European Journal of Obstetrics & Gynecology and Reproductive Biology 240 (2019) 172–177

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Attained pregnancy among women with a prosthetic heart valve

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ARTICLE INFO

Article history:
Received 23 June 2019
Accepted 30 June 2019

Keywords:
Prosthetic heart valves
Recognized pregnancy rate
Livebirths
Mechanical heart valves

ABSTRACT

Background: Women with prosthetic heart valves are at higher risk for adverse outcomes during pregnancy. The rates of achieved pregnancy, regardless of the pregnancy outcome, are largely unknown in this group of women.
Objective: To determine the rate of pregnancy in women with prior heart valve replacement, and compare that to women without known heart disease.
Study Design: A retrospective matched population-based cohort study was done between April 1994 and March 2017, in Ontario, Canada, where universal health care is available. Administrative healthcare databases were used to identify study participants, exposures and outcomes. Each woman of child-bearing age who had a bioprosthetic or mechanical mitral or aortic valve replacement (valve replacement group) was matched to four women without heart disease (community comparison group) – by age, year of cohort entry, any recent prior pregnancy, geographic area of residence and income level. Starting after the date of cohort entry (defined as the date valve replacement date in the valve replacement group), participants were assessed for a recognized pregnancy, namely, a livebirth, stillbirth, miscarriage or induced abortion. Hazard ratios (HR) and 95% confidence intervals (CI) were further adjusted for age, immigrant status and comorbid medical conditions.
Results: 1596 women with a valve replacement were matched with 6378 women in the community comparison group. After a median (interquartile range, IQR) duration of follow-up of 3.1 (1.0–5.6) and 2.7 (1.0–6.0) years, respectively, 98 women in the valve replacement group achieved a recognized pregnancy (0.63 per 100 person-years), compared to 607 women in the community comparison group (0.88 per 100 person-years) – an adjusted HR of 0.72 (95% CI 0.57-0.89). Within the valve replacement group, those with a mechanical valve were less likely to achieve a recognized pregnancy than those with a bioprosthetic valve (adjusted HR 0.57, 95% CI 0.38-0.87).
Conclusion: Women who undergo aortic or mitral valve replacement are less likely to achieve a pregnancy than matched counterparts without heart disease. This information, and the reasons for why this is so, can inform decisions about the timing of valve replacement and pregnancy planning.

Introduction

Heart disease is a leading cause of maternal and perinatal mortality and morbidity in pregnancy. Maternal mortality is about 10 times higher in pregnant women with heart disease than those without heart disease [1–3]. Pregnant women with prosthetic heart valves, particularly of the mechanical type, are especially at high risk for adverse outcomes [4–9]. An international registry of 212 pregnancies in women with prosthetic heart valves reported a 42% complication rate in those with a mechanical valve, and a 22% complication rate in those with a bioprosthetic valve [10]. Reasons for adverse events are partly attributed to the increased cardiac output of pregnancy, and its effect on valve function, alongside the added risk of mechanical valve thrombosis [4,5,9,11].

Despite the reported higher risk, the actual number of women with a prosthetic heart valve who achieve a pregnancy is unknown. Current risk estimates are likely biased by referral

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https://doi.org/10.1016/j.ejogrb.2019.06.038
0301-2115/

and ascertainment bias [4,5,9–12]. In an effort to reduce the influence of these biases, the current study was undertaken to determine the rate of achieved pregnancy in women with prior heart valve replacement, and to compare the rate of achieved pregnancy and livebirth pregnancy in women with and without heart valve replacement.

Materials and methods

A population-based retrospective matched cohort study was completed in the province of Ontario, Canada, using linked health care administrative databases held at Institute for Clinical Evaluative Sciences (ICES). All Ontario residents are enrolled in the Ontario Health Insurance Plan (OHIP), which covers all cardiac and obstetrical health care, including free access to induced abortion services [13]. More than 99% of births occur in hospital [14].

