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ORIGINAL RESEARCH

Maternal and Fetal Outcomes in Pregnant Patients With Mechanical and Bioprosthetic Heart Valves

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BACKGROUND: Guidelines for choice of prosthetic heart valve in people of reproductive age are not well established. Although biologic heart valves (BHVs) have risk of deterioration, mechanical heart valves (MHVs) require lifelong anticoagulation. This study aimed to characterize the association of prosthetic valve type with maternal and fetal outcomes in pregnant patients.

METHODS AND RESULTS: Using the 2008 to 2019 National Inpatient Sample, we identified all adult patients hospitalized for delivery with prior heart valve implantation. Multivariable regressions were used to analyze the primary outcome, major adverse cardiovascular events, and secondary outcomes, including maternal and fetal complications, length of stay, and costs. Among 39 871 862 birth hospitalizations, 4152 had MHVs and 874 had BHVs. Age, comorbidities, and cesarean birth rates were similar between patients with MHVs and BHVs. The presence of a prosthetic valve was associated with over 22-fold increase in likelihood of major adverse cardiovascular events (MHV: adjusted odds ratio, 22.1 [95% CI, 17.3–28.2]; BHV: adjusted odds ratio, 22.5 [95% CI, 13.9–36.5]) as well as increased duration of stay and hospitalization costs. However, patients with MHVs and BHVs had no significant difference in the odds of any maternal outcome, including major adverse cardiovascular events, hypertensive disease of pregnancy, and ante/postpartum hemorrhage. Similarly, fetal complications were more likely in patients with valve prostheses, including a 4-fold increase in odds of stillbirth, but remained comparable between MHVs and BHVs.

CONCLUSIONS: Patients hospitalized for delivery with prior valve replacement carry substantial risk of adverse maternal and fetal events, regardless of valve type. Our findings reveal comparable outcomes between MHVs and BHVs.

Key Words: anticoagulation ■ heart valve prostheses ■ pregnancy ■ thrombosis ■ valvular heart disease

Valvular heart disease coupled with the significant hemodynamic changes of pregnancy has been linked with a myriad of adverse obstetric outcomes.[1–5] For people of reproductive age with symptomatic valvular heart disease, preconception valve replacement is recommended.[6] Presently, replacement valves may be mechanical or bioprosthetic (typically bovine or porcine), with each carrying distinct advantages and drawbacks.[7] Notably, bioprosthetic valves do not require long-term anticoagulation but suffer from accelerated structural deterioration in young patients, necessitating early reoperation.[8,9] The more durable mechanical valves have a potential long-term mortality benefit over bioprosthetic valves and are currently recommended for patients younger than 65 years of age.[6,10] However, mechanical valves are at greater risk of thromboembolism and require lifelong anticoagulation with vitamin K antagonists, raising concern about bleeding and teratogenicity during pregnancy.[11–13]

Given such considerations, it is important to optimize the selection of prosthetic heart valves, particularly for individuals of reproductive age considering

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CLINICAL PERSPECTIVE

What Is New?

- Pregnant individuals with prior heart valve replacement are at greater risk of major adverse cardiovascular events as well as increased length of stay and costs compared with individuals without a prosthetic valve.
- Mechanical and bioprosthetic heart valves have comparable odds of adverse maternal and fetal outcomes, including ante/postpartum hemorrhage, congenital anomalies, and stillbirth.

What Are the Clinical Implications?

- The presence of a valve prostheses, regardless of valve type, places pregnant people at substantial risk of adverse maternal and fetal events during delivery.
- Individuals with prior valve replacement who become pregnant warrant specialized, multidisciplinary cardio-obstetrics care for management of labor and delivery.
- Preconception counseling can help guide shared decision-making and optimize choices of treatment for patients of reproductive age with valvular heart disease.

Nonstandard Abbreviations and Acronyms

BHV	bioprosthetic heart valve
MACE	major adverse cardiovascular events
MHV	mechanical heart valve
nHV	no prosthetic heart valve
NIS	National Inpatient Sample

pregnancy. Presently, there is no consensus on the valve choice that minimizes risk to both the mother and the fetus. Recent literature has shown that bioprosthetic valves pose a decreased risk of thrombosis, bleeding, and maternal and fetal death compared with mechanical valves.[14,15] However, available studies are limited in scope, and large-scale data remain lacking. To our knowledge, the largest series to date on this topic examines a cohort of only 417 individuals.[14] Therefore, the present cross-sectional study characterized the association of heart valve type with maternal and fetal outcomes in pregnant inpatients across the United States. We hypothesized that prior valve replacement, particularly mechanical valves, would be associated with increased maternal and fetal complications, length of stay, and costs.

METHODS

Data Availability

All data that support the findings of this study are available through the Healthcare Cost and Utilization Project central distributor online: https://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp

Data Source and Study Population

This was a retrospective cohort study using data from the 2008 to 2019 National Inpatient Sample (NIS). Maintained by the Healthcare Cost and Utilization Project, the NIS is the largest publicly available all-payer inpatient database in the United States and samples 20% of all hospital discharges.[16] Using robust survey-weighting algorithms, the NIS provides accurate estimates for ≈97% of all hospitalizations in the United States. Due to the deidentified nature of the NIS, this study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

All delivery hospitalizations were identified using a previously published combination of *International Classification of Diseases, Ninth and Tenth Revisions* (*ICD-9/10*) and diagnosis-related group codes.[17] Patients with a mechanical (V43.3, Z95.2) or bioprosthetic heart valve (V42.2, Z95.3) were subsequently identified using *ICD-9/10* diagnosis codes and grouped into mechanical heart valve (MHV) and bioprosthetic heart valve (BHV) categories, respectively. Patients with no prosthetic heart valve were identified as nHV.

Only patients between 18 and 50 years of age were included for further analysis. Patients with more than 1 type of heart valve implant as well as those undergoing valve replacement were not considered for further analysis. Records with missing data for age, sex, race, insurance status, income, elective status, and in-hospital mortality were also excluded (10.3%). A comprehensive breakdown of variable missingness is shown in Figure 1.

