JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 21, 2018

PUBLISHED BY ELSEVIER

Pregnancy Outcomes in Women With Heart Disease

The CARPREG II Study

Candice K. Silversides, MD, MS,[a,b] Jasmine Grewal, MD,[c] Jennifer Mason, RN,[a,b] Mathew Sermer, MD,[a,b] Marla Kiess, MD,[c] Valerie Rychel, MD,[d] Rachel M. Wald, MD,[a,b] Jack M. Colman, MD,[a,b] Samuel C. Siu, MD, SM, MBA[a,b,e]

ABSTRACT

BACKGROUND Identifying women at high risk is an important aspect of care for women with heart disease.

OBJECTIVES This study sought to: 1) examine cardiac complications during pregnancy and their temporal trends; and 2) derive a risk stratification index.

METHODS We prospectively enrolled consecutive pregnant women with heart disease and determined their cardiac outcomes during pregnancy. Temporal trends in complications were examined. A multivariate analysis was performed to identify predictors of cardiac complications and these were incorporated into a new risk index.

RESULTS In total, 1,938 pregnancies were included. Cardiac complications occurred in 16% of pregnancies and were primarily related to arrhythmias and heart failure. Although the overall rates of cardiac complications during pregnancy did not change over the years, the frequency of pulmonary edema decreased (8% from 1994 to 2001 vs. 4% from 2001 to 2014; p value = 0.012). Ten predictors of maternal cardiac complications were identified: 5 general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions); 4 lesion-specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, coronary artery disease); and 1 delivery of care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index (CARPREG II [Cardiac Disease in Pregnancy Study]).

CONCLUSIONS Pregnancy in women with heart disease continues to be associated with significant morbidity, although mortality is rare. Prediction of maternal cardiac complications in women with heart disease is enhanced by integration of general, lesion-specific, and delivery of care variables. (J Am Coll Cardiol 2018;71:2419-30)

In the presence of maternal heart disease, the physiologic changes of pregnancy can result in maternal morbidity and mortality (1,2). Our understanding of pregnancy risk and how to care for women with heart disease during pregnancy has been evolving over the past 2 decades (3-6). The multicenter CARPREG (Cardiac Disease in Pregnancy Study) was the first to develop a risk index to predict the likelihood of maternal cardiac complications from general maternal clinical and echocardiographic data obtained during the baseline antepartum visit (6,7). The CARPREG risk index has been widely used, independently validated, and expanded by others in an attempt to improve risk prediction for their patient population (4,8-10). The ZAHARA (Zwangerschap bij Aangeboren

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Division of Cardiology, University of Toronto Pregnancy and Heart Disease Research Program, Mount Sinai Hospital/Sinai Health System, and Toronto General Hospital/University Health Network, Toronto, Ontario, Canada; [b]Department of Obstetrics & Gynaecology, Division of Maternal-Fetal Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; [c]Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [d]Department of Obstetrics and Gynecology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; and the [e]Division of Cardiology, University of Western Ontario, London, Ontario, Canada. This study was supported in part by operating grants provided by the Heart and Stroke Foundation of Canada (NA 5662), Canadian Institutes of Health Research (MOP 111139 and 119353), and the Canadian Foundation for Innovation. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 26, 2017; revised manuscript received January 25, 2018, accepted February 27, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.02.076

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HF = heart failure

LVOT = left ventricular outflow tract

mWHO = modified World Health Organization

NYHA = New York Heart Association

WHO = World Health Organization

HARtAfwijking [Pregnancy in Women With Congenital Heart Disease]) risk score was a weighted risk score that included components of the CARPREG risk index (9). The consensus-based modified World Health Organization (mWHO) classification was proposed to be a more comprehensive risk stratification method (5,11,12). However, pregnancy risk assessment is likely more complex than current models that only utilize general or lesion-specific predictors. A prediction model incorporating specific cardiac diagnosis, general cardiac variables, and factors related to process of care has not been developed.

SEE PAGE 2431

At the same time that risk scores were increasingly incorporated into clinical practice, specialized multidisciplinary clinics to coordinate the care of this population were established (13–15). Whether application of risk scores and the establishment of specialized clinics have had an impact on maternal cardiac outcomes has not been examined. Therefore, our objectives were to: 1) examine cardiac complications during pregnancy, including less common complications, and their temporal trends; and 2) derive a comprehensive risk stratification index that would include clinical and echocardiographic variables, the specific anatomic cardiac lesion, and variables related to delivery of care.

METHODS

STUDY POPULATION. This study cohort consisted of consecutive pregnancies in women with heart disease receiving care at 2 large Canadian tertiary care hospitals. Women with congenital heart disease, acquired heart disease, or arrhythmias receiving ongoing care or referred for consultation in the Toronto (since 1994) and Vancouver (since 2005) pregnancy programs were prospectively recruited. The inclusion criteria and study protocol are based on the CARPREG study and have been described previously (6). The local research ethics board approved the study.

All women underwent cardiac assessment at baseline and were then followed serially throughout pregnancy and until 6 months postpartum. Pregnancies in women who underwent termination or had a miscarriage (fetal death at <20 weeks gestation) were excluded. Baseline clinical, electrocardiographic, and echocardiographic variables were collected at the time of the first antenatal visit and included maternal age, parity, cardiac lesion, prior cardiac intervention, New York Heart Association (NYHA) functional class, maternal cyanosis confirmed by oximetry, cardiac rhythm, ventricular systolic function, valvular function, and right ventricular systolic pressure. Systemic ventricular ejection fraction was calculated using validated methods (16). For systemic right ventricles, ejection fraction was visually estimated. Right ventricular systolic function was visually evaluated as normal or impaired. Valvular area and gradients and severity of valvular regurgitation were measured using standardized criteria (17,18).

RISK CLASSIFICATION. For comparison of risk index models, all pregnancies were classified according to their CARPREG score, ZAHARA score, and mWHO risk category (Online Table 1) (6,9,12). The CARPREG risk score consists of 4 predictors and increasing number of predictors corresponds to increasing risk of maternal cardiac complications during pregnancy. The ZAHARA is a weighted risk score and the sum of the points corresponds to an estimated risk of adverse events. The mWHO classification provided a range of risk estimates from class I (no increase in maternal mortality and no/mild increase in morbidity) to class IV (extremely high risk of maternal mortality or severe morbidity). As no risk estimates were published with the original mWHO risk classification, we utilized results of a subsequent study that reported event rates both for their entire study population as well as for advanced countries (11).