Data sources

We linked several administrative health care databases housed at ICES, as follows: 1) Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), 2) Registered Persons Database (RPDB), 3) National Ambulatory Care Reporting System (NACRS), 4) Same Day Surgery database (SDS), 5) Ontario Cancer Registry (OCR), 6) Immigration, Refugees and Citizenship Canada (IRCC)'s Permanent Residence Database, 7) OHIP Claims database, 9) MOMBABY database, which links the hospital record of a pregnant women with that of her newborn, 10) Ontario Diabetes Database (ODD), 11) Ontario Hypertension dataset (HYPER), 12) Ontario Asthma dataset (ASTHMA), and 12) Chronic Obstructive Pulmonary Disease dataset (COPD) [15–19]. Neighborhood-level income quintile and rural/urban residence were determined using Statistics Canada definitions. A description of these databases is provided in Supplemental Table 1, and elsewhere [20–22].

The abovementioned datasets were linked using unique encoded identifiers, and analyzed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Study participants

Ontarian women aged ≤ 50 years, who had undergone a mitral or aortic heart valve replacement between April 1, 1994 and March 31, 2016, comprised the "valve replacement group". A bioprosthetic or mechanical valve replacement was determined by Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) or Canadian Classification of Health Interventions (CCI) codes at the time of the surgery. The reason for valve replacement was not known. The date of the valve replacement constituted the cohort entry date (i.e., time zero for follow-up). We excluded women who had a valve replacement or repair prior to the cohort entry date, prior complex congenital heart surgery, prior pulmonic or tricuspid valve replacement or valvuloplasty, or a prior hysterectomy, oophorectomy or salpingectomy.

In the formation of the comparison group, we identified all Ontarian women who did not undergo heart valve replacement or have any prior heart disease – the "community comparison group". The same exclusions applied to the valve replacement group were also applied to this group. We randomly assigned a date of cohort entry to all women in the community comparison group, following the distribution of cohort entry dates of the valve replacement group. Four women in the community comparison group were then matched to each woman in the valve replacement group, using greedy matching without replacement, by age at cohort entry +/- 2 years, fiscal year of cohort entry, geographic area of residence (i.e., the same Local Health Integration Network, which is 1 of 14 sub-regions in Ontario responsible for the provision of health services), any recognized pregnancy within 3 years prior), and neighborhood income quintile (i.e., the two lowest quintiles [1,2] or the three