Patient Characteristics and Outcomes

Patient, operative, and hospital characteristics including age, income level, insurance status, race, and hospital teaching status were defined in accordance with the Healthcare Cost and Utilization Project data dictionary. Other race includes American Indian, Alaska Native, and other race as defined in the data dictionary.[16] Cesarean birth and multiple gestation were ascertained using previously published *ICD-9/10* diagnosis and procedure codes.[18,19] Similarly, comorbidities, such as diabetes, hypertension, obesity, pulmonary disease, coagulopathy, hypothyroidism, rheumatoid arthritis/collagen vascular diseases, anemia, liver disease, and end-stage renal disease, were identified using *ICD-9/10* diagnosis codes. Maternal

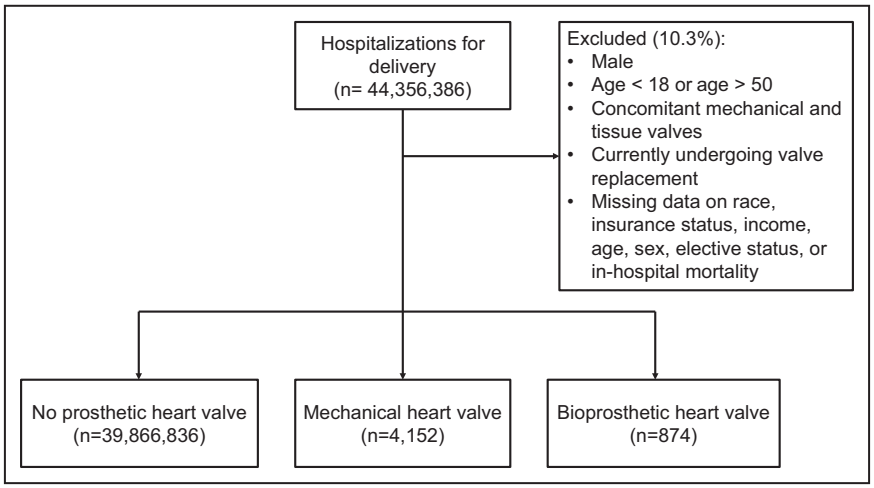

Figure 1. Flow chart of patient inclusion.
Using the 2008 to 2019 National Inpatient Sample (NIS) database, an estimated 39 871 862 birth hospitalizations were identified, including 5026 (0.01%) with a prosthetic heart valve. Of pregnant patients with prostheses, 4152 (82.6%) had mechanical and 874 (17.4%) had bioprosthetic valves.

complications, including gestational diabetes, preterm premature rupture of membranes, placental abruption, chorioamnionitis, antepartum or postpartum hemorrhage, respiratory complications, blood transfusion, and acute kidney injury, were similarly ascertained. Fetal complications, including congenital anomalies, poor fetal growth, spontaneous and induced abortion, preterm birth, and stillbirth were also tabulated (Table S1). Hypertensive disease of pregnancy was defined as a composite of gestational hypertension; preeclampsia, hemolysis, elevated liver enzymes, and low platelets syndrome; and eclampsia.[20,21] Overall index hospitalization costs were calculated by application of center-specific cost-to-charge ratios to overall hospitalization costs and were inflation adjusted to the 2019 Personal Health Care Index.[22]

The primary outcome of interest was major adverse cardiovascular events (MACE), defined as a composite of in-hospital mortality, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, valve thrombosis, pulmonary embolism, arterial embolism, obstetric-related pulmonary embolism, cardiac complications of anesthesia or other sedation in labor and delivery, cardiogenic shock, and cardiac arrest as derived from previous literature.[18,19] This composite outcome of MACE was used because NIS does not allow for reporting of events with n<10 to protect privacy.[16] Individual maternal and fetal complications, length of stay, and hospitalization costs were secondarily evaluated (Table S1).

Statistical Analysis

Categorical variables are reported as frequencies (%) while continuous variables are summarized as medians with interquartile range. To assess significance of differences across groups, we used the Pearson's chi-square test for categorical variables and the Kruskal–Wallis test and Mann–Whitney *U* test for continuous ones. Given the large sample size of the nHV group, we used previously published methods to measure the effect sizes of outcome differences and estimate the clinical importance of significantly different comparisons.[23] Effect sizes of ≤0.2 are considered small, 0.5 medium, and >0.8 large. The significance of temporal trends was assessed using a nonparametric test.[24] Multivariable linear and logistic regression models were developed to evaluate the independent association between history of valve replacement and outcomes of interest. Variable selection was performed by applying elastic net regularization, a technique that combines least absolute shrinkage and selection operator and Ridge regression methodology to reduce collinearity while applying penalties to decrease overfitting.[25] Optimization of the final model was based on area under the receiver operating characteristic (C-statistic). Regression outcomes are reported as adjusted odds ratios (aOR) for categorical variables or beta coefficients (β) for continuous variables, with 95% CI for both. Statistical significance was set at α=0.05. All statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX).

RESULTS

Demographic Comparison

Of an estimated 39 871 862 birth hospitalizations considered for analysis, 5026 (0.01%) had a replaced heart valve (Figure 1). Of these, 4152 (82.6%) had mechanical

Table 1. Comparison of Baseline Patient, Operative, and Hospital Characteristics by Type of Valve Replacement

Parameter	No valve (n=39 866 836)	Mechanical (n=4152)	Bioprosthetic (n=874)
Age, y	28 (24–33)	29 (25–33)	30 (25–33)
Race or ethnicity			
Asian	5.8	5.8	3.4
Black	14.3	17.8	11.8
Hispanic	21.1	12.6	13.9
White	53.4	59.2	66.8
Other	5.4	4.6	4.0
Cesarean birth	33.2	43.9	51.8
Multiple gestation	1.7	2.2	1.7
Elective admission	49.6	44.6	55.7
Comorbidities			
Chronic diabetes	1.0	1.3	0
Chronic hypertension	0.5	3.6	1.6
Obesity	6.6	8.3	8.5
Chronic pulmonary disease	4.2	10.3	11.2
Coagulopathy	1.8	6.4	8.7
Hypothyroidism	3.0	4.4	5.7
Rheumatoid arthritis/collagen vascular diseases	0.3	2.5	2.8
Anemia	1.4	2.4	2.3
Liver disease	0.2	1.4	1.7
End-stage renal disease	0.1	1.8	0.6
Income quartile			
76th–100th percentile	22.7	19.4	26.4
51st–75th percentile	24.8	27.0	25.0
26th–50th percentile	25.0	26.3	22.6
0th–25th percentile	27.8	27.3	26.1
Payer status			
Private	50.9	47.5	54.4
Medicare	0.7	4.1	4.5
Medicaid	43.0	43.4	36.0
Other	5.4	5.0	5.1
Hospital region			
Northeast	16.8	14.8	17.9
Midwest	18.3	22.2	21.8
South	40.0	38.2	27.4
West	24.8	24.8	33.0
Hospital bed size			
Small	14.6	8.2	5.4
Medium	29.3	19.4	19.9
Large	56.1	72.4	74.8
Hospital teaching status			
Nonmetropolitan	9.5	5.1	3.5
Metropolitan nonteaching	32.1	16.0	15.2
Metropolitan teaching	58.4	79.0	81.3

