Outcomes and Long-term Effects of Pregnancy in Women With Biologic and Mechanical Valve Prostheses

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The optimal choice of prosthetic heart valve for women of child-bearing age is not well established. We conducted this retrospective cohort study to compare pregnancy outcomes and maternal mortality and morbidity, including long-term valve reoperation, between women with biologic and mechanical valve replacements. Women ≤50 years of age with prosthetic heart valve implantation and subsequent pregnancy in California, New Jersey, and New York State between 1990 to 2015 were identified using mandatory state inpatient databases. Average follow-up time was 9.4 years (SD 6.7 years). Of 11,930 women who underwent 14,017 valve replacements, pregnancies in 417 women with 241 biologic valves, and 217 mechanical valves were identified. Women with mechanical prostheses experienced significantly higher rates of pregnancy loss, with almost 2/3 of pregnancies ending in either spontaneous or induced abortion, and hemorrhage and thromboembolic events during delivery. Delivery was a significant risk factor for reoperation for both biologic (hazard ratio 2.5, 95% confidence interval 1.6 to 3.8 after time-dependent propensity matching) and mechanical (hazard ratio 2.3, 95% confidence interval 1.3 to 4.1 after time-dependent propensity matching) prostheses. Half of reoperations in women with mechanical valves who experienced pregnancy occurred within 1 year after delivery, and most were associated with mitral valve thrombosis. In conclusion, pregnancy accelerates time to reoperation for both biologic and mechanical prostheses. Mechanical valves are at particular risk for near-term valve failure after delivery, and compared with bioprostheses, are associated with higher rates of adverse events during pregnancy. **(Am J Cardiol 2018;122:1738–1744)**

Valvular heart disease is not a common maternal condition during pregnancy, but it disproportionately affects maternal outcomes.[1,2] For symptomatic women with severe valvular heart disease, valve replacement is recommended before pregnancy where medical therapy has failed and valve repair is not feasible.[3,4] The 2 types of prostheses—mechanical and biologic—carry different risks and benefits. Mechanical valves require lifelong anticoagulation which, during pregnancy, is associated with adverse fetal outcomes and maternal complications.[5–8] Biologic prostheses are more likely to result in a successful pregnancy outcome but are less durable, particularly in young adults in whom rates of structural valve degeneration are accelerated.[9,10] The evidence-base for valve selection in these patients is largely limited to small, single-center series. Additionally, the valve models studied are now several decades old and reported performances may not accurately reflect current outcomes. This retrospective cohort study was therefore designed to determine contemporary outcomes of pregnancy and the long-term effects of pregnancy on time to reoperation in women with prosthetic heart valves in California, New Jersey, and New York State.

Methods

Data were obtained from the Office of Statewide Health Planning and Development database in California, the Hospital Discharge Data Collection System database in New Jersey, and the Statewide Planning and Research Cooperative System database in New York State from January 1, 1990 to September 30, 2015. These all-payer administrative databases prospectively collect patient-level data on all in-state hospitalizations and ambulatory surgery and emergency room admissions, with each patient allocated a unique identifier which enables longitudinal analysis across multiple visits.

Women ≤50 years of age who underwent aortic or mitral valve replacement, defined using *International Classification of Diseases, Ninth Revision,* Clinical Modification (ICD-9-CM) procedure codes, 35.21 to 35.24, were included. Delivery hospitalizations were identified from the inpatient data using a validated method based on both ICD-9-CM and diagnosis-related group codes.[11] Each prosthesis was included in the analysis as a separate entity. The life span of each valve began at the time of implantation and concluded with reoperation, patient death, or censoring. If a woman became pregnant during the life span of a valve, the time to pregnancy was defined as the interval between valve implantation and the delivery admission. In an effort to standardize the time of exposure of valves to pregnancy,

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valves implanted ≤35 weeks before the delivery admission were excluded from analysis. Women with multiple valve replacements were not excluded, and presence of a concomitant valve was controlled for in subsequent analyses.