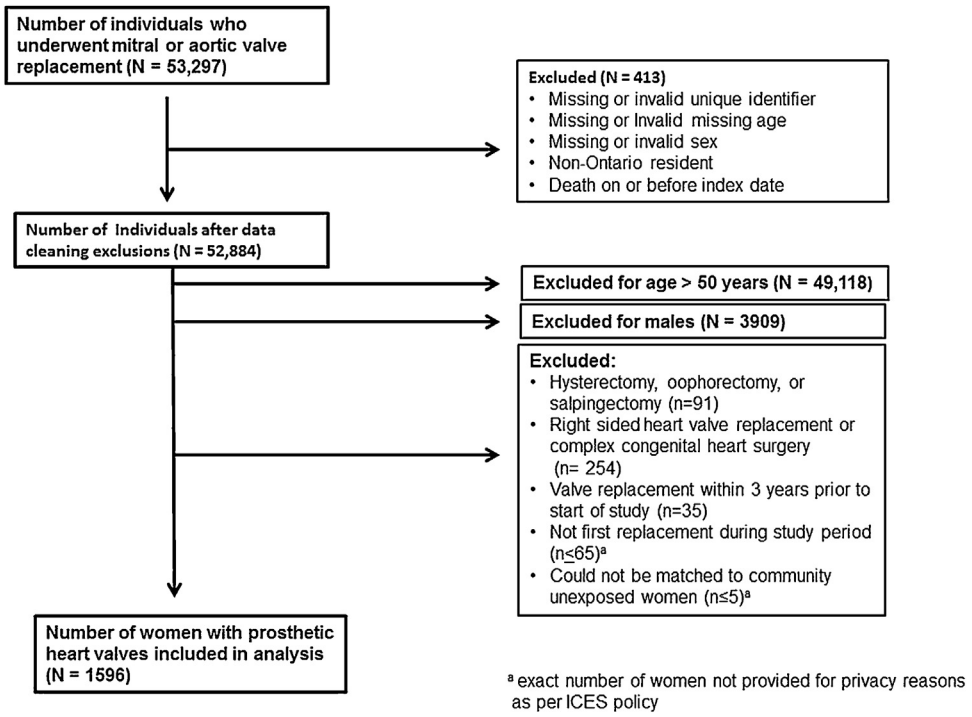

Fig. 1. Flow diagram for creation of the cohort of women with a heart valve replacement.

highest quintiles [3–5]). Women from either group who were not matched based on these criteria were excluded.

Covariates and outcomes

All study outcomes and covariate conditions were based on the diagnostic codes from the abovementioned administrative health care databases (Supplemental Table 2). Comorbid conditions included hypertension, diabetes mellitus, pulmonary disease, renal disease, cancer, collagen vascular disease, thyroid disease, cerebrovascular disease, and peripheral vascular disease. The primary study outcome was a recognized pregnancy, defined as the first pregnancy after cohort entry culminating in a livebirth, stillbirth ≥20 weeks' gestation, miscarriage <20 weeks' gestation or an induced abortion. A "recognized pregnancy" required an interaction with the Ontario health system, and recorded within the administrative databases used herein. The secondary outcome was a pregnancy resulting in a livebirth. Study follow-up ended on March 31, 2017, or at a censoring event (i.e., death, subsequent hysterectomy, oophorectomy or salpingectomy), whichever occurred first.

Data analyses

Discrete data were expressed as proportions, and continuous data as a median and interquartile range (IQR). Differences in baseline characteristics between the valve replacement group and community comparison group were assessed using weighted standardized differences, with a value ≥ 0.10 considered an important difference. Time-to-event analyses were performed using marginal Cox regression, comparing the rate of women with first recognized pregnancy in the valve replacement group to that in the community comparison group, and expressed as a hazard ratio (HR) and 95% confidence interval (CI). The same approach was taken for the outcome of pregnancy resulting in a livebirth. HRs were then adjusted for baseline characteristics whose weighted standardized difference between groups was ≥ 0.10, or that were chosen *a priori* as clinically important: age at cohort entry, immigrant status, and any comorbid conditions (hypertension, diabetes mellitus, pulmonary disease, renal disease, cancer, collagen vascular disease, thyroid disease, cerebrovascular disease or peripheral vascular disease). As matching on age at cohort entry was +/- 2 years, this variable was included in the multivariable models, to account for any residual confounding. In a further analysis confined to women in the valve replacement group, the outcomes of recognized pregnancy and a livebirth pregnancy were compared between women with a mechanical heart valve and those with a bioprosthetic valve, without matching, but adjusting for age at cohort entry, the presence of any aforementioned comorbid condition, immigrant status, neighborhood income quintile, any prior pregnancy within 3 years of cohort entry, and rural residence. The level of significance was set at 2-sided P-value < 0.05. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

To provide clinical context, the proportion of pregnancies that comprised of a livebirth, induced abortion, and miscarriage was separately calculated within the valve replacement and community control groups. A statistical comparison in the latter proportions was not performed due to difference in follow-up time intervals between the two groups. A similar approach was used when the valve replacement group was separated by into women with a mechanical or a bioprosthetic valve.

Table 1
Characteristics of women with a prior heart valve replacement, and their matched comparison group of women without known cardiac disease. All data are shown as a number (%) unless otherwise specified.

