# Prospective Multicenter Study of Pregnancy Outcomes in Women With Heart Disease

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on behalf of the Cardiac Disease in Pregnancy (CARPREG) Investigators

***Background***—The maternal and neonatal risks associated with pregnancy in women with heart disease receiving comprehensive prenatal care have not been well defined.

***Methods and Results***—We prospectively enrolled 562 consecutive pregnant women with heart disease and determined the outcomes of 599 pregnancies not ending in miscarriage. Pulmonary edema, arrhythmia, stroke, or cardiac death complicated 13% of pregnancies. Prior cardiac events or arrhythmia, poor functional class or cyanosis, left heart obstruction, and left ventricular systolic dysfunction independently predicted maternal cardiac complications; the cardiac event rate can be predicted using a risk index incorporating these predictors. Neonatal complications (20% of pregnancies) were associated with poor functional class or cyanosis, left heart obstruction, anticoagulation, smoking, and multiple gestations.

***Conclusions***—Pregnancy in women with heart disease is associated with significant cardiac and neonatal complications, despite state-of-the-art obstetric and cardiac care. Maternal cardiac risk can be predicted with the use of a risk index. **(*Circulation*. 2001;104:515-521.)**

**Key Words:** pregnancy ■ heart diseases ■ prognosis



In the presence of maternal heart disease, the circulatory changes of pregnancy may result in decompensation or death of the mother or fetus.[1–3] Current risk estimates are primarily based on studies that were retrospective, focused on a particular cardiac lesion, or examined populations managed at a single institution or from an earlier era.[1–9] To assess outcomes comprehensively in a contemporary cohort, we prospectively examined the frequency and predictors of pregnancy-related complications in Canadian women with heart disease. To enhance the risk stratification of pregnant women with heart disease, we developed and validated a risk index for the prediction of cardiac complications during pregnancy.

## Methods

This study prospectively enrolled 562 pregnant women with heart disease (aged 28±6 years) receiving care in 13 Canadian cardiac and obstetric teaching hospitals (55 000 deliveries per year) during 617 pregnancies. All pregnant women with congenital or acquired cardiac lesions or those with cardiac arrhythmias referred to a participating center from October 1994 to November 1999 were eligible for enrollment. To be eligible for inclusion, patients in whom cardiac arrhythmia was the primary diagnosis must have had symptomatic sustained tachyarrhythmias or bradyarrhythmias requiring treatment before pregnancy. Women with isolated mitral valve prolapse (moderate or mild mitral regurgitation) or those referred for termination of pregnancy were excluded. All centers received research ethics approval for this study, and subjects gave informed consent.

Baseline data recorded at the first prenatal visit included age, gestational age, New York Heart Association (NYHA) functional class, parity status, comorbid conditions, prior cardiac events (for those who underwent cardiac intervention, only events after intervention were considered), cardiac lesions, prior surgery/interventions, cyanosis (oxygen saturation <90%), medications, use of cigarettes and/or alcohol, educational status (surrogate for socioeconomic status), 12-lead ECG, transthoracic echocardiographic assessment of systemic (left) and venous (right) ventricular systolic function,[10] Doppler quantitation of inflow or outflow obstruc-

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A list of additional investigators can be found in the Appendix.

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tion,[11,12] Doppler quantitation of valvular regurgitation,[13,14] and systolic pulmonary artery pressure.[15]

Follow-up data were obtained from clinical visits during the second trimester (<28 weeks), third trimester (28 to 37 weeks), peripartum period (onset of labor until hospital discharge), and at 6 weeks and 6 months postpartum. For patients who did not deliver at the recruiting hospital (35%), follow-up data were obtained by reviewing discharge summaries from their obstetric centers and by contacting their physicians. Newborns of mothers with congenital heart disease were examined for recurrence of disease; pediatric echocardiography was performed in all infants with abnormal cardiac examinations.