CARDIAC OUTCOMES. Adverse maternal cardiac outcomes during antepartum, peripartum, and postpartum periods were recorded up until the sixth postpartum month and verified by review of health records. Primary cardiac outcomes were defined as any of the following: maternal cardiac death; cardiac arrest; sustained arrhythmia requiring treatment; left-sided heart failure (HF) defined as pulmonary edema; right-sided HF; stroke or transient ischemic attack; cardiac thromboembolism; myocardial infarction; and vascular dissection (6). Secondary outcomes were classified as a decline in NYHA functional class by ≥2 classes during the antepartum period or the need for urgent invasive treatment procedure/surgery during pregnancy and up to the sixth postpartum week; this cutoff of 6 weeks postpartum was set to exclude elective procedures that were deferred due to pregnancy.

DATA ANALYSIS. Analyses were performed using SPSS version 22.0 (Windows, IBM Corp., Armonk, New York). Data are represented as mean ± SD or as proportions. Based on prior studies, the following high-risk groups were used in the analysis: at least mild reduction in systemic ventricular systolic

function (ejection fraction <55%), high-risk valve lesions/left ventricular outflow tract (LVOT) obstruction (aortic valve area <1.5 cm^2, subaortic gradient >30 mm Hg, mitral valve area <2 cm, or moderate to severe mitral regurgitation), mechanical valves, pulmonary hypertension (right ventricular systolic pressure ≥50 mm Hg in the absence of right ventricular outflow obstruction), high-risk aortopathy (Marfan syndrome, bicuspid aortopathy with aortic dimension >45 mm, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, or prior aortic dissection or pseudoaneurysm), and coronary artery disease (defined as angiographically proven coronary obstruction or past myocardial infarction) (1,2,6,9,19). No prior cardiac interventions included women who had not had any of the following interventions: cardiac repair of congenital lesions; valvular replacements or repairs; or percutaneous or operative treatment of arrhythmias. Primary and secondary maternal cardiac events were calculated separately. The frequency of primary cardiac events was stratified according to CARPREG scores and mWHO risk categories.

Time trends in primary maternal cardiac events in the Toronto cohort were examined before and after 2001. In 2001, the CARPREG study results were incorporated into risk stratification and the care of pregnant women with heart disease was consolidated at the Toronto site; therefore, 2001 was chosen as a breakpoint at which began a period of potential improvement in clinical care. Differences in baseline characteristics and outcomes between women who delivered prior to 2001 compared with those who delivered after 2001 were examined using chi-square, Fisher exact, or Student's *t*-tests. For those cardiac complications in which there was a significant difference in event rates between the 2 time periods, inverse probability of treatment weighting was utilized to confirm that the differences in event rates were propensity adjusted for temporal differences in baseline characteristics (20) (Online Table 2).

To determine predictors of primary cardiac events, the total study group was randomly divided into a derivation set and validation set corresponding to 66% and 34% of the entire group. Analyses to determine predictors were performed only in the derivation group. Candidate variables included baseline demographics, general, and lesion-specific characteristics, as well as the components of CARPREG, ZAHARA, and mWHO classification systems. Univariate analysis to identify predictors of adverse events was performed using chi-square, Fisher exact, or Student's *t*-tests as appropriate. Univariate predictors of adverse events with p valves of <0.1 were entered

TABLE 1 Baseline Characteristics

Pregnancies	1,938
Clinical assessment	
Maternal age 18-35 yrs (30.6 ± 5.6 yrs, range 14 to 45 yrs)	1,530 (79.0)
Nulliparous	989 (51.0)
Body mass index, kg/m^2 (n = 1,685)	25.0 ± 5.9 12.9-61.2
Twins or triplets	52 (2.7)
Late pregnancy assessment (first antenatal visit after 20 weeks gestation)	676 (34.9)
Smoking	145 (7.5)
Prior hypertension, gestational hypertension, or diabetes mellitus	112 (5.8)
Prior cardiac events (HF, stroke, or transient ischemic attack)* or arrhythmia	531 (27.4)
NYHA functional class III/IV or cyanosis at baseline	47 (2.4)
Cardiac medications at first antenatal visit	361 (18.6)
Diuretic	35 (1.8)
Beta-blocker or antiarrhythmic drugs	304 (15.7)
Digoxin	42 (2.2)
Anticoagulation	90 (4.6)
No prior cardiac intervention	909 (46.9)
Cardiac diagnosis	
Congenital heart disease	1,235 (63.7)
Acquired heart disease	443 (22.9)
Isolated cardiac arrhythmias	260 (13.4)
High-risk cardiac lesions	
High-risk left-sided valve disease/LVOT obstruction	294 (15.2)
At least mild systemic ventricular systolic dysfunction	263 (13.6)
Pulmonary hypertension	58 (3.0)
High-risk aortopathy	52 (2.7)
Mechanical heart valve	43 (2.2)
Coronary artery disease	38 (2.0)

Values are n, n (%), mean ± SD, or range. *In those women who underwent cardiac surgery, only cardiac events after their cardiac surgery were considered.
HF = heart failure; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

TABLE 2 Incidence of Adverse Cardiac Event Rates During Pregnancy (N = 1,938)

Any maternal cardiac events	307 (15.8)
Maternal cardiac death	6 (0.3)
Maternal cardiac arrest	8 (0.4)
Arrhythmias	181 (9.3)
Any left- or right-sided HF	120 (6.2)
Left-sided HF	106 (5.5)
Right-sided HF	19 (1.0)
Stroke	13 (0.7)
Myocardial infarction	8 (0.4)
Dissection	7 (0.4)
Cardiac thromboembolism	6 (0.3)

Values are n (%). Events are not mutually exclusive.
HF = heart failure.