	Valve Replacement Group (N = 1596 women)	Community Comparison Group (N = 6378 women)	Weighted standardized difference
Median (IQR) age at cohort entry, years	43 (36-47)	43 (36-47)	0.00
Lowest residential income area[a]	777 (48.7)	3,105 (48.7%)	0.00
Rural residence	210 (13.2)	766 (12.0)	0.04
Immigrant to Ontario[b]	262 (16.4)	943 (14.8)	0.06
Comorbid conditions			
Hypertension	457 (28.6)	508 (8.0)	0.62
Diabetes	141 (8.8)	192 (3.0)	0.28
Pulmonary disease	443 (27.8)	708 (11.1)	0.5
Renal disease	108 (6.8)	29 (0.5)	0.35
Cancer	65 (4.1)	89 (1.4)	0.18
Cerebrovascular disease	111 (7.0)	9 (0.1)	0.38
Peripheral vascular disease	65 (4.1)	16 (0.3)	0.27
Thyroid disease	111 (7.0)	262 (4.1)	0.15
Collagen vascular disease	199 (12.5)	361 (5.7)	0.28
Any recognized pregnancy, prior to the date of heart valve replacement	112 (7.0)	442 (6.9)	0.00

[a]Residing within the two lowest neighborhood income quintiles, [b] Denotes immigrants who landed in Ontario, but not those who landed in another province/territory and moved to Ontario afterwards.

Results

A total of 1596 women comprised the valve replacement group, and were matched to 6378 women in the community comparison group (Fig. 1). Key baseline characteristics of the two groups are provided in Table 1. In the valve replacement group, the median age of valve replacement (age at cohort entry) was 43 years. The valve replacement group had a higher frequency of comorbid conditions than the community control group.

There was a total of 15,489 person-years follow-up for the valve replacement group and 69,289 person-years follow-up for the community comparison group. The median (IQR) duration of follow-up for women who had a recognized pregnancy was 3.1 (1.0–5.6) years in the valve replacement group and 2.7 (1.0–6.0) years in the community comparison group. There were 98 women in the valve replacement group who experienced a recognized

Table 2
Outcome of a first recognized pregnancy or a first livebirth among women with a prior heart valve replacement compared to women in the matched community comparison group. All data are shown as a number (%) unless otherwise specified.

	Valve replacement group (N = 1596 women)		Community comparison group (N = 6378 women)		Hazard ratio (95% CI)	
Outcome	Number of women (%)	Rate per 100 person-years	Number of women (%)	Rate per 100 person-years	Unadjusted	Adjusted[a]
Recognized pregnancy	98 (6.1)	0.63 (0.51-0.76)	607 (9.5)	0.88 (0.81-0.95)	0.69 (0.56-0.86)	0.72 (0.57-0.89)
Pregnancy resulting in livebirth	52 (3.3)	0.33 (0.24 - 0.42)	471 (7.4)	0.67 (0.61 - 0.73)	0.48 (0.36- 0.63)	0.50 (0.37-0.67)

[a]Adjusted for age at cohort entry, immigrant status, and any comorbid conditions (hypertension, diabetes mellitus, pulmonary disease, renal disease, cancer, collagen vascular disease, thyroid disease, cerebrovascular disease or peripheral vascular disease).

pregnancy (0.63 women per 100 person-years, 95% CI 0.51-0.76) versus 607 women in the community comparison group (0.88 women per 100 person-years, 95% CI 0.88-0.95) – an unadjusted HR of 0.69 (95% CI 0.56-0.86), and an adjusted HR of 0.72 (95% CI 0.57-0.89) (Table 2). The valve replacement group also had a lower rate of any pregnancy with a livebirth (0.33 women per 100 person-years, 95% CI 0.24-0.42) than the community comparison group (0.67 per 100 person-years, 95% CI 0.61-0.73), with an unadjusted HR of 0.48 (95% CI 0.36-0.63) and an adjusted HR of 0.50 (95% CI 0.37-0.67) (Table 2). Of the 98 women in the valve replacement group who had a recognized pregnancy in the study period, 52 (53%) women had at least one livebirth, in contrast to 471 women (78%) with at least one livebirth among the 607 women in the community comparison group with a recognized pregnancy (Fig. 2). The rates of induced abortion and miscarriage are also shown in Fig. 2.

