 2 shows details of BPV function, clinical characteristics, and adverse CEs.

There were 35 FEs complicating 28% of the pregnancies. Two fetal deaths occurred in the 2 women who required valve replacement surgery during pregnancy.

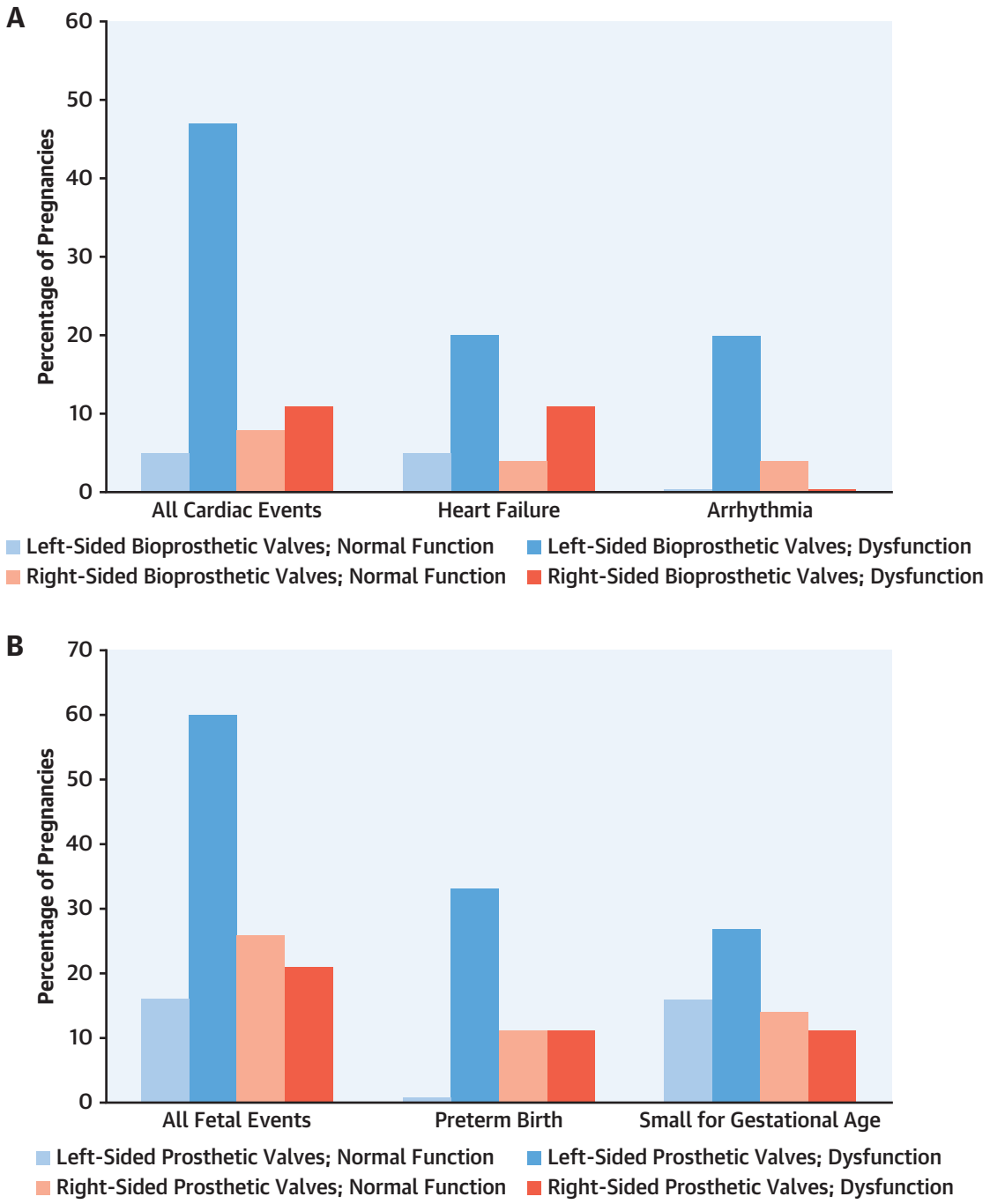
DIFFERENCES IN MATERNAL CEs BASED ON VALVE FUNCTION AND VALVE POSITION. Adverse CEs were more common in women with SVD compared with women with normally functioning BPVs (26% vs 8%; $P = 0.005$). The CE rate was higher in women with left-sided compared with right-sided BPVs (24% vs 9%; $P = 0.03$), and this increased risk with left-sided BPVs was driven by the high rates in women with SVD. In the presence of SVD of any left-sided BPV, CEs occurred in 47% of pregnancies compared with a significantly lower CE rate of 5% ($P = 0.01$) in those with normally functioning left-sided BPVs. In contrast, in women with right-sided BPVs, CEs were not more common in pregnancies with SVD (11% with SVD vs 8% without SVD; $P = 0.67$) (**Figure 1A,** Supplemental Tables 3 and 4).