TABLE 3 Pregnancies Complicated by Cardiac Death and/or Cardiac Arrest

	Description of the Event	Timing of Event	Outcomes
Pregnancy termination or fetal death at <20 weeks			
HCM; history of atrial arrhythmia and ICD	Cardiac arrest	17-week gestation age	Death
Rastelli procedure; history of arrhythmia	Cardiac arrest	14-week gestation age	Death
Cyanotic congenital heart disease	Fatal pulmonary hemorrhage	3 months after termination of pregnancy	Death
Pregnancies that progressed beyond 20 weeks gestation			
Bicuspid aortic valve post Bentall procedure; mechanical aortic valve	SVT followed by cardiac arrest	26 weeks gestation	Death, thrombus on aortic prosthesis on autopsy
Congenitally corrected transposition; history of arrhythmias	SVT postpartum cardiac arrest	First postpartum week	Death
Severe secondary pulmonary hypertension from systemic lupus erythematosus	Progressive right HF, cardiac arrest	First postpartum week	Death
Congenitally corrected transposition; severe systemic atrioventricular regurgitation; pulmonary hypertension	Spontaneous ventricular tachycardia and then ventricular fibrillation	Fourth postpartum month	Successfully resuscitated
Dilated cardiomyopathy; severe LV systolic dysfunction	Ventricular fibrillation arrest	First postpartum week	Successfully resuscitated
Resected subpulmonic stenosis with pacemaker for bradyarrhythmia	At home death, presumably from a cardiac cause	Fifth postpartum month	Death
Repaired atrioventricular defect; severe left atrioventricular valvular regurgitation	Urgent surgery for refractory HF, post-operative hemorrhage from coagulopathy	7 weeks postpartum	Death
Dilated cardiomyopathy; moderate LV systolic dysfunction	Cardiac arrest	36 weeks gestation	Successfully resuscitated
Combined aortic stenosis and insufficiency; history of stroke	Cardiac arrest and pulseless electrical activity documented	38 weeks gestation	Successful resuscitation after caesarean delivery of live fetus
Complete transposition with Mustard procedure; systemic ventricular systolic dysfunction	Stroke	Third postpartum month	Death
Dilated cardiomyopathy; moderately reduced LV systolic function	Ventricular fibrillation arrest	First week postpartum	Successfully resuscitated

HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricle; SVT = supraventricular tachycardia.

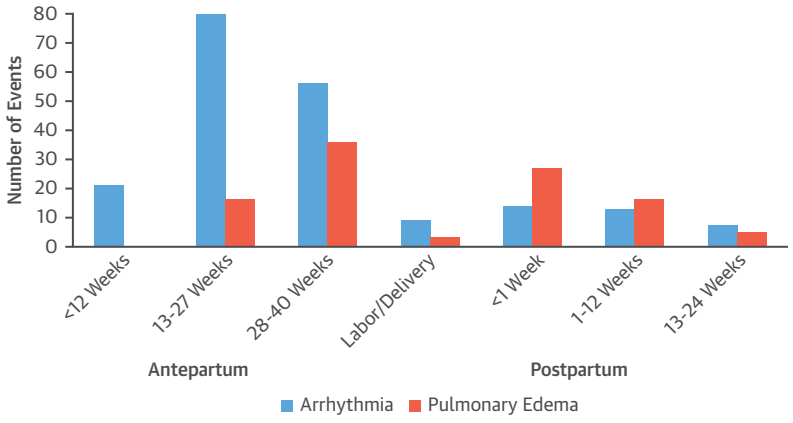
into a multivariate logistic regression model using backward elimination with a level of significance of 0.05. To maximize the likelihood of detecting lesion-specific predictors, variables that represent lesion-specific conditions or any mWHO component, not closely correlated with the other demographic or general candidate variables, were also entered into this multivariate model. Highly correlated variables were combined into a single variable.

The results of the multivariate model were converted into a point-based risk score (CARPREG II risk index). The discriminative (C-statistic) and calibrative (Hosmer-Lemeshow statistic) accuracy of the CARPREG II risk index were determined in the derivation group and then in the validation group. The discriminative and calibrative accuracies of previously published risk classification (original CARPREG, ZAHARA, and mWHO) in the validation group were also determined.

RESULTS

Between 1994 and 2014, 2,032 pregnancies in women with heart disease were eligible for inclusion. Of these, 94 pregnancies (5%) were excluded either because of patient refusal (12 pregnancies), termination (40 pregnancies), or spontaneous abortion (42 pregnancies); 19 terminations were for cardiac indications. The study group comprised 1,938 pregnancies that progressed beyond 20 weeks gestation, including 289 pregnancies (14%) that were enrolled in the original CARPREG study. Table 1 shows the baseline characteristics of the study cohort. Structural heart disease was common (86.6%), of which congenital heart disease was the most common cardiac diagnosis (63.7% of pregnancies). The CARPREG risk score was 0 in 1,135 pregnancies (59%), 1 in 703 pregnancies (36%), and >1 in 100 pregnancies (5%). The mWHO class was I in 258 pregnancies (13%), II in 512 pregnancies (26%), II to III in 743 pregnancies (38%), III in 185 pregnancies (10%), and IV in 104 pregnancies (5%). In 136 pregnancies (7%) the mWHO class could not be determined because the cardiac lesion was not included in the risk classification. Baseline echocardiograms were not performed in 8 pregnancies in women with cardiac arrhythmias, all of whom were documented to have normal systemic ventricular systolic function and no valvular

FIGURE 1 Timing of Complications in Women Who Develop Arrhythmias or Congestive HF During Pregnancy

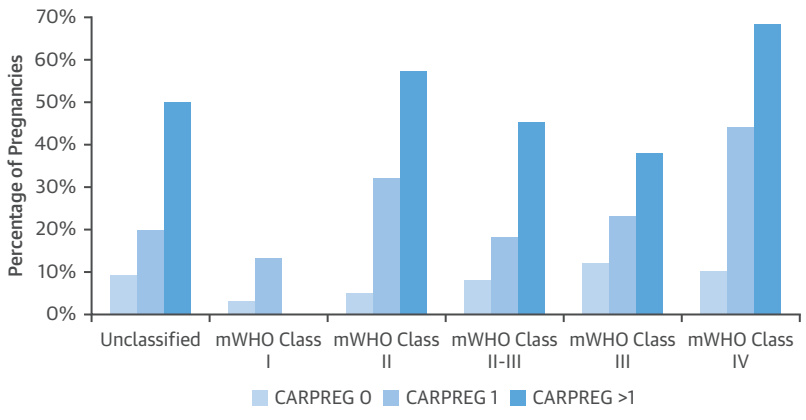


The x-axis shows the timing of presentation in women who develop arrhythmias **(blue bars)** or pulmonary edema **(orange bars).** The y-axis shows the total number of adverse events. HF = heart failure.

dysfunction prior to pregnancy. These 8 cases were assumed to have normal cardiac structure and function for the purpose of the analysis.