Values are % or median (interquartile range).

and 874 (17.4%) had bioprosthetic valves. Over the 12-year study period, the prevalence of mechanical valves remained consistently higher than bioprosthetic ones with no significant trend (NPtrend=0.43). Compared with those without a prosthetic valve, patients with valves were older (nHV: 28 years [interquartile range:

Table 2. Unadjusted Maternal and Fetal Outcomes Stratified by Valve Replacement Type

Parameter	No valve (n=39 866 836)	Mechanical (n=4152)	Bioprosthetic (n=874)	*P* value† (All groups)	*P* value‡ (Mech vs Bio)
Major adverse cardiac events	166 519 (0.4)	509 (12.3)	111 (12.6)	<0.001	0.91
Mortality	3364 (0.01)	<10*	0	0.003	0.64
Acute myocardial infarction	1164 (0.003)	<10	<10	<0.001	0.64
Heart failure	4660 (0.01)	39 (0.9)	0	<0.001	0.19
Arrhythmia	139 301 (0.3)	465 (11.2)	106 (12.1)	<0.001	0.94
Cerebrovascular events	3072 (0.01)	<10	0	0.001	0.64
Valve thrombosis	–	10 (0.2)	<10	–	0.49
Other thromboembolic events	17 236 (0.04)	10 (0.2)	<10	<0.001	0.49
Cardiac complications of anesthesia/sedation	1991 (0.01)	0	0	0.98	–
Cardiogenic shock	662 (0.002)	0	0	0.99	–
Cardiac arrest	3238 (0.01)	0	0	0.96	–
Other maternal complications					
Gestational diabetes	2 761 464 (6.9)	232 (5.6)	75 (8.6)	0.22	0.12
Hypertensive disease of pregnancy	3 636 395 (9.1)	393 (9.5)	103 (11.8)	0.42	0.18
Preterm premature rupture of membranes	2 576 850 (6.5)	278 (6.7)	85 (9.7)	0.21	0.15
Placental abruption	427 523 (1.0)	89 (2.1)	10 (1.1)	0.01	0.59
Chorioamnionitis	897 336 (2.3)	78 (1.9)	30 (3.4)	0.46	0.40
Ante/postpartum hemorrhage	1 483 489 (3.7)	293 (7.1)	74 (8.5)	<0.001	0.47
Respiratory complications	64 421 (0.2)	54 (1.3)	10 (1.1)	<0.001	0.92
Blood transfusion	466 100 (1.2)	229 (5.5)	43 (5.0)	<0.001	0.73
Acute kidney injury	24 912 (0.06)	24 (0.6)	0	<0.001	0.26
Fetal complications					
Congenital anomalies	393 213 (1.0)	105 (2.5)	25 (2.9)	<0.001	0.85
Poor fetal growth	1 114 699 (2.8)	269 (6.5)	54 (6.2)	<0.001	0.75
Abortion, spontaneous/induced	55 524 (0.1)	25 (0.6)	0	0.002	0.30
Preterm birth	2 334 353 (5.9)	418 (10.1)	128 (14.7)	<0.001	0.05
Stillbirth	296 047 (0.7)	126 (3.0)	30 (3.4)	<0.001	0.94
Any fetal complication	3 815 244 (9.6)	803 (19.4)	223 (25.5)	<0.001	0.06
Outcomes					
Length of stay, d	2 (2–3)	3 (2–4)	3 (2–4)	<0.001	0.55
Cost, $1000s	4.1 (2.9–5.8)	6.0 (4.0–9.9)	5.8 (4.3–9.5)	<0.001	0.72

Values are n (%) or median (interquartile range).

*Healthcare Cost and Utilization Project National Inpatient Sample does not allow reporting of <10 events in order to protect individuals' privacy.

†Groups with no valve, mechanical valve, and bioprosthetic valve were compared using the Pearson's chi-square test for categorical variables and Kruskal–Wallis test for continuous ones.

‡Groups with mechanical and bioprosthetic valve were compared using the Pearson's chi-square test for categorical variables and Mann–Whitney *U* test for continuous ones.

24–33] versus MHV: 29 [25–33] versus BHV: 30 [25–33]) and had higher burden of preexisting comorbidities (Table 1). Specifically, rates of hypertension (nHV: 0.5% versus MHV: 3.6% versus BHV: 1.6%), obesity (6.6% versus 8.3% versus 8.5%), pulmonary disease (4.2% versus 10.3% versus 11.2%), and coagulopathy (1.8% versus 6.4% versus 8.7%) were higher in the groups with MHV and BHV. In addition, patients in the MHV and BHV cohorts more frequently underwent cesarean birth (nHV: 33.2% versus MHV: 43.9% versus BHV: 51.8%) compared with the nHV group (Table 1). Of note, there were no significant differences in age, comorbidities, cesarean birth, or multiple gestation rates between the cohorts with MHVs and BHVs (Table 1). However, the cohort with BHVs was most frequently admitted on an elective basis, compared with MHVs and nHV (BHV: 55.7% versus MHV: 44.6% versus nHV: 49.6%; Table 1).

Maternal Outcomes

Unadjusted maternal outcomes are shown in Table 2. Compared with patients with nHV, patients with MHVs and BHVs experienced higher rates of MACE (nHV: 0.4% versus MHV: 12.3% versus BHV: 12.6%, *P*<0.001), primarily driven by arrhythmia (nHV: 0.3% versus MHV: 11.2% versus BHV: 12.1%, *P*<0.001;

Table 2). Effect sizes of these comparisons were ≈0.60, indicating both clinical and statistical significance (Table S2). Further, the groups with MHVs and BHVs faced greater rates of antepartum or postpartum hemorrhage, respiratory complications, and blood transfusion, with blood transfusion having a clinically significant effect size (Table 2, Table S2). However, the incidence of gestational diabetes, hypertensive disease of pregnancy, preterm premature rupture of membranes, and chorioamnionitis were comparable across the cohorts. Of note, there were no significant differences in rates of MACE or other maternal complications between the groups with MHVs and BHVs (Table 2).

Compared with nHV, MHV and BHV deliveries experienced longer length of stay (nHV: 2 days [interquartile range: 2–3] versus MHV: 3 days [2–4] versus BHV: 3 days [2–4], $P<0.001$) and accrued greater hospitalization costs ($4100 [interquartile range: 2900-5800] versus $6000 [4000-9900] versus $5800 [4300-9500], $P<0.001$). Effect sizes of these comparisons were >0.2, indicating clinical significance (Table S2).