There was no significant difference in FEs between pregnancies with and without SVD (38% vs 24%; $P = 0.12$) and between pregnancies with left-sided BPVs compared with right-sided BPVs (35% vs 25%; $P = 0.27$). However, the FE rate differed between women with left-sided BPVs with and without SVD (60% vs 16%; $P = 0.012$), whereas there was no significant difference in FE rate between women with right-sided BPVs with and without SVD (21% vs 26%; $P = 0.77$) (**Figure 1B**).

DETERMINANTS OF ADVERSE CEs AND FEs. The results of the univariate analysis for CE and FE are shown in **Tables 4 and 5**, respectively. On multivariable analysis, dysfunction of any left-sided prosthetic valve (OR: 20.6; 95% CI: 2.4-179.1; $P = 0.006$), maternal age >35 years (OR: 49.8; 95% CI: 4.9-502.6; $P = 0.001$), and the composite "high-risk" variable (OR: 4.5; 95% CI: 1.6-12.5; $P = 0.004$) were related to CEs. On adjusted analysis, 3 other covariates (cardiac medications, BMI ≥30 kg/m^2, and acquired valvular heart disease) were not significantly related to cardiovascular events. Similarly, dysfunction of any left-sided prosthetic valve was significantly related to FEs (OR: 3.5; 95% CI: 1.02-11.8; $P = 0.046$) on adjusted analysis; the other 2 adjustment covariates (BMI ≥30 kg/m^2 and New York Heart Association functional class III or IV) were not significantly related to FEs.

When secondary analyses were performed using general estimating equations, the findings were similar. Dysfunction of any left-sided prosthetic valve (OR: 20.5; 95% CI: 2.4-171.4; $P = 0.005$), maternal age >35 years (OR: 49.3; 95% CI: 4.5-544.4; $P = 0.001$), BMI >30 kg/m^2 (OR: 7.3; 95% CI: 1.4-39.0; $P = 0.019$),

FIGURE 1 Relationship Between Adverse Pregnancy Outcome and Bioprosthetic Valve Function



(A) Cardiac events in left-sided and right-sided bioprosthetic valves with normal function and with structural valve dysfunction. **(B)** Fetal events in left-sided and right-sided bioprosthetic valves with normal function and with structural valve dysfunction. Pregnant women with structural valve dysfunction of any left-sided bioprosthetic valve were at highest risk for cardiac **(A)** and fetal **(B)** adverse events.