Within the valve replacement group, the rate of a recognized pregnancy was lower in those with a mechanical valve (0.44 women per 100 person-years) than a bioprosthetic valve (1.41 women per 100 person-years) – an adjusted HR of 0.57 (95% CI 0.38-0.87)(Fig. 3). Of the 98 recognized pregnancies in the 54 women with a mechanical valve, 42 (43%) ended in induced abortion and 25 (26%) in miscarriage. In contrast, of the 70 pregnancies in 44 women with a bioprosthetic valve, 8 (31%) ended in induced abortion and 22 (11%) in miscarriage. The rate of livebirth pregnancy was 0.17 women per 100 person-years in women with a mechanical valve and 0.96 women per 100 person-years in those with a bioprosthetic valve (adjusted HR 0.34, 95% CI 0.19- 0.61) (Fig. 3).

Comment

Principal findings

In this population based cohort study of women of reproductive age, those who had a prior heart valve replacement had lower

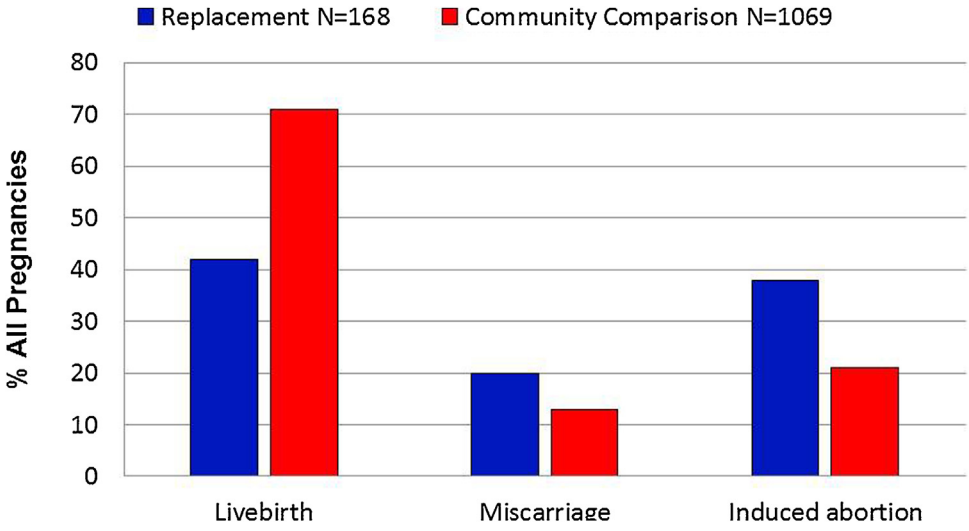

Fig. 2. Proportion of pregnancies resulting in a livebirth, miscarriage or induced abortion, contrasting the heart valve replacement (blue) group with the community comparison group (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