On multivariable logistic regression (C-statistic=0.68), MHVs and BHVs were associated with over 22-fold increase in likelihood of MACE relative to nHV (Table 3). Pregnancies with valve prostheses also had greater adjusted odds of developing ante/postpartum hemorrhage, respiratory complications, and blood transfusion, compared with nHV (Figure 2). However, the cohort with BHVs did not have altered odds of MACE (aOR, 1.13 [95% CI, 0.68–1.89], $P=0.64$), hypertensive disease of pregnancy (aOR, 1.44 [95% CI, 0.68–3.02], $P=0.34$), placental abruption (aOR, 0.54 [95% CI, 0.12–2.40], $P=0.42$), ante/postpartum hemorrhage (aOR, 1.03 [95% CI, 0.52–2.04], $P=0.94$), and blood transfusion (aOR, 0.90 [95% CI, 0.42–1.94], $P=0.79$), compared with MHVs (Figure 3). Similarly, risk-adjusted length of stay and costs were both increased in the cohorts with MHVs and BHVs compared with nHV but had no significant difference between valve types (Tables S3 and S4).

Table 3. Patient and Hospital Characteristics Associated With Major Adverse Cardiovascular Events (MACE) Among All Deliveries

Parameter	aOR (95% CI)	*P* value
Valve type		
No valve	Reference	
Mechanical	22.1 (17.3–28.2)	<0.001
Bioprosthetic	22.5 (13.9–36.5)	<0.001
Age (per year)	1.02 (1.02–1.02)	<0.001
Race or ethnicity		
White	Reference	
Asian	0.70 (0.66–0.74)	<0.001
Black	1.04 (1.01–1.08)	0.02
Hispanic	0.64 (0.62–0.67)	<0.001
Other	0.78 (0.74–0.83)	<0.001
Year of hospitalization	0.98 (0.97–0.98)	<0.001
Elective admission	0.85 (0.83–0.88)	<0.001
Cesarean birth	1.89 (1.85–1.93)	<0.001
Comorbidities		
Chronic hypertension	4.11 (3.82–4.42)	<0.001
Chronic pulmonary disease	2.21 (2.13–2.30)	<0.001
Chronic coagulopathy	3.06 (2.91–3.21)	<0.001
Hypothyroidism	1.47 (1.40–1.55)	<0.001
Income quartile		
76th–100th percentile	Reference	
51st–75th percentile	1.07 (1.03–1.11)	<0.001
26th–50th percentile	1.10 (1.06–1.15)	<0.001
0th–25th percentile	1.10 (1.05–1.14)	<0.001
Payer status		
Private	Reference	
Medicare	2.08 (1.90–2.27)	<0.001
Medicaid	1.07 (1.04–1.10)	<0.001
Other	1.07 (1.02–1.13)	0.01
Hospital teaching status		
Nonmetropolitan	Reference	
Metropolitan nonteaching	0.99 (0.94–1.05)	0.79
Metropolitan teaching	1.39 (1.32–1.46)	<0.001
Hospital region		
Northeast	Reference	
Midwest	0.98 (0.93–1.04)	0.56
South	0.90 (0.86–0.94)	<0.001
West	0.96 (0.92–1.01)	0.16

[a]OR indicates adjusted odds ratio.
Model C-statistic=0.68.

Fetal Outcomes

Compared with the cohort with nHV, fetuses in the groups with MHVs and BHVs experienced greater rates of congenital anomalies (nHV: 1.0% versus MHV: 2.5% versus BHV: 2.9%), poor fetal growth (2.8% versus 6.5% versus 6.2%), spontaneous/induced abortion (0.1% versus 0.6% versus 0), preterm birth (5.9% versus 10.1% versus 14.7%), and stillbirth (0.7% versus 3.0% versus 3.4%; Table 2). A composite of all fetal complications indicated clinically significant increase in adverse outcomes among the cohorts with MHVs and BHVs (9.6% versus 19.4% versus 25.5%, effect size: MHV 0.28, BHV 0.43; Table S2). Like the maternal outcomes, all rates of fetal outcomes were not significantly different between patients with MHVs and BHVs (Table 2).

After adjustment for patient and hospital factors, pregnant patients with valve prostheses had greater likelihood of fetal complications compared with patients without a