TABLE 4 Determinants of Adverse Maternal Cardiac Events

	No Cardiac Event (n = 109)	Adverse Cardiac Event (n = 16)	*P* Value
Maternal characteristics			
Maternal age, y	30 ± 5	36 ± 5	<0.001
Maternal age >35 y	14 (13)	9 (56)	<0.001
Years since valve implantation	6 ± 5	8 ± 4	0.06
Nulliparity	51 (47)	5 (31)	0.25
Late pregnancy assessment (>20 wk gestation)	23 (21)	2 (13)	0.43
Prior cardiac event[a]	18 (17)	12 (75)	<0.001
Any comorbidities (diabetes, hypertension)	8 (7)	1 (6)	0.88
History of smoking	12 (11)	1 (6)	0.57
Body mass index ≥30 kg/m^2 [b]	11/106 (10)	6 (38)	0.003
New York Heart Association functional class III or IV	1 (1)	3 (19)	0.007
Cardiac medications			
Any cardiac medication except anticoagulation or aspirin at first visit	8 (7)	6 (38)	0.001
Aspirin	24 (22)	3 (19)	0.77
Cardiac diagnosis			
Acquired valvular heart disease	8 (7)	5 (31)	0.007
Complex congenital heart disease[c]	59 (54)	5 (31)	0.10
Bioprosthetic valve dysfunction			
Dysfunction left-sided prosthetic valve	8 (7)	7 (44)	<0.001
Dysfunction right-sided prosthetic valve	17 (16)	2 (13)	0.75
Other echocardiographic features			
Subaortic ventricular dysfunction[d]	9 (8)	5 (31)	0.012
Subpulmonic ventricular dysfunction (mild)	32 (29)	5 (31)	0.88
Dysfunction of any native left-sided valve[e]	2 (2)	1 (6)	0.31
Dysfunction of any native right-sided valve[e]	14 (13)	4 (25)	0.21

Values are mean ± SD, n (%), or n/N (%). *P* values describe differences between pregnancies with and without cardiac events. [a]Prior heart failure, arrhythmia, or thromboembolic event. [b]3 values for body mass index were missing (all from the pregnancies without cardiac events). [c]Tetralogy of Fallot, transposition of the great arteries, pulmonary atresia with intact ventricular septum, atrioventricular septal defect, Ebstein anomaly, and truncus arteriosus communis. [d]Ejection fraction <55%. [e]Moderate or severe stenosis or regurgitation.

and the composite "high-risk" variable (OR: 4.5; 95% CI: 1.4-14.2; $P = 0.011$) were associated with CEs. Again, dysfunction of any left-sided prosthetic valve was significantly related to FEs (OR: 3.5; 95% CI: 1.03-11.5; $P = 0.044$).

DISCUSSION

This is the first study to focus on SVD in young women with BPVs and its impact on pregnancy outcomes. In this cohort of women from 2 Canadian tertiary care cardio-obstetric centers, more than one-quarter of all pregnant women with BPVs had SVD, although time since valve replacement surgery was, on average, only 6 ± 3 years. SVD was more than twice as common in women with left-sided BPVs compared with those with right-sided BPVs. CEs were most common in pregnancies with left-sided BPVs, driven by the high event rate in those with SVD (47% of pregnancies). In comparison, CEs were less common in women with right-sided BPVs, and there was no difference in pregnancies with or without SVD. FEs occurred in 28% of pregnancies, and the FE rate was particularly high in women with left-sided BPVs with SVD.

STRUCTURAL VALVE DYSFUNCTION. In this study, SVD was identified in 27% of pregnancies at the first antenatal assessment. The durability of BPVs is reduced in young patients, in whom SVD may be accelerated,[4,7,26] because of higher functional demand and a more active immune system.[26,27] In an older study, valve loss (defined as either reoperation or valve-related death) 10 years after surgery was described in up to 82% of young women between 12 and 35 years of age with aortic, mitral, and tricuspid BPVs.[5] In a more contemporary cohort of young adults <50 years of age, the need for reoperation after 10 years was about 14% for BPVs in the mitral position[28] and in the aortic position.[29] In one other study reporting on patients younger than 40 years with left-sided BPVs, the median time interval to reoperation was only 8 years.[30] However, rates of hemodynamically significant SVD were higher than the reoperation rate.[4,7] In contrast, for pulmonary BPVs, a longer durability of 12.6 years has been described.[6]