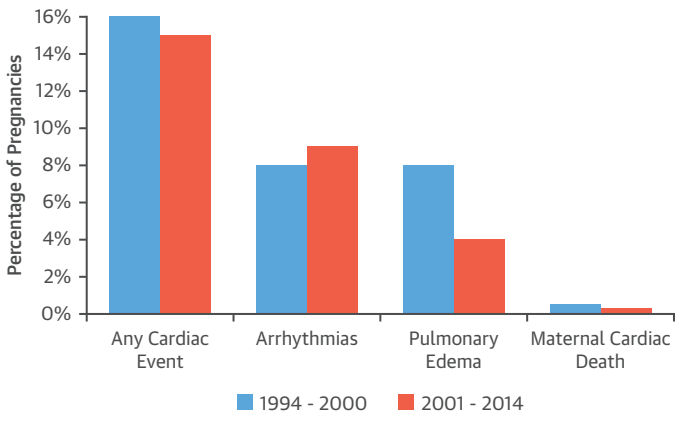
ADVERSE CARDIAC EVENTS. In the study group, adverse maternal cardiac events occurred in 307 pregnancies (16%) (Table 2). Maternal cardiac death or cardiac arrest was rare and occurred in 11 pregnancies (0.6%). Although the study group excluded pregnancies that did not progress beyond 20 weeks, there were 3 maternal cardiac deaths in the excluded group occurring in women with hypertrophic cardiomyopathy, repaired transposition of the great arteries, and uncorrected cyanotic congenital lesion. Table 3 summarizes the circumstances of the pregnancies complicated by cardiac death or cardiac arrest. Compared with the study group, a higher proportion of pregnancies that did not progress beyond 20 weeks gestation were in women with NYHA

FIGURE 2 Incidence of Maternal Cardiac Events Within Each mWHO Risk Group and Stratified According to the CARPREG Risk Score



The x-axis shows each modified World Health Organization (mWHO) class with the corresponding frequency of adverse primary maternal cardiac events (y-axis). The overall maternal cardiac event rate during pregnancy for mWHO I, mWHO II, mWHO II to II, WHO III, and mWHO IV was 3.1%, 21.7%, 12.8%, 21.1%, and 35.6%, respectively. There was a 12.5% event rate in pregnancies in which the mWHO class could not be determined. Each of the mWHO classes is further stratified according to CARPREG risk scores: 0 **(light blue)**, 1 **(medium blue)**, and >1 **(dark blue)**. CARPREG = Cardiac Disease in Pregnancy Study.

FIGURE 3 Changes in the Incidence of Adverse Cardiac Events Over Time



Blue bars represent the incidence of cardiac complications during pregnancy in the years 1994 to 2000, and the **orange bars** represent the incidence in the years 2001 to 2014.

functional class III/IV or cyanotic (17% vs. 2%), systemic ventricular dysfunction (27% vs. 14%), pulmonary hypertension (10% vs. 3%), or mechanical valves (12% vs. 2%) ($p < 0.005$ excluded vs. included pregnancies).

Overall, most complications occurred in the antepartum period. In the 307 pregnancies with a maternal cardiac complication, at least 1 antepartum event occurred in 223 pregnancies (73%). Of the total number of 383 cardiac events that occurred in these 307 pregnancies, 64% of cardiac events occurred during the antepartum period, while the other events occurred during labor and delivery (4%), or in the postpartum months following discharge (32%). The most common cardiac complications were arrhythmias (9.3% of pregnancies) and HF (6.2% of pregnancies). Most arrhythmias occurred in the antenatal period, whereas congestive HF more commonly occurred in the third trimester or early postpartum (Figure 1). Figure 2 shows the frequency of adverse cardiac events according to the mWHO classification and stratified according to the patients' CARPREG risk score. The addition of CARPREG risk score information further stratified risk within each mWHO class. Importantly, within each mWHO class, there was a wide range of cardiac event rates associated with individual diagnosis groups. For example, in the 6 diagnostic groups that composed mWHO class III, the cardiac event rate ranged from 7.1% to 28.2%. Secondary cardiac events occurred in 61 pregnancies (3%) and comprised either deterioration of maternal functional status by ≥2 NYHA functional classes (39 pregnancies) or need for urgent interventions (24 pregnancies) during pregnancy or the first 6 postpartum weeks. A primary or secondary cardiac event occurred in 333 pregnancies (17%).

TRENDS IN ADVERSE CARDIAC EVENTS OVER TIME. Time trends in the Toronto cohort (n = 1,448) were examined between 1994 and 2000 and 2001 and 2014. There were no significant differences in the age distribution, prior history of stroke or HF, comorbid conditions (diabetes mellitus, gestational hypertension, or hypertension), or proportion of pregnancies in women with congenital heart disease between the 2 time periods. Compared with the earlier era, women who underwent pregnancies in the later era were more likely to be on cardiac medications (14% vs. 21%, 1994 to 2000 vs. 2001 to 2014; $p = 0.005$) or underwent assessment <20 weeks gestation (64.8% vs. 75.0%, 1994 to 2000 vs. 2001 to 2014; $p < 0.001$). The proportion of high-risk pregnancies, characterized as having CARPREG risk score >1 or mWHO class III or IV, was not significantly different between the 2 time periods (22.2% vs. 18.4%; 1994 to 2000 vs. 2001 to 2014; $p = 0.11$). Figure 3 shows the temporal changes in event rates. Overall, there was no significant difference in frequency of maternal cardiac complications between the time periods (16% [n = 66] of pregnancies between 1994 and 2000 vs.15% [n = 151] of pregnancies between 2001 and 2014; $p = 0.57$). Maternal cardiac deaths were uncommon in either time period (0.5% [n = 2] of pregnancies between 1994 and 2000 vs. 0.3% [n = 3] of pregnancies between 2001 and 2014; $p = 0.63$). Arrhythmias occurred with similar frequency in the 2 time periods (8% [n = 35] of pregnancies between 1994 and 2000 vs. 9% [n = 98] of pregnancies between 2001 and 2014; $p = 0.62$). However, the frequency of pulmonary edema during pregnancy decreased over time (8% [n = 35] of pregnancies between 1994 and 2001 vs. 4% [n = 44] of pregnancies between 2001 and 2014; propensity adjusted $p = 0.012$). Whereas there was no difference in the frequency of right HF ($p = 0.73$), stroke ($p = 0.29$), myocardial infarctions ($p = 0.33$), vascular dissection ($p = 0.56$), or cardiac thromboembolism ($p = 1.00$) between the 2 time periods, in total these 5 types of nonfatal complications occurred in 3 pregnancies (0.7%) and 16 pregnancies (1.5%) during the 1994 to 2000 and 2001 to 2014 periods, respectively.