Baseline comorbidities were defined using ICD-9-CM diagnosis codes from the valve implantation admission and any previous hospitalizations within 2 years of implantation (Table 1 of the Data Supplement). Comorbidities were then recalculated for every year out from the time of valve implantation, considering any additional admissions during that time period, until the end of the valve's life span. This set of comorbidities was used in time-dependent propensity matching. Additional comorbidities were defined from codes present on the delivery admission, based on ICD-9-CM diagnosis codes from a validated, maternal comorbidity index.[12] These comorbidities were used in the analysis of maternal morbidity during delivery.

Outcomes of interest were pregnancy loss, maternal mortality and morbidity during delivery, and valve reoperation. Patients who did not experience death or valve reoperation within the study period were censored on September 30, 2015. Dates of death were identified using inpatient admissions and states' Vital Statistics death records linked with discharge data. Measures of maternal morbidity during the delivery admission included hemorrhage, acute cardiac events, thromboembolic events, and severe maternal morbidity (defined in Table 2 of the Data Supplement). Severe maternal morbidity is a composite measure endorsed by the Centers of Disease Control and Prevention which includes both life-threatening maternal conditions and life-saving procedures.[13] Finally, for women with both inpatient and outpatient data available, we reported all outcomes of pregnancy, including delivery, abortion, fetal death, and maternal death. This analysis is further described in the Methods section and Table 3 of the Data Supplement.

We compared baseline characteristics using chi-square tests for categorical variables and *t* tests for continuous variables. Cochran-Armitage trend tests were used to evaluate trends in valve type selection and pregnancy outcomes over the study period. Multivariable logistic regression models were used to identify risk factors associated with pregnancy loss and severe maternal morbidity and hemorrhage during delivery. Patients with concomitant biologic and mechanical valves at the time of pregnancy were placed in the mechanical valve group based on the assumption that they were likely receiving anticoagulation therapy.

To evaluate the association between pregnancy and time to reoperation, we used 2 different methods, and both incorporated 2 important time factors: time from valve implantation to pregnancy and time from pregnancy to valve reoperation.

In the first analysis, pregnancy was treated as a time-dependent covariate in Cox regression models using the start-stop method in the SAS procedure PHREG. The full study cohort was used. Biologic and mechanical valve types were analyzed in separate Cox regression models with reoperation as the dependent variable. Independent variables included pregnancy, patient age at the time of valve implantation, year of valve implantation, valve position (aortic or mitral), presence of concomitant valves, race, and baseline comorbidities. Similar models were also constructed with death within the study period as the dependent variable to evaluate the association between pregnancy and long-term maternal mortality.

In the second analysis, we used time-dependent propensity scoring to match women with pregnancy at the time of earliest delivery with controls "at risk" for pregnancy within the same year after valve implantation. Controls were any woman with valve implantation and without exposure to pregnancy during the study period that was free from reoperation, death, or censoring at the time of matching. Methods for time-dependent propensity matching have been described in several recent studies.[14,15] This approach allowed us to incorporate events between valve implantation and pregnancy in the propensity score calculation and match women with controls whose opportunity for pregnancy was similar to theirs at the time of delivery. Details of matching are included in the Data Supplement. For the propensity-matched cohorts, Cox regression models were constructed with reoperation as the dependent variable. Pregnancy was incorporated as a time-dependent covariate using the start-stop method in the SAS procedure PHREG. As we were unable to control for the time from each subsequent pregnancy to our outcome of interest (valve reoperation), for women with multiple sequential pregnancies outcomes were censored at the time of the second pregnancy. Related sensitivity analyses were also carried out and described in the Data Supplement.

All tests were 2-tailed with a critical p value of 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

This study was approved by the Committee for the Protection of Human Subjects of the State of California, the Institutional Review Board of Rowan University of the State of New Jersey, the Data Protection Review Board of the New York State Department of Health, and the Program for Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai Medical Center. The approval included a waiver of informed consent.