We also found important differences in the rates of SVD between women with left- and right-sided BPVs at the time of pregnancy. Forty-four percent of women with left-sided BPVs had SVD on average 7 ± 3 years after surgery, and 21% of women with right-sided BPVs had SVD on average 11 ± 7 years after surgery, probably reflecting earlier degeneration of left-sided BPVs due to higher functional demand in a high-pressure vs a low-pressure circulation. Better overall outcomes for young patients after the Ross operation in comparison with other aortic valve substitutes has been reported.[26,31,32] In a Toronto cohort after the Ross operation, 11.5% of the patients needed reoperation because of dysfunction of the autograft in the aortic position within 20 years.[33] In our study, only 1 pregnant woman (5% [n = 1 of 20]) had dysfunction of the pulmonary autograft in the aortic position 18 years after surgery. In our pregnant cohort, the low prevalence of valve dysfunction was likely due to the short follow-up time between surgery and pregnancy. It is believed that degeneration of autograft valves is less frequent because of the living tissue and favorable hemodynamic status.[26,32]

RELATIONSHIP BETWEEN ADVERSE MATERNAL CEs AND SVD. Adverse CEs were more common in women with SVD compared with women with normally functioning BPVs (26% vs 8%) and were more frequent in women with left-sided compared with

right-sided BPVs (**Central Illustration**). Women with left-sided BPVs had less complex underlying cardiac anatomy, either simple congenital heart disease or rheumatic heart disease, compared with women with right-sided BPVs and yet had worse outcomes. Notably, the increased risk in women with left-sided BPVs was driven primarily by the high rate of CEs in those pregnancies with SVD (47%), whereas the CE rate in women with normal function of left-sided BPVs was low (5%). The limited ability to tolerate the hemodynamic changes of pregnancy in the setting of left-sided obstructive lesions has been previously reported.[17,18,34] During pregnancy, there is an augmented plasma and stroke volume. With a fixed left-sided inflow or outflow obstruction, the increase of cardiac output leads to an increase in transvalvular gradients and in left atrial (mitral valve obstruction) or left ventricular (aortic valve obstruction) pressure.[35,36] Furthermore, the physiological tachycardia of pregnancy decreases diastolic filling time, contributing to higher left atrial pressures in women with mitral valve obstruction.[36,37] In contrast, women with right-sided BPVs had more complex congenital heart disease such as tetralogy of Fallot, pulmonary atresia, and Ebstein anomaly. Notwithstanding, CE rates in our study were lower and in line with previous reports.[19,38] SVD of right-sided BPVs had no significant impact on CE risk (8% without vs 11% with SVD), showing that right-sided stenotic and regurgitant lesions are usually well tolerated during pregnancy.[39,40]

TABLE 5 Determinants of Adverse Fetal or Neonatal Events

	No Fetal Event (n = 90)	Adverse Fetal Event (n = 35)	*P* Value
Maternal characteristics			
Maternal age, y	31 ± 5	31 ± 7	0.54
Maternal age >35 y	17 (19)	6 (17)	0.82
Years since valve implantation	5 ± 4	6 ± 6	0.53
Nulliparity	37 (41)	19 (54)	0.19
Late pregnancy assessment (>20 wk gestation)	15 (17)	10 (29)	0.14
Prior cardiac event[a]	22 (24)	8 (23)	0.85
Any comorbidities (diabetes, hypertension)	7 (8)	2 (6)	0.69
History of smoking	8 (9)	5 (14)	0.38
Body mass index ≥30 kg/m^2 [b]	10/88 (11)	7/34 (21)	0.19
New York Heart Association functional class III or IV	0 (0)	4 (11)	0.005
Cardiac medications			
Any cardiac medication except anticoagulation or aspirin at first visit	7 (8)	7 (20)	0.06
Aspirin	20 (22)	7 (20)	0.79
Cardiac diagnosis			
Acquired valvular heart disease	9 (10)	4 (11)	0.81
Complex congenital heart disease[c]	49 (54)	15 (43)	0.25
Bioprosthetic valve dysfunction			
Dysfunction left-sided prosthetic valve	6 (7)	9 (26)	0.003
Dysfunction right-sided prosthetic valve	15 (17)	4 (11)	0.47
Other echocardiographic features			
Subaortic ventricular dysfunction[d]	10 (11)	4 (11)	0.96
Subpulmonic ventricular dysfunction (mild)	27 (30)	10 (29)	0.88
Dysfunction of any native left-sided valve[e]	2 (2)	1 (3)	0.84
Dysfunction of any native right-sided valve[e]	10 (11)	8 (23)	0.10