PREDICTORS OF ADVERSE CARDIAC EVENTS. Results of univariate analysis are displayed in Table 4. On multivariate analysis, there were 10 independent predictors of primary maternal cardiac events (Table 4). These 10 predictors are broadly grouped into 3 categories: 1) 5 general cardiac factors:

prior cardiac events (history of HF, stroke, or transient ischemic attack) or arrhythmia, NYHA functional class III or IV or cyanosis, high-risk valve lesion/LVOT obstruction, at least mild systemic ventricular systolic dysfunction, and absence of prior cardiac interventions; 2) 4 lesion-specific variables: mechanical prosthesis, coronary artery disease, high-risk aortopathy, and pulmonary hypertension; and 3) 1 variable related to process of care: late pregnancy assessment. These 10 variables included 2 predictors from the original CARPREG study (prior cardiac events or arrhythmia, NYHA functional class III or IV or cyanosis), and 2 modified CARPREG predictors (high-risk valve lesion/LVOT obstruction; at least mild systemic ventricular systolic dysfunction). The remaining variables were not in the original CARPREG risk score.

CARPREG II RISK SCORE. Table 4 shows the 10 predictors and their weighted point score in the derivation group. The new risk index, the CARPREG II risk index, is divided into 5 categories based on the sum of the points for a given pregnancy: 0 to 1 points (477 pregnancies); 2 points (222 pregnancies); 3 points (204 pregnancies); 4 points (138 pregnancies); and >4 points (228 pregnancies) (Online Figure 1). The predicted risks for primary cardiac events stratified according to point score were 0 to 1 points (5%), 2 points (10%), 3 points (15%), 4 points (22%), and >4 points (41%). The predicted and actual frequency of primary cardiac events in the derivation and validation groups are shown in Figure 4. In the derivation group, the CARPREG II risk index had a C-statistic of 0.77 (95% confidence interval [CI]: 0.74 to 0.81). In the validation group, the CARPREG II risk index had a C-statistic of 0.78 (95% CI: 0.73 to 0.83) compared with the original CARPREG risk index C-statistic of 0.74 (95% CI: 0.68 to 0.79), ZAHARA model C-statistic of 0.70 (95% CI: 0.65 to 0.76), mWHO C-statistic for global data of 0.50 (95% CI: 0.43 to 0.57), and the C-statistic for mWHO risk index for advanced countries of 0.56 (95% CI: 0.50 to 0.62). The Hosmer-Lemeshow statistic was not statistically significant ($p = 0.47$ and $p = 0.49$ for derivation and validation groups, respectively) for the CARPREG II risk index, indicating no overall significant differences between predicted versus actual frequency of adverse events across all risk groups. In contrast, the Hosmer-Lemeshow statistic was statistically significant, indicating significant differences between predicted and observed frequency of events across risk groups, for the original CARPREG ($p = 0.004$), ZAHARA ($p < 0.001$), mWHO risk index for global data ($p < 0.001$), and mWHO for advanced countries ($p < 0.001$) in the validation group (Online Figure 2).

There was no change in the discriminative and calibrative accuracy of the CARPREG II risk index when only pregnancies during the post-2000 period were included (n = 523; C-statistics: 0.77; 95% CI: 0.72 to 0.83; Hosmer-Lemeshow statistic $p = 0.83$), when both primary and secondary cardiac events were

TABLE 4 Univariate and Multivariate Predictors of Adverse Cardiac Events During Pregnancy

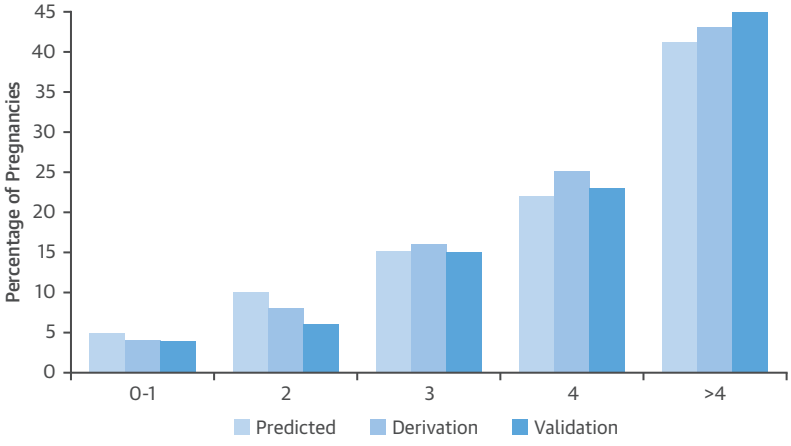
	Univariate Predictors		
	No CV Events (n = 1,067)	CV Events (n = 202)	p Value
Maternal age <18 or >35 yrs	219 (20.5)	57 (28.2)	0.016
Nulliparous	548 (51.4)	109 (54)	0.54
Body mass index ≥30 kg/m^2	145/940 (15.4)	32/167 (19.2)	0.25
Late pregnancy assessment (first antenatal visit after 20 weeks gestation)	363 (34.0)	90 (44.6)	0.005
Smoking	90 (8.4)	13 (6.4)	0.34
Prior hypertension, gestational hypertension, or diabetes mellitus	53 (5.0)	14 (6.9)	0.253
Prior cardiac events or arrhythmia	225 (21.1)	112 (55.4)	<0.001
NYHA functional class III or IV or cyanosis at baseline	17 (1.6)	15 (7.4)	<0.001
Cardiac medications at baseline	174 (16.3)	67 (33.2)	<0.001
Anticoagulation at baseline	35 (3.3)	18 (8.9)	<0.001
Significant left-sided valve disease/LVOT obstruction	148 (13.9)	42 (20.8)	0.013
Mechanical valve	15 (1.4)	9 (4.5)	0.008
Coronary artery disease	20 (1.9)	8 (4.0)	0.071
High-risk aortopathy	27 (2.5)	6 (3.0)	0.64
At least mild systemic ventricular systolic dysfunction	125 (11.7)	53 (26.2)	<0.001
Pulmonary arterial hypertension	25 (2.3)	12 (5.9)	0.009
No prior cardiac interventions	498 (46.7)	113 (55.9)	0.017
Systemic right ventricle*	41 (3.8)	14 (6.9)	0.058
Peripartum cardiomyopathy with residual LV dysfunction*	3 (0.3)	3 (3.5)	0.055