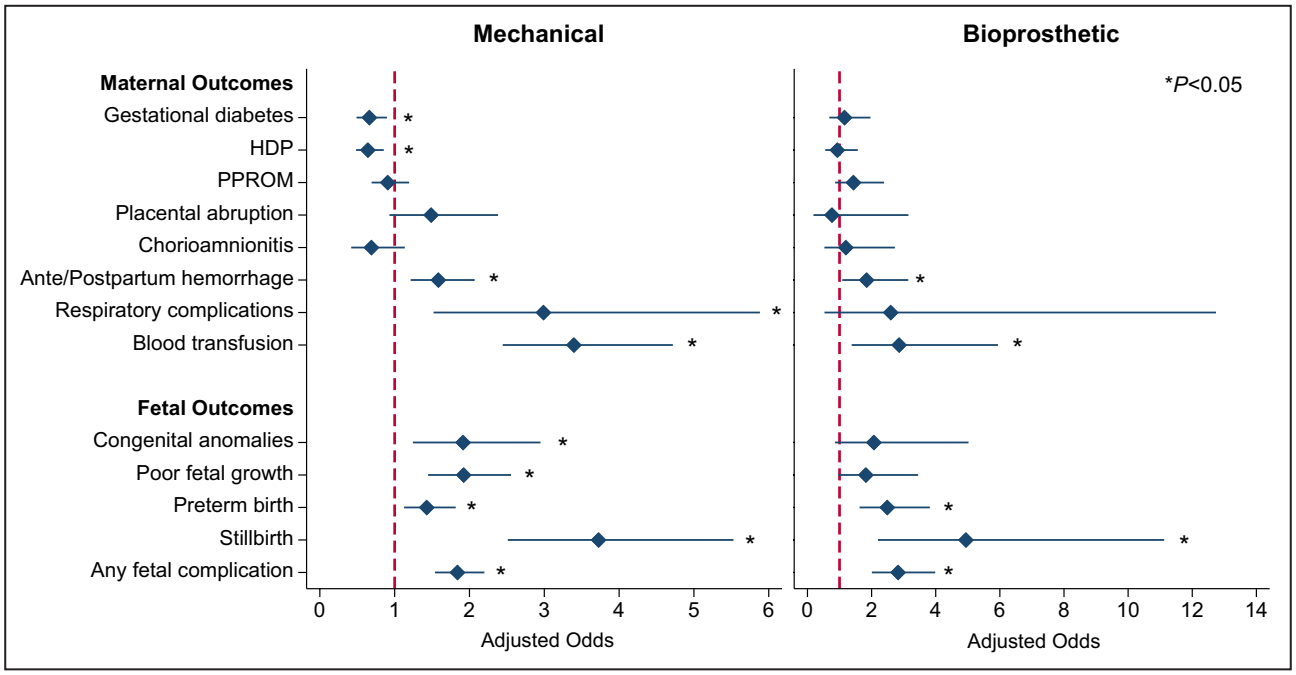

Figure 2. Adjusted maternal and fetal outcomes in pregnancies with valve prostheses.
Adjusted odds ratios accounted for valve type, age, race, year of hospitalization, elective admission, cesarean birth, comorbidities as in Table 3, income quartile, payer status, hospital teaching status, and region. Outcomes of patients with mechanical and bioprosthetic valves were assessed relative to patients with no prosthetic valve. Pregnancies with valve prostheses had increased odds of maternal complications, such as ante/postpartum hemorrhage and requiring blood transfusion, as well as fetal complications, such as preterm birth and stillbirth. HDP indicates hypertensive disease of pregnancy; and PPROM, preterm premature rupture of membranes. *P<0.05.

valve (Figure 2). However, the cohorts with MHVs and BHVs had no significant differences in the odds of any fetal complications including congenital anomalies (aOR, 1.04 [95% CI, 0.37–2.89], P=0.94), poor fetal growth (aOR, 0.95 [95% CI, 0.47–1.92], P=0.89), preterm birth (aOR, 1.56 [95% CI, 0.93–2.60], P=0.09), and stillbirth (aOR, 1.82 [95% CI, 0.65–5.08], P=0.25; Figure 3).

DISCUSSION

Using a nationally representative cohort of patients with prior valve replacement, we assessed maternal and fetal outcomes of pregnancy with mechanical versus bioprosthetic heart valves. Approximately 80% of individuals with prostheses had MHVs, which remained steady over the 12-year study period. Compared with the general pregnant population, patients with any type of prosthesis experienced over 22-fold increase in odds of MACE as well as greater likelihood of ante/postpartum hemorrhage, increased length of stay and hospitalization costs. However, the likelihood of MACE or any other adverse maternal event was comparable between those with MHVs and BHVs even after adjustment for baseline characteristics. Risk of fetal complications including congenital anomalies and stillbirth was also similar between the 2 valve types. Several of these findings warrant further discussion.

Demographics

Similar to prior literature, the median age of our study cohorts ranged from 28 to 30 years of age.[15] Notably, the vast majority of individuals with valve prostheses had MHVs, which is consistent with current guidelines based on patient age. According to the American College of Cardiology/American Heart Association guidelines, MHV is recommended for valve durability in patients under 50 years of age, unless anticoagulation is not desired, unable to be monitored, or contraindicated.[6] Furthermore, in congruence with our findings, Batra et al found rates of cesarean birth ranging from 40% to 50% in patients with MHVs and BHVs, with no significant difference between the valve types.[14] Taken in context with the existing literature, the present study examined a nationally representative cohort of delivery hospitalizations with MHVs and BHVs.

Impact of Valve Prostheses

The presence of heart valve prostheses was associated with substantial maternal and fetal morbidity. Although the rate of MACE was <1% in patients without prostheses, both cohorts with MHVs and BHVs had over 12% incidence of MACE. Moreover, these markedly increased rates of morbidity and mortality only captured the time of delivery and did not include

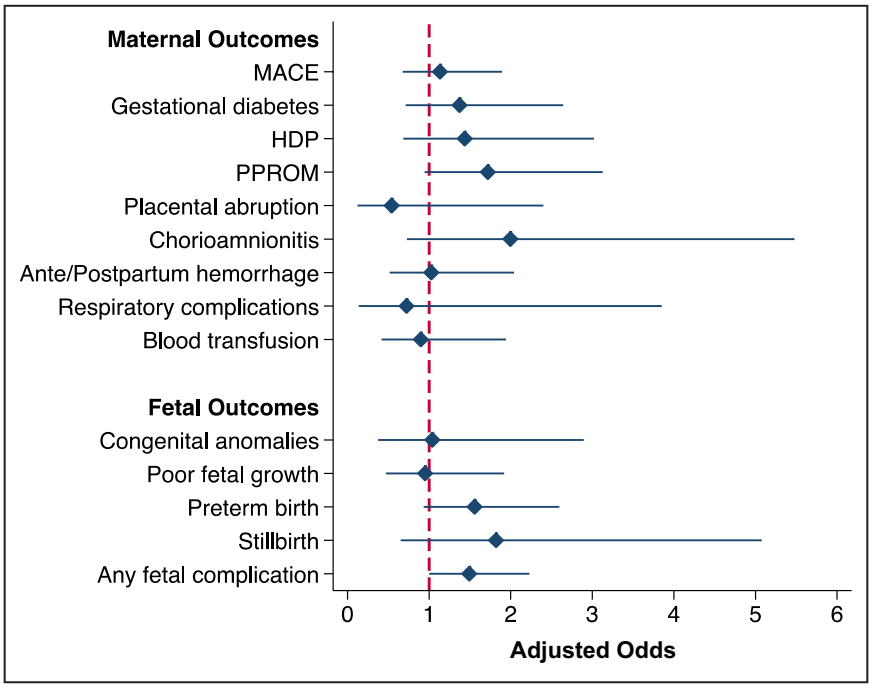

Figure 3. Adjusted maternal and fetal outcomes in bioprosthetic vs mechanical valve patients.
Adjusted odds ratios accounted for valve type, age, race, year of hospitalization, elective admission, cesarean birth, comorbidities as in Table 3, income quartile, payer status, hospital teaching status, and region. Outcomes of patients with bioprosthetic valves were assessed relative to patients with mechanical valves. There were no significant differences in both maternal and fetal outcomes between valve types. HDP indicates hypertensive disease of pregnancy; MACE, major adverse cardiovascular events; and PPROM, preterm premature rupture of membranes.