Results

A total of 11,930 women ≤50 years of age had 14,017 prostheses, 3,629 (26%) biologic, and 10,388 (74%) mechanical implanted between 1990 and 2015. Over the study period, there was a significant trend toward increased use of biologic valves in both the aortic and mitral positions. In the aortic position, rates of biologic implantation increased from 15% in 1990 to 57% in 2015 ($p < 0.001$) and in the mitral position from 13% to 44% ($p < 0.001$) (Figure 1).

There were 417 women with 241 biologic valves and 217 mechanical valves identified as having at least 1 delivery during the study period. At baseline, these women were younger and had a lower burden of coexisting conditions at the time of implantation compared with their never-pregnant counterparts (Table 4 of the Data Supplement). After 2:1 propensity score matching, there were no significant differences between the pregnant and control groups for both the biologic and mechanical cohorts (Table 1). Mean follow-up time was 7.1 years (standard deviation (SD), 5.7

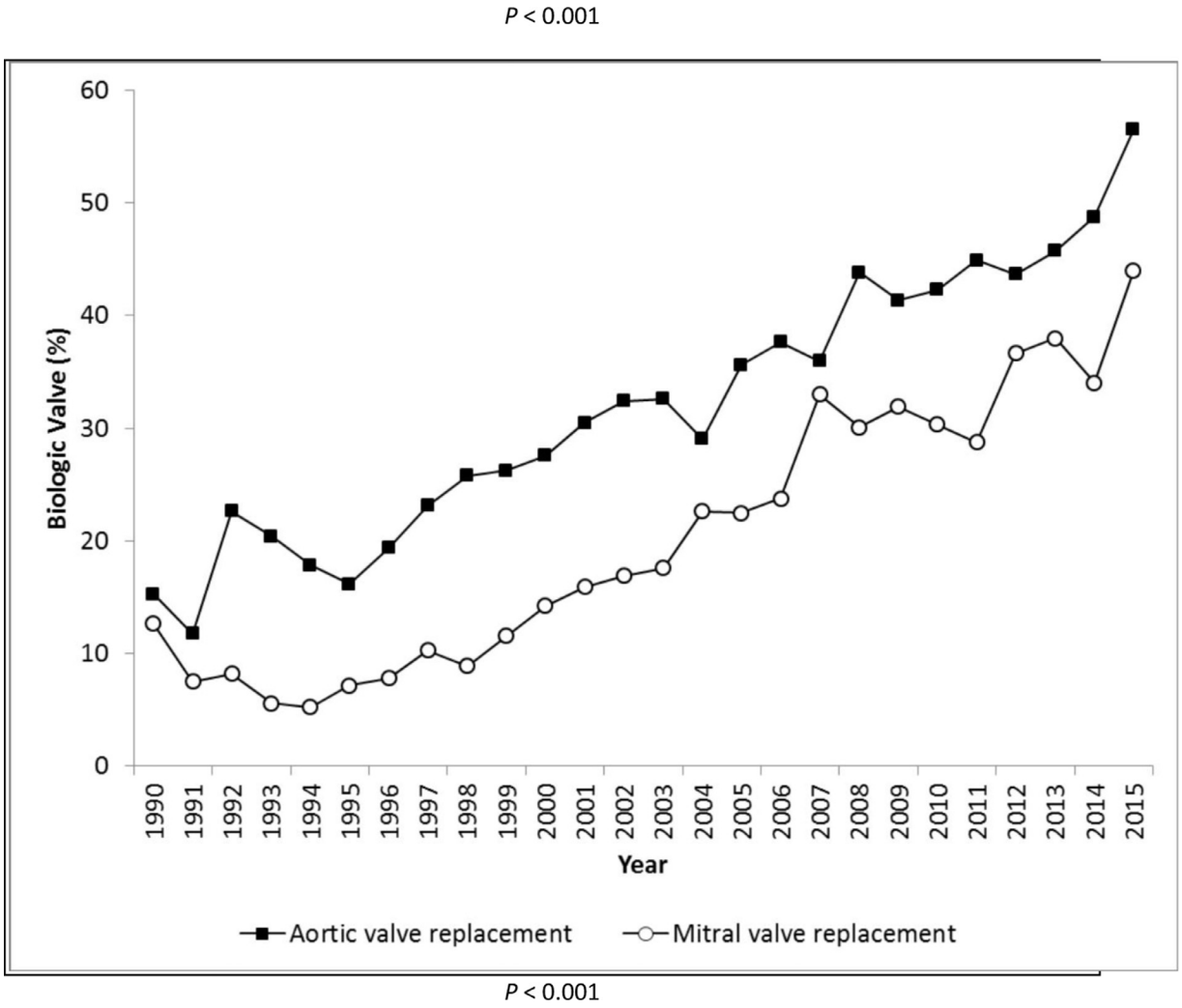

Figure 1. Temporal trends in valve type selection. From 1990 to 2015, 11,930 women ≤50 years of age in California, New Jersey, and New York State had 14,017 prostheses implanted, with a significant trend toward increased use of biologic valves in both the aortic and mitral positions.

years) for women with biologic valves and 10.2 years (SD 6.8 years) for women with mechanical valves.

In the subgroup of 105 women for whom both inpatient and outpatient data were available, there were 114 pregnancies, 64% (n = 73) of which resulted in delivery. There was 1 maternal death before delivery. The rate of pregnancies that successfully progressed to delivery improved over time, from 25% from 2005 to 2006 to 69% from 2014 to 2015 (p = 0.03). Mechanical valves were associated with higher rates of pregnancy loss compared with biologic valves (61% vs 15%; odds ratio [OR], 11.0, 95% confidence interval [CI], 3.6 to 33.6) (Table 5 of the Data Supplement; Figure 2). For women with mechanical valves, approximately 2/3 of lost pregnancies ended in spontaneous abortion and 1/3 ended in induced abortion.