	Multivariate Predictors			
	Beta Coefficient (SE)	OR (95% CI)	p Value	Points
Prior cardiac events or arrhythmia	1.8 (0.2)	5.9 (4.2–8.4)	<0.001	3
Baseline NYHA functional class III–IV or cyanosis	1.6 (0.4)	4.9 (2.2–10.8)	<0.001	3
Mechanical valve	1.4 (0.5)	4.2 (1.6–10.9)	0.003	3
At least mild systemic ventricular systolic dysfunction	0.8 (0.2)	2.3 (1.5–3.5)	<0.001	2
High-risk left-sided valve disease/LVOT obstruction	0.7 (0.2)	2.1 (1.3–3.3)	0.001	2
Pulmonary hypertension	1.2 (0.4)	3.3 (1.5–7.2)	0.003	2
Coronary artery disease	1.1 (0.5)	3.0 (1.1–7.6)	0.03	2
High-risk aortopathy	1.0 (0.5)	2.7 (1.1–7.3)	0.04	2
No prior cardiac intervention	0.5 (0.2)	1.6 (1.1–2.3)	0.01	1
Late pregnancy assessment	0.5 (0.2)	1.6 (1.1–2.3)	0.009	1

Values are n (%) or n/N (%), unless otherwise indicated. *Candidate variables from the mWHO classification system that did not overlap with the other candidate variables.

CI = confidence interval; CV = cardiovascular; OR = odds ratio; other abbreviations as in Tables 1 and 3.

FIGURE 4 CARPREG II Risk Prediction Index: Incidence of Adverse Cardiac Events Stratified According to CARPREG II Risk Scores



PREDICTOR	POINTS
Prior cardiac events or arrhythmias	3
Baseline NYHA III-IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High risk left-sided valve disease/ left ventricular outflow tract obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

The CARPREG (Cardiac Disease in Pregnancy Study) II risk score is based on 10 predictors, shown in the **box.** Each predictor is assigned a weighted point score. The sum of points represents the risk score. Risk scores are categorized into the 5 groups (x-axis). The predicted **(light blue)** and the observed frequency of primary cardiac events in the derivation **(medium blue)** and validation **(dark blue)** groups are shown on the y axis. NYHA = New York Heart Association.

analyzed (C-statistics: 0.77; 95% CI: 0.73 to 0.82; Hosmer-Lemeshow statistic p = 0.63), or when pregnancies that ended prior to 20 weeks gestation (n = 82) were included (C-statistics: 0.78; 95% CI: 0.74 to 0.82; Hosmer-Lemeshow statistic p = 0.43). The results were also unchanged when the 8 pregnancies with missing echocardiographic data were excluded from analysis.