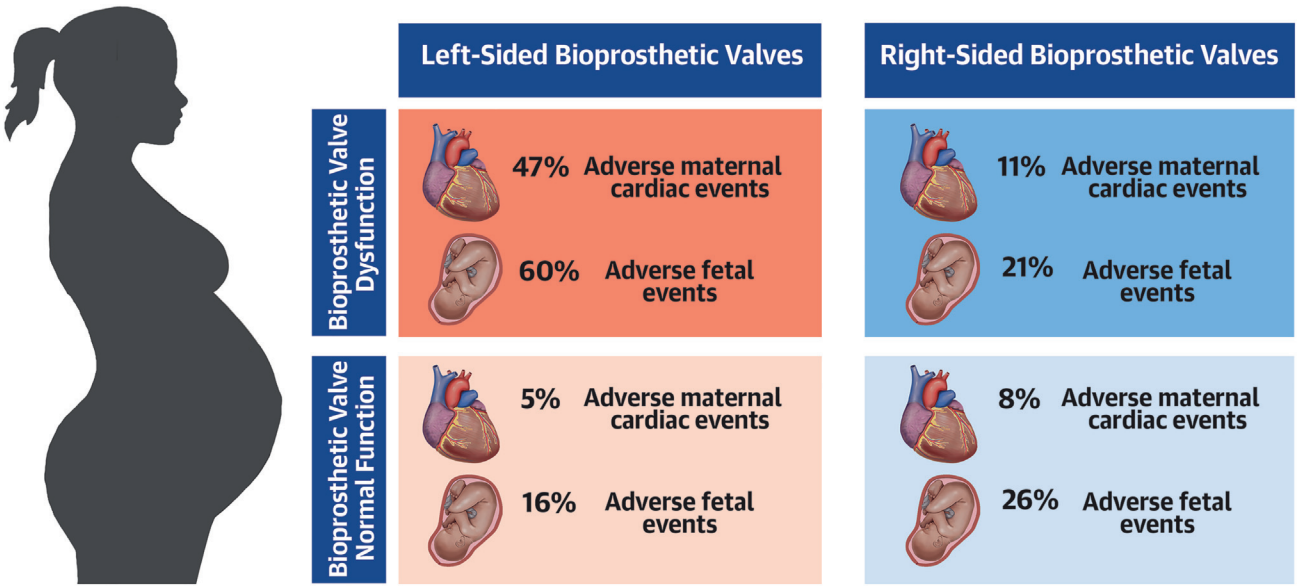
Values are mean ± SD, n (%), or n/N (%). *P* values describe differences between fetal events and no fetal events. [a]Prior heart failure, arrhythmia, or thromboembolic event. [b]3 values for body mass index were missing (2 from the pregnancies without fetal events and one from a pregnancy with a fetal event). [c]Tetralogy of Fallot, transposition of the great arteries, pulmonary atresia with intact ventricular septum, atrioventricular septal defect, Ebstein anomaly, and truncus arteriosus communis. [d]Ejection fraction <55%. [e]Moderate or severe stenosis or regurgitation.

ADVERSE FEs AND SVD. FEs occurred in 28% of all pregnancies. High FE rates in pregnancies of women with BPVs have been previously described, in 10% to 29% of preterm births[1,8,16,19] and 13% to 20% of small-for-gestational-age babies.[1,8,14-16,19] Maternal cardiac disease, particularly left ventricular obstruction and poor functional class, negatively affect fetal outcomes,[41] which is thought to be linked, at least in part, to an impaired ability of the mother to increase cardiac output during pregnancy adequately.[42] We observed the highest rate of FEs in women with left-sided SVD (60%), supporting the concept that lesions associated with limitations on cardiac output impair the growing fetus.