In the main cohort, there were 571 deliveries among 417 women. One maternal death occurred during delivery. In just under half of all deliveries, cesarean sections were performed, with no significant difference in rates between women with biologic and mechanical valves (44% vs 42%, p = 0.68). Compared with biologic valves, mechanical valves were associated with higher rates of both hemorrhage (16% vs 6%, p < 0.001; OR 2.3, 95% CI 1.2 to 4.4) and severe maternal morbidity (15% vs 6%, p < 0.001; OR 1.9, 95% CI 1.0 to 3.7), with blood transfusion as the most common flag for morbidity (Tables 6 and 7 of the Data Supplement; Figure 2). Thromboembolic events occurred in 3% of deliveries with rates significantly higher in women with mechanical valves, driven mostly by higher incidence of valve thrombosis (p < 0.001). Incidence of acute cardiac events was minimal, occurring in <3% of all deliveries, with no significant difference between the 2 groups.

In the multivariable time-to-event analysis which included all women with biologic valves, pregnancy was a significant risk factor for reoperation (hazard ratio [HR] 1.3, 95% CI 1.1 to 1.6; Table 8 of the Data Supplement). After propensity matching, 241 biologic valves in women who experienced pregnancy were matched to 482 at-risk controls. Risk of reoperation was significantly higher for those biologic valves with pregnancy compared with those without (HR 2.5, 95% CI 1.6 to 3.8). Results were similar in sensitivity analyses (Table 9 of the Data Supplement). Median time from the most recent delivery to reoperation

Table 1
Baseline characteristics by pregnancy status for biologic and mechanical prostheses, after propensity matching