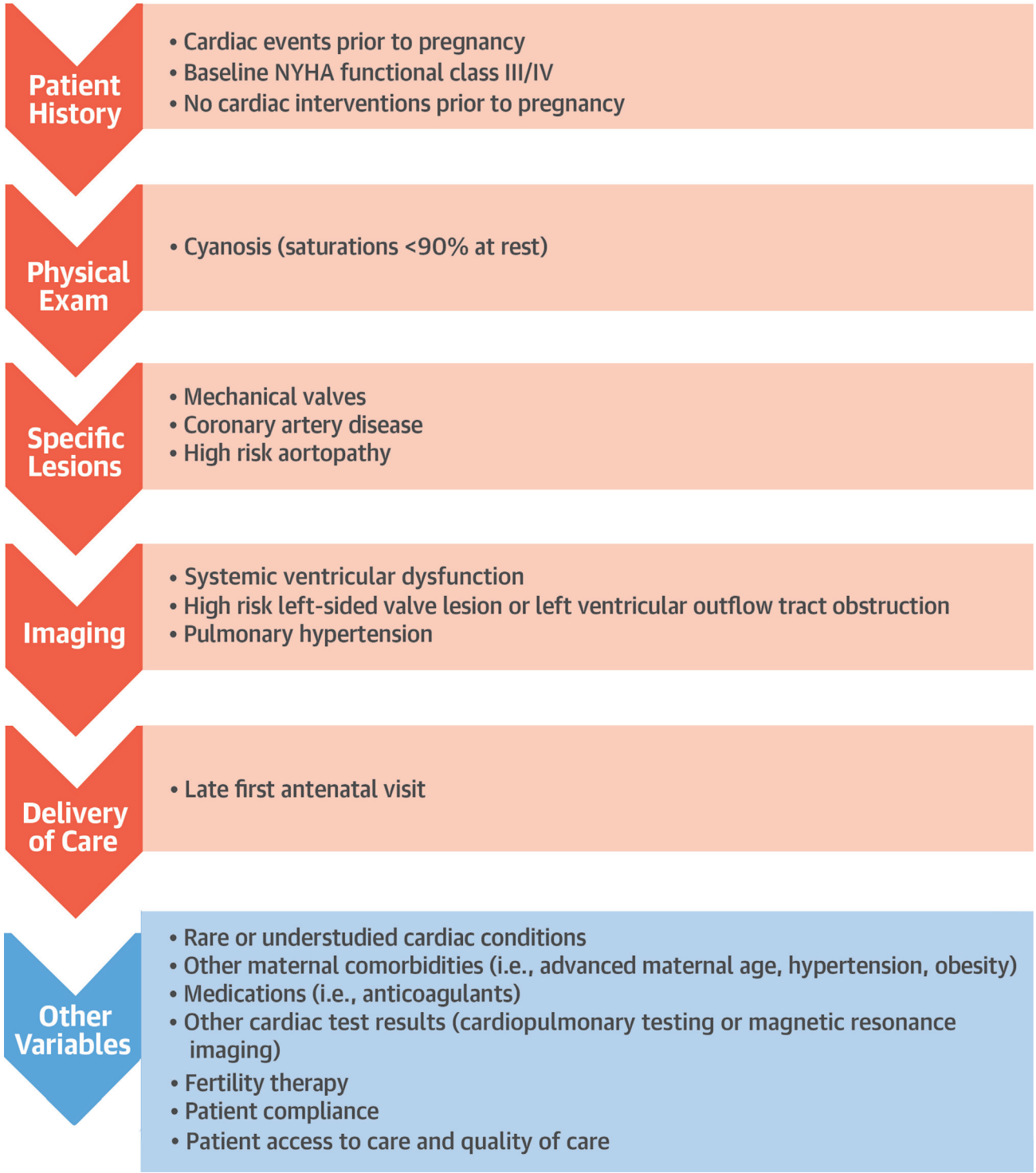
DISCUSSION

This prospective study of a consecutive group of pregnant women receiving state-of-the-art care at 2 large Canadian obstetric centers contributes important observations that are applicable to the clinical care of this expanding population. First, cardiac complications in pregnant women with heart disease remain common (16% of pregnancies) and are primarily related to maternal arrhythmias and HF (**Central Illustration**). Even in the lowest risk group, there is approximately a 5% risk of complications. Most complications occurred in the antenatal period, although specific complications, such as HF or arrhythmias, have distinct periods of risk. Although the overall rates of cardiac complications during pregnancy have not changed over the years, the frequency of pulmonary edema has decreased over time. Finally, process of care (i.e., late pregnancy assessment) is an important factor of pregnancy outcomes. This variable, along with general and lesion-specific maternal characteristics, can be incorporated into a new comprehensive CARPREG II risk index to predict maternal cardiac complications during pregnancy.

Our prospective study design and consecutive recruitment maximizes the ability to capture complete data on pregnancy outcomes from the antepartum period until the postpartum months, as the cardiovascular changes of pregnancy do not fully resolve until the sixth postpartum month (21). This comprehensive study shows that whereas pregnancy in women with heart disease is still associated with significant morbidity, maternal cardiac mortality is rare. However, cardiac mortality remains much higher than that in the general obstetric population (22–25).

This study design allows for an accurate assessment of cardiac risks during pregnancy. Studies that are based on hospital admission or administrative data capture complications at the time of hospital admission or delivery and may underestimate overall pregnancy risks because not all cardiac complications will result in hospitalization (15,22,25,26). Risk estimates also need to be interpreted in the context of the study group's access to care, as a multinational study demonstrated that maternal outcomes in pregnant women with heart disease are better in developed countries than in developing countries, even though most patients were receiving care at tertiary care centers (5). Our study population has universal access to state-of-the-art care by multidisciplinary teams with expertise in the management of high-risk pregnancies, thereby minimizing the influence of access and practice variation on patient outcomes. The large

CENTRAL ILLUSTRATION **Predictors of Adverse Events in Pregnant Women With Heart Disease**



Silversides, C.K. et al. J Am Coll Cardiol. 2018;71(21):2419–30.

Determining cardiac risk in pregnant women with heart disease requires integration of risk score estimates, individual factors, and clinical judgment. The **red arrows** show the variables in the CARPREG II risk score used to predict adverse cardiac events in pregnant women with heart disease. In addition to the variables in the CARPREG II risk score, there may be other factors that impact outcomes for the individual patient. The **blue arrow** shows some of the other variables to consider when estimating pregnancy risks.

sample size allowed us to quantitate the risk of less common, but serious cardiac complications, in other words, maternal death and cardiac arrest. Importantly, our study demonstrated that serious cardiac events can occur anytime during pregnancy.

As with most studies, we excluded pregnancies that did not progress beyond 20 weeks gestation. However, we observed a higher mortality (3.6%) in the small group of women who did not carry their pregnancy past 20 weeks gestation compared with the study group (0.3%). As pregnancies that did not progress beyond 20 weeks have a higher proportion of women with pulmonary hypertension, ventricular dysfunction, or mechanical valves, women with these high-risk lesions may be particularly vulnerable to the hemodynamic changes of early pregnancy and require further study (5,9,10,27).

We found that the majority of cardiac complications occurred in the antepartum period, followed by the postpartum period, with the lowest frequency at the time of labor and delivery. Additionally, the timing of presentation for women with arrhythmia complications differed when compared with the complications of women with HF. Cardiac arrhythmias were more likely to present in the second trimester, whereas HF was more likely to present in the third trimester or postpartum, concordant with prior studies (28,29). The hemodynamic and hormonal changes of pregnancy likely have different impacts in the presence of an arrhythmic substrate versus a structural cardiac abnormality. Although physicians and patients are often concerned about cardiac complications at the time of delivery, this study demonstrates that pregnant women with heart disease remain at risk before and beyond the peripartum period. Therefore, antenatal and postpartum surveillance will need to be tailored accordingly. Outcome studies that do not follow patients beyond the early postpartum period will underestimate the frequency of complications.

We documented a decrease in frequency of pulmonary edema over time. This reduction cannot be attributed merely to changing case mix, as the difference between the early and later era remained even after propensity adjustment. The decrease in frequency of pulmonary edema occurred after the integration of the CARPREG risk score in our management approach in 2001, at the same time that the maternal cardiac clinic was formally established. The decreasing event rates may have been secondary to better surveillance, early initiation of medication, or to the team approach to the care of women at risk for HF. Specific studies designed to improve outcomes in this population are still needed. Whereas the reasons for the decreased frequency of pulmonary edema remain to be elucidated, this is not a unique observation as care at a specialized clinic is associated with improved outcomes in adults with complex congenital cardiac lesions (30).

Our study extends prior knowledge about risk stratification of pregnant women with heart disease. The original CARPREG index was based on general clinical and echocardiographic characteristics and can be broadly applied across a wide range of cardiac conditions. However, the original CARPREG index did not incorporate emerging lesion-specific risk estimates. Subsequently, other groups have focused more on incorporation of lesion-specific predictors in their classification systems (9–12,27). This study demonstrates that combining lesion-specific and general factors provides better predictive accuracy than either approach alone. Compared with other published risk indices, including the original CARPREG score, CARPREG II risk index had the highest discriminative and calibrative accuracy in our study group. Importantly, in the CARPREG II risk index, clinical predictors such as history of prior cardiac events and maternal functional class or cyanosis were associated with a higher odds ratio and thereby assigned higher point values than the other predictors. This finding reinforces the foundational role of careful cardiovascular clinical assessment in risk stratifying pregnant women with heart disease. In addition to the variables identified in our risk score, there may be other factors that affect outcomes, and risk assessment for the individual patient will need to integrate risk score estimates, known lesion-specific information, and clinical judgment by an experienced physician. Finally, women who receive late pregnancy assessment had more frequent adverse cardiac outcomes during pregnancy, which may be attributed to delayed access to appropriate risk stratification, follow-up, and management plan. Further studies are required to determine the patient and provider factors responsible for delays in referral. Nevertheless, this novel observation supports the recommendation for early referral to a specialized center for assessment during pregnancy. This recommendation for specialty assessment of all pregnant women with heart disease is reinforced by the 5% risk of cardiac complications in the lowest risk group, concordant with prior studies (6,9,11,12).