further complications that may have developed in the high-risk postpartum period. Patients with prosthetic heart valves also had significantly increased odds of developing hemorrhage and requiring blood transfusion, which may be explained by these patients' higher cesarean birth rate and need for anticoagulation.[26,27] Additionally, the substantial risk of adverse fetal events was evident with ≈4-fold increase in odds of stillbirth regardless of prosthetic valve type. Emphasis of both maternal and fetal risks is critical when counseling patients of reproductive age in need of valve replacement surgery. Our findings add significant numbers to the existing literature on adverse pregnancy outcomes in patients with prosthetic heart valves.[14–15,28–30]

Mechanical Versus Bioprosthetic Heart Valves

Interestingly, we found no significant difference in the odds of adverse maternal outcomes, namely MACE and ante/postpartum hemorrhage, between patients with MHVs and BHVs. Although previous literature has generally reported BHVs to be linked with decreased risk of hemorrhage and valve thrombosis in pregnant people, these studies are dated and primarily limited in size and generalizability.[14,15,31,32] Use of a national cohort and pragmatic sampling of NIS enables our study to better account for the variability across hospitals and patient groups. Although MHV has traditionally been linked with long-term warfarin anticoagulation, recent studies have shown an increasing trend of direct-acting oral anticoagulant usage for both MHVs and BHVs, suggesting that any anticoagulation regimen should be considered with caution in pregnant patients.[33] In addition, newer mechanical valve models that require lower anticoagulation dosages may be contributing to differences in adverse outcomes.[34] For example, the 2017 American College of Cardiology/American Heart Association guidelines suggest an international normalized ratio range of 1.5–2.0 for the On-X aortic valve compared with 2.5 for conventional bileaflet and tilting disc valves.[9] However, 2 other prominent guidelines from the American College of Chest Physicians and European Society of Cardiology provide conflicting recommendations.[35,36] A central issue with management of prosthetic valves in pregnancy is the lack of standardized care. Further investigation is needed to better understand and standardize the anticoagulation

regimens employed during pregnancy in the presence of prosthetic heart valves.

Notably, the 2 prosthetic valve types presented similar likelihood of fetal complications, including congenital anomalies, poor fetal growth, preterm birth, and stillbirth. These findings differ from previous limited reports suggesting reduced fetal demise in pregnant people with BHVs compared with MHVs.[14,15] Traditionally, the exposure to warfarin in the first trimester of pregnancy has been thought to result in embryopathy rates ranging from 5% to 7%.[25,37] However, these rates may have changed for contemporary mechanical valve models that require lower doses to reach effective anticoagulation.[9,34] Additionally, our results are perhaps reflective of closer adherence to the American College of Cardiology/American Heart Association guidelines for valvular heart disease in pregnancy, which suggest substitution of vitamin K antagonists with dose-adjusted low-molecular weight heparin during the first trimester to reduce fetal loss.[6] Moreover, the cohort with BHVs includes patients with and without a baseline indication for anticoagulation, and the heterogeneity of antithrombotic therapy in clinical practice is a significant consideration in the interpretation of our results.[33] Our findings suggest that the mere presence of any valve prosthesis, along with its required anticoagulation, has a more significant impact on maternal and fetal complications than the specific valve type. Further evaluation of contemporary anticoagulation regimens for prosthetic heart valves and their impact on pregnancy outcomes is warranted. Centralizing the care for individuals considering both valve replacement and pregnancy with access to cardiology, surgery, and obstetrics teams may help optimize preconception counseling and mitigate risk of adverse maternal and fetal outcomes.

Study Limitations

The present study has several important limitations. Given the low incidence of valvular heart disease in pregnancy, the NIS was valuable in allowing for a large, representative US sample and has been previously employed to study pregnancy outcomes in patients with cardiovascular disease.[18,19] However, the data are limited to inpatient, delivery-related hospitalizations, and information on miscarriage, outpatient abortions, late maternal morbidity and mortality, and fetal complications is likely underestimated. Due to the retrospective nature of our study, there may have been unintentional selection bias including the variability in each surgeon and center's choice of valve type. Furthermore, the NIS lacks clinical granularity regarding maternal data such as the valve position, type of anticoagulation used, and interval between valve replacement and pregnancy. Additionally, the longevity of each valve type and need for repeat cardiac surgery could not be assessed. Despite the inherent limitations of the retrospective

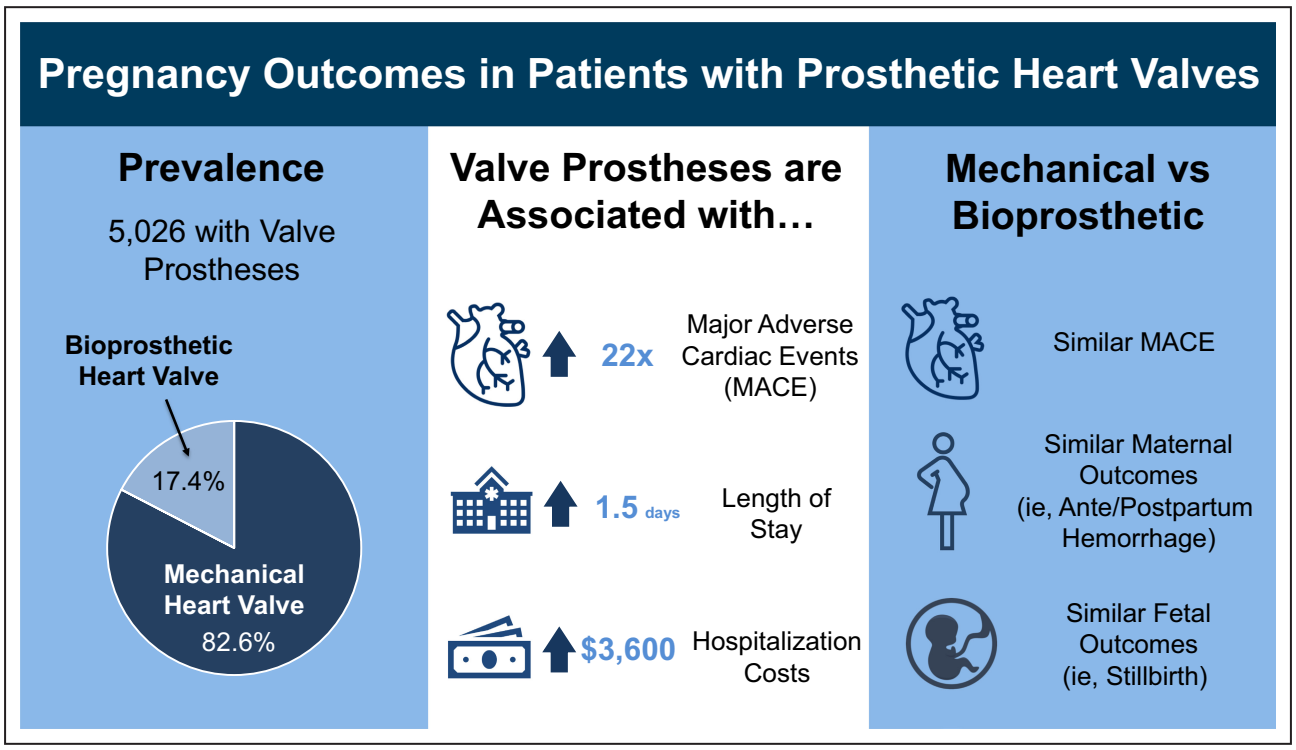

Figure 4. Study summary.
MACE indicates major adverse cardiovascular events.

study design and data source, we used the largest all-payer inpatient database to assess these valve types at a national level, allowing for enhanced generalizability of our findings.