	Biologic valves			Mechanical valves		
	Pregnant (n = 241)	Never pregnant (n = 482)	Standardized difference	Pregnant (n = 217)	Never pregnant (n = 434)	Standardized difference
Age at valve implantation (years), mean ± SD	26.4 ± 7.0	26.9 ± 15.4	0.04	25.6 ± 7.6	26.4 ± 14.1	0.07
White	105 (44%)	217 (45%)	0.08	70 (32%)	134 (31%)	0.10
Black	31 (13%)	52 (11%)		41 (19%)	99 (23%)	
Hispanic	38 (16%)	82 (17%)		43 (20%)	83 (19%)	
Asian	27 (11%)	49 (10%)		17 (7.8%)	30 (6.9%)	
Other	40 (17%)	82 (17%)		46 (21%)	88 (20%)	
Valve position − aortic (versus mitral)	156 (65%)	313 (65%)	0.01	94 (43%)	199 (46%)	0.05
Concurrent valves present	81 (34%)	159 (33.0%)	0.01	45 (21%)	97 (22%)	0.04
Coagulopathy	45 (19%)	88 (18%)	0.01	50 (23%)	95 (22%)	0.03
Atrial arrhythmia	34 (14%)	68 (14%)	0.01	57 (26%)	104 (24%)	0.05
Congestive heart failure	103 (43%)	193 (40%)	0.06	122 (56%)	227 (52%)	0.08
Hypertension	35 (15%)	76 (16%)	0.04	45 (21%)	84 (19%)	0.03
Pulmonary hypertension	51 (21%)	108 (22%)	0.03	63 (29%)	126 (29%)	0.01
Coronary artery disease	16 (6.6%)	33 (6.9%)	0.01	33 (15%)	66 (15%)	0.01
Diabetes mellitus	11 (4.6%)	16 (3.3%)	0.06	<11*	26 (6.0%)	0.06
Chronic obstructive pulmonary disease	31 (13%)	67 (14%)	0.03	33 (15%)	52 (12%)	0.09
Chronic kidney disease	<11*	11 (2.3%)	0.08	<11*	19 (4.4%)	0.04
Liver disease	24 (10%)	48 (10%)	0.01	17 (7.8%)	42 (9.7%)	0.07
Year of valve operation						
1990-1995	31 (13%)	63 (13%)	0.03	50 (23%)	126 (29%)	0.01
1996-2000	70 (29%)	134 (28%)		86 (40%)	127 (29%)	
2001-2005	60 (25%)	134 (28%)		43 (20%)	95 (22%)	
2006-2010	65 (27%)	120 (25%)		28 (13%)	73 (17%)	
2011-2015	15 (6%)	31 (6%)		<11*	13 (3.0%)	

SD = standard deviation.
* Numbers are suppressed based on Data Use Agreements with the Office of Statewide Health Planning and Development database in California, the Hospital Discharge Data Collection System database in New Jersey, and the Statewide Planning and Research Cooperative System database in New York State.

was 4.8 years (interquartile range 1.4 to 8.6 years), with 12/52 (23%) reoperations in women with pregnancy occurring within 1 year after delivery. Of these 52 biologic valves with pregnancy that required reoperation, 31 were in the aortic position (60%) and 21 were in the mitral position (40%). Pregnancy was not a significant risk factor for maternal mortality (HR 0.9, 95% CI 0.6 to 1.3; Table 10 of the Data Supplement).

In the multivariable time-to-event analysis using the full cohort of patients with mechanical valves, pregnancy was a significant risk factor for reoperation (HR 2.0, 95% CI 1.6 to 2.6; Table 11 of the Data Supplement). After propensity matching, 217 mechanical valves in women who experienced pregnancy were matched with 434 at-risk controls. Risk of reoperation was significantly higher for mechanical valves with pregnancy compared with mechanical valves without (HR 2.3, 95% CI 1.2 to 4.2). Results were similar in sensitivity analyses (Table 9 of the Data Supplement). Of the 30 mechanical valves in women who experienced pregnancy and had subsequent reoperation, 2/3 were in the mitral position (19/30, 63%). Almost half of reoperations (13/30, 43%) occurred within 1 year of delivery, most of which were performed on valves at the mitral position (11/13) and had diagnosis codes for valve-related complications, including valve thrombosis (10/13). Pregnancy was not a significant risk factor for maternal mortality (HR 1.3, 95% CI 0.9 to 1.8; Table 12 of the Data Supplement).

Discussion

In this retrospective cohort study of women ≤50 years of age with a history of valve replacement from California, New Jersey, and New York State between 1990 and 2015, we found an increasing trend toward placement of biologic valves, which were associated with improved maternal and fetal outcomes. Women with mechanical prostheses experienced significantly higher rates of pregnancy loss, with fewer than half of pregnancies progressing to delivery, and maternal morbidity during delivery. Our analysis suggests that pregnancy increases the likelihood of valve reoperation for both biologic and mechanical prostheses, with half of reoperations on mechanical valves occurring within 1 year of delivery and mostly at the mitral position.