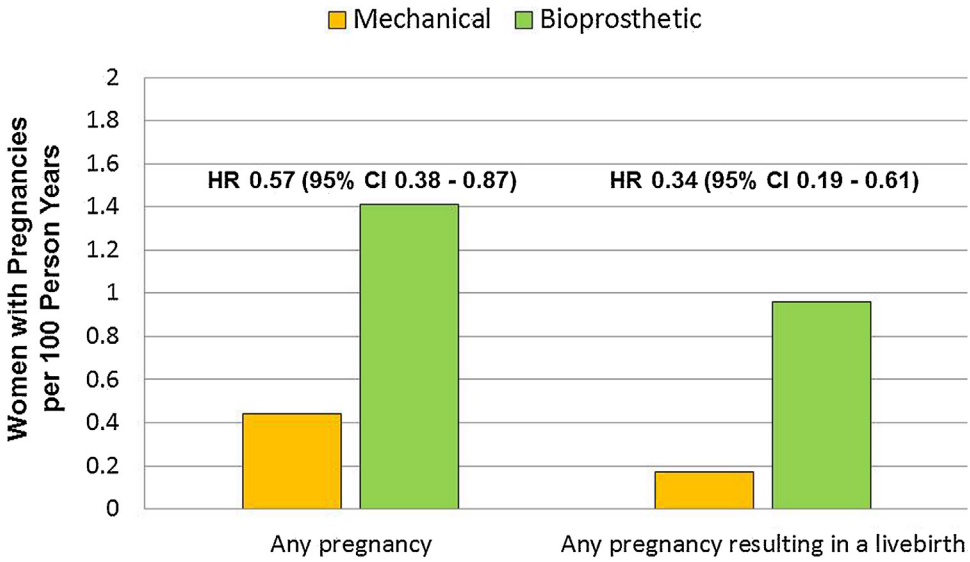

Fig. 3. Rate of any recognized pregnancy, as well as a pregnancy resulting in a livebirth, among women with a mechanical heart valve (yellow) vs. a bioprosthetic heart valve (green). Hazard ratios (HR) were adjusted for age at cohort entry, the presence of any comorbid condition, immigrant status, neighborhood income quintile, any prior pregnancy within 3 years of cohort entry and rural residence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 3
Studies of pregnancy outcomes in women with prosthetic heart valves[a].

Study site	Era study conducted	Type of prosthetic heart valve(s)	Number of pregnancies	Induced abortion rate (%)	Miscarriage rate (%)	Stillbirth rate (%)	Livebirth rate (%)
Single center, Egypt [27]	1986-1999	Mechanical	100	Not stated	28	11	61
Nationwide, Denmark [25]	1977-2007	92% Mechanical	155	27	33	1	39
Single center, Egypt [28]	Not stated	Mechanical	100	Not stated	29	16	55
International registry [10]	2009-2014	Mechanical and Bioprosthetic	Mechanical 212 Bioprosthetic: 134	1 –	16 2	3 0	80 98
210 centers, UK [12]	2013-2015	Mechanical	58	7	9	5	78
Multi-Center, Belgium and The Netherlands [23]	1991-2013	Mechanical and Bioprosthetic	Mechanical: 28 Bioprosthetic: 74	4 5	30 16	Not stated	Not stated
Multi-Center, Bangladesh [29]	2012-2017	Mechanical and Bioprosthetic	Mechanical: 182 Bioprosthetic: 83	Not stated	35 6	Not stated	65 94
Current study	1994-2017	Mechanical and Bioprosthetic	Mechanical: 98 Bioprosthetic: 70	38	20	0	42

[a]Studies published on or after 2000 with study sample comparable to present study (≥ 50 women); studies reporting low dose (nonstandard) anticoagulation regimen were also excluded.

pregnancy and livebirth rates than their community counterparts without known heart disease. Both pregnancy and a livebirth were less likely in women with a mechanical valve than a bioprosthetic valve.

Strengths and limitations

Most prior studies of pregnancy outcomes in women with prosthetic heart valves were likely influenced by referral and ascertainment bias, as they originated from sub-specialized centers (Table 3). The current population-based study minimized such bias by capturing all women with a heart valve replacement, and all pregnancies, within a province-wide universal healthcare system. While the number of pregnancies in the current study is modest, our sample contains the largest reported number of women of reproductive age with a prosthetic heart valve residing in a high-income country. Lack of access to abortion services, or the availability of abortion data, may have led to an underestimation of the rates of induced abortion or miscarriage in prior studies [10,12,23] – a feature that was likely overcome herein, with the exception of miscarriages in women who did not seek medical attention.