STUDY LIMITATIONS. Despite our large sample size, some patients with uncommon and complex lesions may be under-represented. For instance, Eisenmenger syndrome, which has a high maternal morbidity and mortality, was not specifically

addressed in our risk index. This again highlights the importance of an experienced physician who can incorporate lesion-specific information and clinical judgment into risk assessment. Whereas our risk index had the best calibrative accuracy, it may come at the cost of user friendliness. As our prediction index was derived and validated in a setting of universal access to obstetric care and to an expert maternal cardiology team, it may perform less well in populations with variable access to state-of-the-art care. Thus, validation at other centers are needed to ascertain the generalizability of this CARPREG II risk index.

CONCLUSIONS

Pregnancy in women with heart disease continues to be associated with significant morbidity, although mortality is rare. Arrhythmia and HF are the most common maternal cardiac complications, but there has been a reduction in the frequency of pulmonary edema over time. Prediction of maternal cardiac complications in women with heart disease requires integration of clinical information, echocardiographic parameters, the specific maternal cardiac lesion, and process of care variables. Careful cardiovascular clinical assessment remains the foundation of risk stratification of pregnant women with heart disease. Future studies will need to understand how process of care affects maternal outcomes in pregnant women with heart disease.

ACKNOWLEDGMENT The Pregnancy and Heart Disease Research Program gratefully acknowledges support from the Toronto General and Western Hospital Foundation and the generous donations provided by Mrs. Josephine Rogers and the Allan E. Tiffin Trust.

ADDRESS FOR CORRESPONDENCE: Dr. Candice K. Silversides, Cardiology, Mount Sinai Hospital, 700 University Avenue, Room 9-913, Toronto, Ontario M5G 1Z5, Canada. E-mail: candice.silversides@uhn.ca.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: The risk of maternal mortality in pregnant women with heart disease is rare. However, cardiac complications occur and the risk of complications can be estimated by integrating general cardiac risk predictors, lesion-specific risk information, and factors related to process of care.

TRANSLATIONAL OUTLOOK: Additional studies are needed to identify specific components of cardiovascular and obstetrical care that improve outcomes for pregnant women with heart disease.

REFERENCES

1. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part II. J Am Coll Cardiol 2016;68:502–16.

2. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol 2016;68:396–410.

3. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 1997;96:2789–94.

4. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. Circulation 2006;113:517–24.

5. Roos-Hesselink JW, Ruys TP, Stein JI, et al., for the ROPAC Investigators. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J 2013;34:657–65.

6. Siu SC, Sermer M, Colman JM, et al., for the CARPREG Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515–21.

7. Siu SC, Colman JM, Sorensen S, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. Circulation 2002;105:2179–84.

8. Stangl V, Schad J, Gossing G, Borges A, Baumann G, Stangl K. Maternal heart disease and pregnancy outcome: a single-centre experience. Eur J Heart Fail 2008;10:855–60.

9. Drenthen W, Boersma E, Balci A, et al., for the ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010;31:2124–32.

10. Liu H, Huang TT, Lin JH. Risk factors and risk index of cardiac events in pregnant women with heart disease. Chin Med J (Engl) 2012;125:3410–5.

11. van Hagen IM, Boersma E, Johnson MR, et al., for the ROPAC and EORP Team. Global cardiac risk assessment in the Registry of Pregnancy and Cardiac Disease: results of a registry from the European Society of Cardiology. Eur J Heart Fail 2016;18:523–33.

12. European Society of Gynecology, Association for European Paediatric Cardiology, German Society for Gender Medicine, et al., for the ESC Committee for Practice Guidelines. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147–97.

13. Grewal J, Silversides CK, Colman JM. Pregnancy in women with heart disease: risk assessment and management of heart failure. Heart Fail Clin 2014;10:117–29.

14. Kafka H, Johnson MR, Gatzoulis MA. The team approach to pregnancy and congenital heart disease. Cardiol Clin 2006;24:587–605. vi.

15. Davidson WR Jr.. Pregnancy in adult congenital heart disease: special delivery. JAMA Cardiol 2017;2:671–2.

16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

17. Baumgartner H, Hung J, Bermejo J, et al., for the American Society of Echocardiography. European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23, quiz 101–2.

18. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

19. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. Eur J Heart Fail 2016;18:1119–28.

20. Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. Can J Cardiol 2016;32:259–65.

21. Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol 1987;94:1028–39.

22. Hameed AB, Lawton ES, McCain CL, et al. Pregnancy-related cardiovascular deaths in California: beyond peripartum cardiomyopathy. Am J Obstet Gynecol 2015;213:379.e1–10.

23. Briller J, Koch AR, Geller SE. Maternal cardiovascular mortality in Illinois, 2002–2011. Obstet Gynecol 2017;129:819–26.

24. Lima FV, Yang J, Xu J, Stergiopoulos K. National trends and in-hospital outcomes in pregnant women with heart disease in the United States. Am J Cardiol 2017;119:1694–700.

25. Opotowsky AR, Siddiqi OK, D'Souza B, Webb GD, Fernandes SM, Landzberg MJ. Maternal cardiovascular events during childbirth among women with congenital heart disease. Heart 2012;98:145–51.

26. Hayward RM, Foster E, Tseng ZH. Maternal and fetal outcomes of admission for delivery in women with congenital heart disease. JAMA Cardiol 2017;2:664–71.

27. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al., for the ZAHARA-II Investigators. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. Heart 2014;100:1373–81.

28. Grewal J, Siu SC, Ross HJ, et al. Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol 2009;55:45–52.

29. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. Heart 2014;100:231–8.

30. Mylotte D, Pilote L, Ionescu-Ittu R, et al. Specialized adult congenital heart disease care: the impact of policy on mortality. Circulation 2014;129:1804–12.

KEY WORDS arrhythmia, cardiology, cardiomyopathy, congenital heart disease, heart failure, mortality, outcomes, pregnancy, risk score, valve disease

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