With the exception of recent data from the Registry of Pregnancy and Cardiac Disease, current estimates of pregnancy outcomes for women with valve replacement have been largely based on results from single-center series. Outcomes vary considerably, with reported rates of pregnancy loss associated with mechanical valves ranging from 9% to 59%.[7,8,16–21] By drawing on multi-institutional,

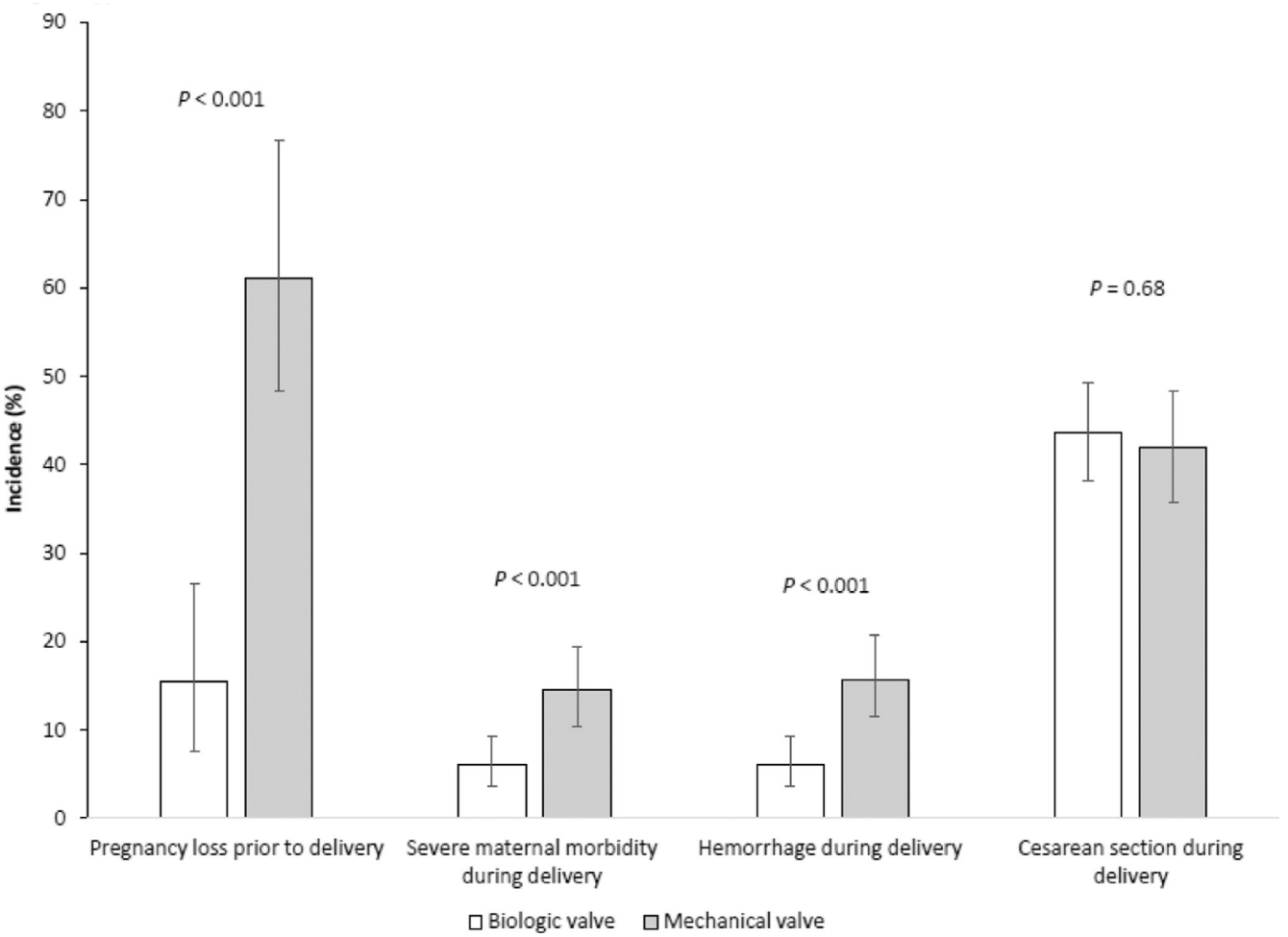

Figure 2. Outcomes of pregnancy and maternal morbidity. Compared with bioprostheses, mechanical valves were associated with significantly higher rates of pregnancy loss and, during delivery, hemorrhage and severe maternal morbidity.

contemporary data and using ambulatory surgery center and emergency department records in addition to inpatient admission records to capture outcomes, this study may present more accurate and generalizable estimates. We observed a significant increase in the proportion of pregnancies that resulted in delivery over the course of the study period. Contributing factors to improvement in pregnancy outcomes may include the increasing prevalence of biologic valves as it becomes standard practice to avoid mechanical valves in this patient population when possible and adherence to guideline recommendations for specialized, multidisciplinary team approaches to management of cardiovascular disease during pregnancy.[4]

Previous studies examining the effect of pregnancy on prostheses have not found evidence of a relation between pregnancy and reduced valve survival. However, there are important limitations inherent in the design of these older studies. First, sample sizes were small and potentially underpowered to detect reported differences in reoperation rates between women with and without pregnancy.[22–24] Second, these studies relied on multivariable models alone to control for differences between women with prosthetic valves who experienced pregnancy and those who did not.[22–26] Our own results demonstrate that this method consistently underestimates the negative effect of pregnancy on prosthesis life span compared with time-dependent propensity matching, likely due to less rigorous risk adjustment.