Prepartum, peripartum, and postpartum complications were grouped into primary cardiac, secondary cardiac, neonatal, or obstetric events. Primary cardiac events were defined as any of the following: pulmonary edema (documented on chest radiograph or by crackles heard over more than one-third of posterior lung fields), sustained symptomatic tachyarrhythmia or bradyarrhythmia requiring treatment, stroke, cardiac arrest, or cardiac death. Secondary cardiac events were defined as a decline in NYHA class (≥2 classes) compared with baseline or need for urgent invasive cardiac procedures during pregnancy or within 6 months after delivery. Neonatal events were defined as any of the following: premature birth (<37 weeks gestation), small-for-gestational-age birthweight (<10th percentile), respiratory distress syndrome, intraventricular hemorrhage, fetal death (≥20 weeks gestation), or neonatal death (within 28 days after birth). Obstetric events included noncardiac death, pregnancy-induced hypertension (PIH), and postpartum hemorrhage (PPH). PIH was defined as an increase of systolic (≥30 mm Hg) and diastolic (≥15 mm Hg) blood pressure. PPH was defined as blood loss >500 mL (vaginal delivery) or >1000 mL (Caesarean section), which required transfusion or was accompanied by a drop in hemoglobin ≥20 g/L.

The study coordinating center (Toronto General Hospital) validated the accuracy of data entry using supporting documentation from participating centers. Primary cardiac and neonatal events were verified by 2 physicians unrelated to the study who were blinded to patient baseline characteristics.

## Data Analysis

Analysis was confined to pregnancies that were not complicated by miscarriage (fetal loss before 20 weeks gestation). Cardiac, neonatal, and obstetric events were analyzed separately. Univariate analyses were performed using $\chi^2$, Fisher's exact, or $t$ tests. Univariate predictors ($P<0.20$) were entered into a logistic regression model ($P=0.05$); correlated variables were combined. Because some women underwent ≥1 pregnancy, the validity of treating each pregnancy as an independent event was confirmed by general estimating equation (GEE) analysis.[16] Analyses were repeated using data from only the first pregnancy.

To determine predictors of cardiac events, the data set was randomly divided into derivation (60% of total pregnancies) and validation (40% of total pregnancies) groups. A retrospectively derived point score (original risk index) related cardiac risks during pregnancy to the number of prenatal characteristics from the following list: heart failure or stroke/transient ischemic attack before pregnancy, cardiac arrhythmia before pregnancy, baseline NYHA class III or IV or cyanosis, left heart obstruction (mitral valve area <2 $cm^2$, aortic valve area <1.5 $cm^2$, or peak left ventricular outflow tract gradient >30 mm Hg), and myocardial dysfunction (systemic ventricular ejection fraction <40% or hypertrophic or restrictive cardiomyopathy).[9] Different combinations of these and other potential predictors most strongly correlated with cardiac outcomes were tested in the derivation set. The coefficients from the logistic regression model were converted into a revised risk index. Additional analyses were performed to identify predictors of (1) the composite outcome of primary and secondary cardiac events and (2) primary cardiac events in the entire data set.

**TABLE 1. Baseline Maternal Characteristics**

| | Number (%) of Pregnancies |
|---|---|
| Age | |
| 18–35 years | 532 (86) |
| <18 or >35 years | 85 (14) |
| Parity status | |
| 0 | 359 (58) |
| 1–5 | 252 (41) |
| >5 | 6 (1) |
| Gestational age at entry | |
| <20 weeks | 424 (69) |
| 20–38 weeks | 193 (31) |
| NYHA functional class | |
| I–II | 596 (96) |
| III | 21 (4) |
| Prior heart failure, transient ischemic attack, or stroke | 24 (4) |
| Cardiac medications | |
| None | 550 (89) |
| Diuretic | 6 (1) |
| Antiarrhythmic or β-adrenergic antagonists | 40 (6) |
| Digoxin | 21 (3) |
| Receiving anticoagulants | 21 (3) |
| Diabetes or hypertension | 22 (4) |
| Central cyanosis | 5 (1) |

# Results

Follow-up was completed for all patients in March 2000. Twenty-three women (24 pregnancies) who underwent terminations were excluded from enrollment; 10 terminations were performed for cardiac indications (symptomatic valvular obstruction or regurgitation [n=7], severe left ventricular dysfunction [n=1], aortic dissection [n=1], and pulmonary hypertension [n=1]). Nine women who refused enrollment were also excluded.

Baseline characteristics of all pregnancies are shown in Table 1. In 21 pregnancies, the mother was in NYHA class III at the baseline visit (valvular stenosis [n=8], cardiomyopathy [n=7], ischemic heart disease [n=3], congenital heart disease [n=2], and severe pulmonary hypertension from systemic lupus erythematosus [n=1]). In 5 pregnancies, the mother was cyanotic due to either unrepaired congenital heart disease (n=4) or severe mitral stenosis and pulmonary hypertension (n=1); in these 5 pregnancies, baseline oxygen saturation ranged from 70% to 88%. There were no differences in baseline characteristics between the 18 pregnancies that ended in miscarriage and those that did not.