CONCLUSIONS

Our findings confirm that the mere presence of a prosthetic heart valve, MHV or BHV, is associated with adverse short-term outcomes in the pregnant individual as well as the fetus, regardless of valve type (Figure 4). As such, optimized preconception counseling by cardiology and obstetrics (maternal fetal medicine) and specialized multidisciplinary cardio-obstetrics care models during the pregnancy are warranted to help guide treatment decisions for people of reproductive age with heart valve prostheses.

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Administrative *International Classification of Diseases, 9th and 10th Revisions* (ICD-9/10) diagnosis (DX) and procedure (PR) codes for maternal and fetal outcomes.

	ICD-9	ICD-10
Major adverse cardiovascular events (MACE)		
Acute myocardial infarction	DX: 410	I10_DX: I21
Heart failure	DX: 428.1, 428.21, 428.23, 428.31, 428.33, 428.41, 428.43	I10_DX: I50.1, I50.21, I50.23, I50.31, I50.33, I50.41, I50.43
Arrhythmia	DX: 426, 427	I10_DX: I44, I45, I47, I48, I49
Cerebrovascular events	DX: 430, 431, 432, 433, 434, 437, 997.01, 997.02	I10_DX: I60, I61, I62, I63, I67, G97.81, G97.82, I97.811, I97.821
Valve thrombosis	DX: 996.71, 996.72	I10_DX: T82.817A, T82.867A
Deep vein thrombosis	DX: 451, 453	I10_DX: I80, I82
Pulmonary embolism	DX: 415.1	I10_DX: T80.0XXA, T81.718A, T81.72XA, T82.817A, T82.818A, I26.90, I26.99
Arterial embolism	DX: 444	I10_DX: I74
Atheroembolism	DX: 445	I10_DX: I75
Obstetrical pulmonary embolism	DX: 673	I10_DX: O88
Cardiac complications of anesthesia or sedation in labor and delivery	DX: 668.1	I10_DX: O74.2
Cardiogenic shock	DX: 785.51	I10_DX: R57.0
Cardiac arrest	DX: 427.5	I10_DX: I46.2, I46.8, I46.9
Other Maternal Complications		
Gestational diabetes	DX: 648.8	I10_DX: O24.41, O24.42, O24.43
Gestational hypertension	DX: 642.3	I10_DX: O13
(Pre-)eclampsia / Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome	DX: 642.4, 642.5, 642.6, 642.7	I10_DX: O11, O14, O15
Preterm premature rupture of membranes (PPROM)	DX: 658.1, 658.2	I10_DX: O42
Placental abruption	DX: 641.2	I10_DX: O45
Chorioamnionitis	DX: 658.4, 659.31	I10_DX: O41.1, O75.3
Antepartum hemorrhage	DX: 640, 641.1, 641.3, 641.8, 641.9	I10_DX: O20, O46, O67
Postpartum hemorrhage	DX: 666	I10_DX: O72
Respiratory complications		
Pneumonia	DX: 481, 482, 997.3	I10_DX: J12, J13, J14, J15, J18
Pneumothorax	DX: 512.1	I10_DX: J95.811

Acute respiratory distress syndrome	DX: 518.82, 770.89	I10_DX: J80, R06.03
Respiratory failure	DX: 518.5	I10_DX: J95.821, J95.822, J96.00, J96.90, J96.20
Ventilation	PR: 96.70, 96.71, 96.72, 93.90	I10_PR: 5A1935Z, 5A1945Z, 5A1955Z, 5A09357, 5A09457, 5A09557
Pulmonary edema	DX: 518.4	I10_DX: J81.0
Tracheostomy	PR: 311, 312	I10_PR: OB11xxx
Blood transfusion	PR: 99.0	I10_PR: 302xxxx
Acute kidney injury	DX: 584	I10_DX: N17
Fetal Complications		
Congenital anomalies	DX: 655.0, 655.1, 655.2, 655.8, 655.9	I10_DX: O35.0, O35.1, O35.2, O35.8, O35.9
Poor fetal growth	DX: 656.5, 764.0, 764.1, 764.9	I10_DX: O36.5, P05
Abortion (spontaneous/induced)	DX: 632, 634, 635, 636, 637, 638, 639	I10_DX: O02.1, O03, O04, O08
Preterm birth	DX: 644.2	I10_DX: O60.1
Stillbirth	DX: 656.4, 768.0, 768.1, V27.1, V27.3, V27.4, V27.6, V27.7, V32, V35, V36	I10_DX: P95, Z37.1, Z37.3, Z37.4, Z37.7, O36.4

Table S2. Effect size (ES) of unadjusted maternal and fetal outcomes stratified by valve replacement type.