The mechanisms by which pregnancy shortens time to reoperation for biologic and mechanical prostheses likely differ. Several observational studies have linked biologic valve failure to structural valve deterioration which is accelerated by the hemodynamic stresses of pregnancy and delivery.[6] Early evidence suggests that pregnancy may not have the same effect on newer biologic valve models, including autografts in the aortic position via the Ross procedure and stentless porcine heterografts.[27] The long-term durability of these valve types after delivery is an important area for future study. Disproportionate rates of early valve failure for mechanical valves at the mitral position may reflect valvular dysfunction secondary to thrombus formation, especially in the setting of disruptions to anticoagulation around delivery and the hypercoagulable state of pregnancy which persists for up to 12 weeks after delivery.[28–30] Recent data from the Registry of Pregnancy and Cardiac Disease found the incidence of valve thrombosis to be as high as 4.7% during pregnancy but did not follow women past 1-week postpartum.[7] Prospective clinical

studies with serial imaging throughout pregnancy and, importantly, after delivery are needed to more fully explain the mechanisms for valve failure.

This study drew from administrative databases, so available clinical data were limited. We did not have access to clinical imaging or information on anticoagulation levels, cardiac or valvular function, or valve models. Information on gestational age or pregnancies that did not result in inpatient delivery admissions was also not available for all years of the study period, so in the main analysis, we were limited to pregnancies that resulted in an inpatient delivery admission. Finally, efforts were made to control for baseline differences that may have guided valve selection. However, unmeasured confounders, particularly in this population where biologic valves are typically favored, likely introduced some degree of selection bias.

In conclusion, pregnancy accelerates time to reoperation for both biologic and mechanical valves. Mechanical valves are associated with significant rates of pregnancy loss and maternal morbidity and, particularly in the mitral position, carry significant risk of early valve failure after pregnancy. This study provides evidence from a contemporary population supporting use of biologic valves and may help inform decision-making in patients who underwent valve replacement before possible pregnancy.

Disclosures

Dr. Chikwe receives speaker honoraria from Edwards Lifesciences.

Footnote

Preliminary data from this study were presented at the American Heart Association's Scientific Sessions 2017, November 11−15, 2017, in Anaheim, California.

Supplementary Data

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.07.020.

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