A total of 546 women underwent 599 completed (>20 weeks gestation) pregnancies. The principal cardiac lesion was congenital in 445 pregnancies (74%), acquired in 127 pregnancies (22%), and arrhythmic in 27 pregnancies (4%; Table 2). Multiple congenital lesions were present in 121 pregnancies. In 30 pregnancies, both congenital and acquired

**TABLE 2. Principal Cardiac Lesions, Prenatal Characteristics, and Complications in Completed Pregnancies**

| | Pregnancies, n | | | Pregnancies With Events, n | | |
|---|---|---|---|---|---|---|
| | Total | Cardiac History | Obstruction/ Low EF | Primary Cardiac* | NYD/ Procedures | Neonatal |
| Congenital acyanotic | | | | | | |
| Shunts | | | | | | |
| Unrepaired | 76 | SVT, 5; VT, 1; CVA, 1 | 2/3 | 5 (CHF, 3; SVT, 2; VT, 1) | 2/0 | 7 |
| Repaired | 66 | SVT, 2 | 1/1 | CHF, 1; SVT, 1 | ... | 10 |
| Coarctation | | | | | | |
| Unrepaired | 8 | ... | 1/0 | ... | ... | 2 |
| Repaired | 43 | CHF, 3 | 10/0 | CHF, 2 | 2/0 | 5 |
| AS/BAV | | | | | | |
| Unrepaired | 57 | CHF, 1; CVA, 1; brady, 1 | 31/0 | CHF, 4; SVT, 1 | 4/2 | 15 |
| Repaired | 16 | ... | 6/0 | VT, 1 | 0/1 | 2 |
| Pulmonary stenosis | | | | | | |
| Unrepaired | 35 | ... | ... | ... | ... | 3 |
| Repaired | 23 | CVA, 1; brady, 1 | ... | ... | 1/0 | 7 |
| Marfan syndrome | 10 | ... | ... | ... | ... | 5 |
| Tetralogy/DORV (repaired) | 53 | SVT, 3; VT, 3 | ... | ... | 2/0 | 11 |
| D-transposition (Repaired) | 25 | CVA and SVT, 1; SVT, 3; brady, 2 | 0/12 | 6 (CHF, 3; SVT, 4; CVA, 1; death, 1) | 1/0 | 3 |
| L-transposition (Unrepaired) | 6 | SVT, 3; brady, 2 | 1/5 | CHF, 2; SVT, 1; brady, 1 | 0/2 | 0 |
| Ebstein anomaly | | | | | | |
| Unrepaired | 9 | SVT, 3 | ... | 2 (CHF, 1; SVT, 2) | ... | 2 |
| Repaired | 3 | SVT, 2 | ... | SVT, 1 | ... | 2 |
| Univentricular connection (repaired) | 5 | CHF, 1 | 0/2 | SVT, 2 | 2/0 | 4 |
| Other† | | | | | | |
| Unrepaired | 3 | ... | ... | CHF, 1 | 1/0 | 0 |
| Repaired | 3 | ... | ... | ... | ... | 1 |
| Congenital cyanotic | 4 | ... | ... | ... | ... | 2 |
| Acquired valvular | | | | | | |
| Unrepaired | 64 | CHF, 5; CVA, 2; SVT, 1; VT, 1; brady, 1 | 36/0 | 14 (CHF, 12; SVT, 3; VT, 1; CVA, 1) | 7/4 | 15 |
| Repaired | 17 | CHF and SVT, 1; CHF, 1; SVT, 3 | 10/0 | 6 (CHF, 4; SVT, 2; CVA, 1) | 3/1 | 7 |
| Cardiomyopathy | | | | | | |
| Dilated | 23 | CHF, 4; CVA, 1; SVT, 3; VT, 1 | 0/13 | 12 (CHF, 7; SVT, 4; CVA, 1; death, 1) | 1/0 | 7 |
| Hypertrophic | 9 | ... | 4/0 | VT, 1 | 0/1 | 3 |
| Ischemic | 11 | ... | 0/2 | CHF, 2 | 0/1 | 3 |
| Pulmonary hypertension‡ | 3 | ... | ... | Death, 1 | ... | 1 |
| Arrhythmias | | | | | | |
| SVT | 14 | SVT, 14 | ... | SVT, 10 | ... | 2 |
| VT | 7 | VT, 7 | ... | VT, 2 | ... | 2 |
| Sick sinus syndrome | 6 | brady, 6 | ... | Brady, 1 | 0/1 | 1 |