Parameter	No Valve (n=39,866,836)	Mechanical (n=4,152)	Bioprosthetic (n=874)	ES (No Valve vs Mech)	ES (No Valve vs Bio)
MACE	166,519 (0.4)	509 (12.3)	111 (12.6)	0.59	0.60
Mortality	3,364 (.01)	<10*	0	0.02	0.02
Acute myocardial infarction	1,164 (.003)	<10	<10	0.01	0.01
Heart failure	4,660 (.01)	39 (0.9)	0	0.17	0.02
Arrhythmia	139,301 (0.3)	465 (11.2)	106 (12.1)	0.57	0.60
Cerebrovascular events	3,072 (.01)	<10	0	0.02	0.02
Valve thrombosis	–	10 (0.2)	<10	–	–
Other thromboembolic events	17,236 (.04)	10 (0.2)	<10	0.05	0.04
Cardiac complications of anesthesia/sedation	1,991 (.01)	0	0	0.02	0.02
Cardiogenic shock	662 (.002)	0	0	0.01	0.01
Cardiac arrest	3,238 (.01)	0	0	0.02	0.02
Other Maternal Complications					
Gestational diabetes	2,761,464 (6.9)	232 (5.6)	75 (8.6)	0.05	0.06
HDP	3,636,395 (9.1)	393 (9.5)	103 (11.8)	0.01	0.09
PPROM	2,576,850 (6.5)	278 (6.7)	85 (9.7)	0.01	0.12
Placental abruption	427,523 (1.0)	89 (2.1)	10 (1.1)	0.09	0.01
Chorioamnionitis	897,336 (2.3)	78 (1.9)	30 (3.4)	0.03	0.07
Ante/Postpartum hemorrhage	1,483,489 (3.7)	293 (7.1)	74 (8.5)	0.15	0.20
Respiratory complications	64,421 (0.2)	54 (1.3)	10 (1.1)	0.14	0.12
Blood transfusion	466,100 (1.2)	229 (5.5)	43 (5.0)	0.25	0.23
Acute kidney injury	24,912 (.06)	24 (0.6)	0	0.11	0.05
Fetal Complications					
Congenital anomalies	393,213 (1.0)	105 (2.5)	25 (2.9)	0.12	0.14
Poor fetal growth	1,114,699 (2.8)	269 (6.5)	54 (6.2)	0.18	0.17
Abortion (spontaneous/induced)	55,524 (0.1)	25 (0.6)	0	0.09	0.06
Preterm birth	2,334,353 (5.9)	418 (10.1)	128 (14.7)	0.16	0.30
Stillbirth	296,047 (0.7)	126 (3.0)	30 (3.4)	0.18	0.20
Any fetal complication	3,815,244 (9.6)	803 (19.4)	223 (25.5)	0.28	0.43
Outcomes					
LOS (days)	2 [2-3]	3 [2-4]	3 [2-4]	0.24	0.24
Cost ($1000s)	4.1 [2.9-5.8]	6.0 [4.0-9.9]	5.8 [4.3-9.5]	0.21	0.27

HDP: Hypertensive Disease of Pregnancy. IQR: Interquartile Range. LOS: Length of Stay. PPROM: Preterm Premature Rupture of Membranes. MACE: Major Adverse Cardiovascular Events. *Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample does not allow reporting of <10 events in order to protect individuals' privacy.

Table S3. Adjusted maternal and fetal outcomes of deliveries with no valve replacement compared to mechanical and bioprosthetic valve cohorts.

Parameter (AOR or ß, 95% CI)	No Valve (n=39,866,836)	Mechanical (n=4,152)	*p*-value	Bioprosthetic (n=874)	*p*-value
Maternal Complications					
Gestational diabetes	Ref	0.7 [0.5-0.9]	0.01	1.2 [0.7-2.0]	0.59
HDP	Ref	0.6 [0.5-0.9]	0.002	0.9 [0.6-1.6]	0.80
PPROM	Ref	0.9 [0.7-1.2]	0.49	1.4 [0.9-2.4]	0.16
Placental abruption	Ref	1.5 [0.9-2.4]	0.10	0.8 [0.2-3.1]	0.71
Chorioamnionitis	Ref	0.7 [0.4-1.1]	0.15	1.2 [0.5-2.7]	0.66
Ante/Postpartum hemorrhage	Ref	1.6 [1.2-2.1]	0.001	1.8 [1.1-3.1]	0.02
Respiratory complications	Ref	3.0 [1.5-5.9]	0.001	2.6 [0.5-12.8]	0.24
Blood transfusion	Ref	3.4 [2.4-4.7]	<0.001	2.9 [1.4-5.9]	0.01
Fetal Complications					
Congenital anomalies	Ref	1.9 [1.2-2.9]	0.003	2.1 [0.9-5.0]	0.11
Poor fetal growth	Ref	1.9 [1.4-2.6]	<0.001	1.8 [1.0-3.5]	0.07
Preterm birth	Ref	1.4 [1.1-1.8]	0.003	2.5 [1.6-3.8]	<0.001
Stillbirth	Ref	3.7 [2.5-5.5]	<0.001	4.9 [2.2-11.1]	<0.001
Any fetal complication	Ref	1.8 [1.5-2.2]	<0.001	2.8 [2.0-4.0]	<0.001
Outcomes					
Length of stay (days)	Ref	1.6 [1.2-2.0]	<0.001	1.0 [0.4-1.7]	0.001
Cost ($1000s)	Ref	3.8 [3.0-4.7]	<0.001	2.5 [1.3-3.6]	<0.001

AOR: Adjusted Odds Ratio; CI: Confidence Interval. HDP: Hypertensive Disease of Pregnancy. PPROM: Preterm Premature Rupture of Membranes.

Table S4. Adjusted odds of maternal and fetal outcomes after bioprosthetic valve replacement (ref: mechanical valve).

Parameter (AOR or ß, 95% CI)	Mechanical (n=4,152)	Bioprosthetic (n=874)	*p*-value
Maternal Complications			
MACE	Ref	1.13 [0.68-1.89]	0.64
Gestational diabetes	Ref	1.37 [0.71-2.64]	0.34
HDP	Ref	1.44 [0.68-3.02]	0.34
PPROM	Ref	1.72 [0.94-3.13]	0.08
Placental abruption	Ref	0.54 [0.12-2.40]	0.42
Chorioamnionitis	Ref	2.00 [0.73-5.48]	0.18
Ante/Postpartum hemorrhage	Ref	1.03 [0.52-2.04]	0.94
Respiratory complications	Ref	0.72 [0.14-3.85]	0.70
Blood transfusion	Ref	0.90 [0.42-1.94]	0.79
Fetal Complications			
Congenital anomalies	Ref	1.04 [0.37-2.89]	0.94
Poor fetal growth	Ref	0.95 [0.47-1.92]	0.89
Preterm birth	Ref	1.56 [0.93-2.60]	0.09
Stillbirth	Ref	1.82 [0.65-5.08]	0.25
Any fetal complication	Ref	1.49 [1.00-2.23]	0.05
Outcomes			
Length of stay (days)	Ref	-0.51 [-1.25–0.24]	0.18
Cost ($)	Ref	-1,295 [-2,697–108]	0.07

AOR: Adjusted Odds Ratio; CI: Confidence Interval. MACE: Major Adverse Cardiovascular Events. HDP: Hypertensive Disease of Pregnancy. PPROM: Preterm Premature Rupture of Membranes.