Matching to a community comparison group, not done previously, provided a valid comparator. Matching or adjustment for socio-economic factors and immigrant status may have reduced unrealized confounding between heart disease, the receipt of valve replacement, and likelihood of achieving a pregnancy. For example, even if a woman born outside of Canada is more susceptible to rheumatic heart disease, she may otherwise be more healthy than a Canadian-born woman – the so-called "healthy immigrant" effect [24]. Nevertheless, the current study did not directly measure cardiac function, the reasons for valve replacement, patient attitudes about pregnancy planning or valve surgery, and the nature of counseling they received. Counseling by care givers with resultant higher use of contraception may contribute to the lower rate of recognized pregnancy in the valve replacement group, while those women who are not at optimal health status for pregnancy may be more likely to be advised to undergo induced abortion. As reported elsewhere, women with a mechanical heart valve may be discouraged from pursuing a pregnancy, related to maternal and fetal risks [25]. It is possible that In addition, women considering a future pregnancy may chose, or be offered, valve replacement with a bioprosthetic valve, to avoid the need for embryopathic warfarin anticoagulation. By the study's necessary design, the valve replacement group was older at the time of their first valve replacement – a median age of 43 years. Even though the comparison group was matched by age, to minimize confounding by age, the current study findings probably do not apply to younger women with a valve replacement, in whom ovarian reserve and fertility are higher [26].

Results in relation to other studies

The key findings of the current study, in contrast to contemporary studies of pregnancy outcomes in women with a prosthetic heart valves, are summarized in Table 3 [10,12,23,25,27–29]. In one population based study of 356 Danish women who had heart valve replacement, the reported pregnancy rate was 22% among those aged 15–40 years [25]. However, the study was limited by its cross sectional design, 67% response rate to the outcome questionnaire, and exclusion of pregnancies before 22 weeks' gestation. An international registry reported only 56 pregnancies in women with mechanical valves across 17 high-income countries that contributed to the study [10]. All prior studies reported livebirth rates higher than that observed herein (Table 3), which may be the result of referral bias, and also their exclusion of women who had an induced abortion of miscarriage.

Clinical implications

The current findings may be important to patients and health care providers. In the counseling of a woman with a prosthetic heart valve contemplating a pregnancy, the absolute and relative probability of achieving a livebirth pregnancy outcome can be outlined. Certainly, optimizing the health of a woman with heart disease before, during and after a pregnancy cannot be underscored. This also applies to those who experience an induced abortion or miscarriage, where the risk to the mother remains relatively high [30]. Our findings may also be relevant to the health resource planning, as pregnant women with prosthetic valves will require specialized care at maternal cardiac centers, which have been associated with temporal reduction in the incidence of left heart failure in women with heart disease [30].

Conclusion

Women who undergo aortic or mitral valve replacement are less likely to achieve a pregnancy than matched counterparts without heart disease. This information can inform decisions about the timing of valve replacement and pregnancy planning. The reason for this difference in pregnancy rates will require further study with incorporation of data from electronic health records, clinical registries, or patient surveys.

Funding source

Samuel Siu was supported in part by an ICES Western Scholar grant from Division of Cardiology and Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario. The sponsors have no involvement in study design, analysis, data interpretation, writing of the paper, or to submit the article for publication.

Acknowledgements

Samuel Siu was supported in part by an ICES Western Scholar grant from Division of Cardiology and Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario. This study was supported by the ICES Western site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Core funding for ICES Western is provided by the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). The opinions, results and conclusions are those of the authors and are independent from the funding sources. No endorsement by ICES, AMOSO, SSMD, LHRI, or the MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements in the material are those of the author(s), and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

We thank Service Ontario for use of Office of the Registrar General (ORG) information on deaths. The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of ORG or Ministry of Government Services. We thank IRCC for allowing access to the Permanent Resident Database. The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those IRCC.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.06.038.

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