Values are No. of pregnancies. AS/BAV indicates congenital aortic stenosis or bicuspid aortic valve; brady, bradycardia; CHF, pulmonary edema; CVA, stroke or transient ischemic attack; DORV, double-outlet right ventricle; Low EF, systemic ventricular ejection fraction <0.40; Obstruction, left heart obstruction; NYD, deterioration in functional class; procedure, urgent invasive cardiac procedure; SVT, supraventricular tachycardia or atrial flutter/fibrillation; and VT, ventricular tachycardia.

*Not mutually exclusive.

†Endocardial fibroelastosis (n=1), dextrocardia with situs inversus (n=2), repaired anomalous origin of left coronary artery from pulmonary artery (n=2), repaired truncus arteriosus (n=1).

‡From primary cause (including 1 patient after heart-lung transplant) or from systemic lupus.

cardiac lesions were present. The cardiac lesion was known before pregnancy in all but 20 pregnancies in which the diagnosis was made prenatally (shunts [n=6], dilated cardiomyopathy [n=6], valvular obstruction [n=6], hypertrophic cardiomyopathy [n=1], and pulmonary hypertension from systemic lupus erythematosus [n=1]).

In 277 pregnancies (46%), the mother had undergone ≥1 surgical intervention before conception; these interventions included closure of shunts (n=121), coarctation repair (n=44), tetralogy of Fallot or double-outlet right ventricle repair (n=53), Mustard repair (n=21), arterial switch (n=1), Rastelli repair (n=4), Fontan repair (n=5), valve repair (n=67) or replacement (mechanical, n=11; tissue, n=33; and pulmonary autograft, n=5), reimplantation of left coronary artery (n=2), resection of subaortic stenosis (n=3), heart-lung transplantation (n=1), and aortocoronary bypass (n=1).

Of the 102 pregnancies that occurred in mothers with left heart obstruction, 48 were in women with mitral stenosis (valve area, 1.3±0.3 $cm^2$; range, 0.8 to 1.9 $cm^2$) and 58 in those with aortic stenosis (valve area, 0.9±0.2 $cm^2$; range, 0.5 to 1.4 $cm^2$; left ventricular outflow tract gradient, 59±24 mm Hg; range, 23 to 150 mm Hg). In 4 pregnancies, the mother had aortic and mitral stenosis. Of the pregnancies in patients with aortic stenosis, 47 had valvular involvement, 7 had subaortic membranes, and 4 had hypertrophic cardiomyopathy. There were 10 pregnancies in patients with Marfan syndrome; 3 of these women had an aortic root diameter >40 mm. There were 52 pregnancies in patients with coarctation of the aorta, of whom 9 had narrowing of the descending aorta (peak Doppler gradients ranged from 50 to 80 mm Hg); the remainder had no or only mild residual narrowing.

Pulmonary hypertension (systolic pulmonary artery pressure >50 mm Hg) was present in 25 completed pregnancies (4%) and was primary (n=1) or the result of congenital heart disease (n=8), rheumatic heart disease (n=13), dilated cardiomyopathy (n=2), or systemic lupus erythematosus (n=1). The systolic pulmonary artery pressure in this group was 65±15 mm Hg (range, 51 to 105 mm Hg). There were no patients with Eisenmenger syndrome.

Echocardiography was not performed in 2 patients. Because their clinical assessments and electrocardiograms were normal, they were assumed to have a normal echocardiogram.

The mother was receiving cardiac medications, aspirin, or anticoagulants at the baseline evaluation in 101 pregnancies (17%). All medications except angiotensin-converting enzyme inhibitors were continued during pregnancies. In the 11 pregnancies in which the mother had a mechanical heart valve, warfarin was replaced by either subcutaneous unfractionated heparin or low-molecular-weight heparin in all except 2 pregnancies. β-Adrenergic antagonists were administered in all but 2 pregnancies in patients with Marfan syndrome (1 patient refused and it was contraindicated in the other).