CLINICAL IMPLICATIONS. Whereas mechanical valves are not recommended in women with right-sided valve disease,[10,11] the best choice of prosthesis in a young woman requiring replacement of the aortic or mitral valve remains a complex decision. We found that SVD was common in young pregnant women with left-sided BPVs, even early after valve replacement, and was associated with an increased risk for CEs and FEs. Although most maternal cardiac complications we report here were treated medically, 1 woman died, 2 required cardiac surgery during pregnancy, and 1 required cardiac surgery immediately after childbirth. This new information needs to be incorporated into clinical decision making when discussing valve selection with young women of childbearing age. In addition, we found that of the 20 pregnancies in women with the Ross operation, only 1 had dysfunction of the autograft, suggesting that this may be a good valve choice for some women, especially at centers with expertise in this procedure.[32,33]

The high rates of SVD in this population of young women with BPVs highlight the need for ongoing close surveillance in such women. Furthermore, for

CENTRAL ILLUSTRATION **Adverse Pregnancy Events in Patients With Bioprosthetic Valves**



Wichert-Schmitt B, et al. J Am Coll Cardiol. 2022;80(21):2014–2024.

Twenty-seven percent of the study cohort had structural valve dysfunction. The figure shows adverse maternal cardiac and fetal events stratified according to valve function and valve position. The risk for adverse maternal cardiac and fetal events was significantly increased in women with structural valve dysfunction (SVD) of any left-sided bioprosthetic valve **(red boxes)**, whereas this association was not seen in women with right-sided SVD **(blue boxes)**.

women with SVD considering pregnancy, preconception counseling is important so that they understand the risks of pregnancy and can make informed pregnancy decisions. In some with significant SVD, prosthetic valve replacement may need to be considered prior to pregnancy.[43] In those women with SVD who become pregnant, frequent clinical and echocardiographic follow-up during pregnancy is advised. In addition, women should be on aspirin for the prevention of valve thrombosis.[43] Delivery plans should be based on the cardiac diagnosis and the severity of SVD. All these women should be followed at centers with cardiac and obstetrical expertise in pregnancy and heart disease.

STUDY LIMITATIONS. This was a retrospective review of a prospective cohort of women with heart disease followed during pregnancy, with the inherent limitations of this type of study design. Because of the small number, women with tricuspid BPVs were underrepresented in the cohort of women with right-sided BPVs, and likely the risk for adverse events in women with tricuspid BPVs was not captured by the present study. Most women with left-sided BPVs have simple congenital or acquired heart disease, and they might not necessarily be routinely cared for at specialized tertiary centers. Therefore, it is possible that more pregnant women with BPV dysfunction were referred to our cardio-obstetric clinics compared with women with normally functioning BPVs, leading to the high percentage of SVD in our cohort of women with left-sided BPV. The transthoracic echocardiograms were obtained at the first antenatal visit, and especially in women who presented later in pregnancy, the increased cardiac output may have led to increased transprosthetic velocities and gradients that might have been lower in a study done earlier during or prior to pregnancy.[44] However, when establishing the diagnosis of SVD, we did not depend on gradients alone but also factored in morphologic signs for degeneration.

CONCLUSIONS

In this study, a large number of women followed at our tertiary cardio-obstetric clinics had dysfunctional BPVs at the time of the first antenatal visit. The risk for adverse maternal CEs and FEs was substantially increased in women with SVD of any left-sided BPV,

whereas this association was not seen in women with right-sided SVD. This new information needs to be incorporated into decision making and highlights that the correct prosthesis choice for young women with significant left-sided valvular lesions remains difficult. Counseling regarding the reduced longevity of left-sided BPVs and its implications for pregnancy outcomes must be included in the discussion.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Structural bioprosthetic valve dysfunction in pregnant women is associated with adverse maternal cardiac and fetal outcomes.

TRANSLATIONAL OUTLOOK: Research is needed to develop longer-lasting bioprosthetic valves or treatments to prevent structural valve dysfunction in young women.

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APPENDIX For supplemental tables, please see the online version of this paper.