In 87 pregnancies, additional medications were initiated during the prepartum period to control heart rate/blood pressure (n=28), to control symptoms (n=23), or after a cardiac complication (n=36). These medications included β-adrenergic antagonists (n=52), digoxin (n=32), furosemide (n=27), subcutaneous unfractionated heparin or low-molecular-weight heparin (n=9), amiodarone (n=4), and vasodilators (n=4); women could receive more than one medication. Before delivery, the mother was receiving cardiac medications, aspirin, or anticoagulants in 167 pregnancies (28%).

The live birth rate was 98%; 164 deliveries (27%) were by Caesarean section. Most Caesarean deliveries (96%) were for obstetric indications; maternal cardiac status was the indication in 4%.

## Cardiac Events and Prediction Rule

A primary cardiac event occurred in 80 completed pregnancies (13%); 55% occurred in the prepartum period. Pulmonary edema and/or cardiac arrhythmia accounted for most of the cardiac events (Table 2). Pulmonary edema was documented by chest radiography in all but 3 episodes; in these 3 episodes, the diagnosis was established by the clinical findings of acute respiratory distress in the early postpartum period with bilateral pulmonary crackles. In 4 pregnancies, pulmonary edema occurred in association with cardiac arrhythmia. Eight of the 42 pregnancies (19%) complicated by pulmonary edema occurred in women with baseline NYHA class III. Episodes of pulmonary edema and tachyarrhythmia initially responded to medical treatment; electrical cardioversion was performed in 2 patients. Anticoagulation was initiated in patients with atrial flutter/fibrillation if they had valvular disease, systemic ventricular systolic dysfunction, or complex congenital heart disease.

Embolic strokes occurred during 4 pregnancies in association with dilated cardiomyopathy, mechanical valve replacement with suboptimal anticoagulation, mitral stenosis, and transposition of the great arteries (after Mustard procedure) with severe systemic ventricular systolic dysfunction (n=1 for each). The woman with a Mustard procedure later died of postpartum heart failure. The other postpartum cardiac deaths were sudden and occurred in 1 mother with dilated cardiomyopathy and 1 with severe pulmonary hypertension from systemic lupus erythematosus. Maternal stroke or cardiac death complicated 6 pregnancies (1%).

The 4 predictors of primary cardiac events were as follows (Table 3): prior cardiac event (heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia; baseline NYHA class >II or cyanosis; left heart obstruction (mitral valve area <2 $cm^2$, aortic valve area <1.5 $cm^2$, or peak left ventricular outflow tract gradient >30 mm Hg by echocardiography); and reduced systemic ventricular systolic function (ejection fraction <40%). The results of GEE analyses were identical; repeated pregnancies within the same mother were statistically independent. When only the first pregnancy was used in the analysis or when the 2 patients with no echocardiographic data were excluded, the results were unchanged. There was no association between prepartum cardiac events and the administration of cardiac medications/aspirin/anticoagulants, either continued from baseline or initiated for blood pressure/heart rate control (event rate, 10% versus 7%, $P=0.19$, for those with versus without medications). There was no association between the type of delivery

**TABLE 3. Multivariate Analyses**

| Complications | Predictor | Odds Ratio (95% Confidence Interval) | *P* |
|---|---|---|---|
| Cardiac | Prior cardiac event or arrhythmia | 6 (3–14) | <0.001 |
| | NYHA functional class >II or cyanosis | 6 (2–22) | 0.009 |
| | Left heart obstruction | 6 (3–14) | <0.001 |
| | Systemic ventricular dysfunction | 11 (4–34) | <0.001 |
| Neonatal | NYHA functional class >II or cyanosis | 3 (1.1–6.1) | 0.035 |
| | Heparin/warfarin during pregnancy | 3 (1.4–8.2) | 0.0093 |
| | Smoking | 2 (1.3–3.9) | 0.0045 |
| | Multiple gestation | 22 (6–85) | <0.001 |
| | Left heart obstruction | 2 (1.01–2.9) | 0.044 |
| Pregnancy-induced hypertension | Nulliparity | 5 (2–17) | 0.012 |
| | Systemic lupus erythematosus | 24 (5–108) | <0.001 |
| | Coarctation of the aorta | 3 (2–10) | 0.027 |
| Postpartum hemorrhage | Peripartum heparin or warfarin | 7 (2–22) | 0.001 |
| | Cyanosis | 27 (4–177) | <0.001 |

and peripartum cardiac event rate (3% versus 4%, $P=0.46$, for vaginal versus Caesarean delivery).

Predictors of primary cardiac events were incorporated into a revised risk index in which each pregnancy was assigned 1 point for each predictor when present. No pregnancy received >3 points. The estimated risk of a cardiac event in pregnancies with 0, 1, and >1 points was 5%, 27%, and 75%, respectively. Importantly, all 3 cardiac deaths (1%) occurred in pregnancies with a risk score ≥1. For the revised risk index, there was excellent agreement between the expected and observed rate of events (Table 4 and Figure). The discriminative accuracy of the original risk index (5 predictors) and revised risk index (4 predictors) was identical (Table 4). Secondary analysis using the entire data set did not identify additional predictors. When criteria for severe mitral (valve area <1 $cm^2$) or aortic (valve area <1 $cm^2$ or peak gradient >64 mm Hg) stenoses were evaluated, the resulting model had lower discriminative accuracy.

A secondary cardiac event occurred in 37 pregnancies (6%; Table 2). Worsening of NYHA class by >2 classes occurred in 26 of the 579 pregnancies in which the baseline NYHA class was I or II. Thirteen patients required urgent invasive cardiac procedures (permanent pacing [n=6], percutaneous mitral valvuloplasty in the prepartum period [n=2], or postpartum aortic valve replacement or aortocoronary bypass surgery [n=5]). A primary or secondary cardiac event or both occurred in 99 pregnancies (17%). The 4 predictors of primary cardiac events were also predictive of the combined likelihood of either a primary or secondary cardiac event (Table 4).

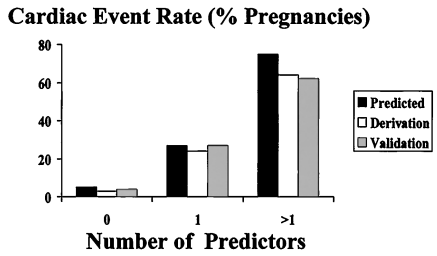
## Neonatal and Obstetric Events

A neonatal event occurred in 122 pregnancies (20%); premature birth (105 pregnancies) and small-for-gestational-age birthweight (22 pregnancies) were the most common events. A total of 62 premature births were due to preterm labor. Seventeen premature births were complicated by respiratory distress syndrome or intraventricular hemorrhage. Fetal and neonatal death complicated 8 and 7 pregnancies, respectively (1% for both). Respiratory distress syndrome, intraventricular hemorrhage, and fetal or neonatal death occurred in 29 pregnancies (5%). In the 6 pregnancies in which the mother received warfarin during all (n=2) or part of pregnancy (n=4; administered before 6 weeks gestation), embryopathy was not observed in this small series. In the 432 live births in mothers with congenital heart disease who did not have a recognized genetic syndrome, the recurrence rate of congenital heart disease was 7%.

**TABLE 4. Accuracy of Risk Index**

| | | Rate of Primary Cardiac Events | | | Rate of Primary or Secondary Cardiac Events, Revised Index | |
|---|---|---|---|---|---|---|
| | | | Validation Group | | | |
| No. of Predictors | Estimated Risk, % | Derivation Group, Revised Index | Revised Index | Original Index | Derivation Group | Validation Group |
| 0 | 5 | 7/249 (3%) | 5/137 (4%) | 5/136 (4%) | 10/249 (4%) | 6/137 (4%) |
| 1 | 27 | 27/111 (24%) | 17/64 (27%) | 16/61 (26%) | 35/111 (31%) | 20/64 (31%) |
| >1 | 75 | 16/25 (64%) | 8/13 (62%) | 9/17 (53%) | 17/25 (68%) | 9/13 (69%) |
| C statistic (95% CI) | | 0.83 (0.77–0.89) | 0.80 (0.72–0.88) | 0.79 (0.71–0.87) | 0.82 (0.76–0.88) | 0.81 (0.74–0.88) |

CI indicates confidence interval.




Frequency of maternal primary cardiac events, as predicted by the risk index and observed in the derivation and validation groups, expressed as a function of the number of cardiac predictors or points.

The 5 predictors of neonatal events were as follows: NYHA class >II or cyanosis during the baseline prenatal visit, maternal left heart obstruction, smoking during pregnancy, multiple gestations, and use of anticoagulants throughout pregnancy (Table 3). If none of the above predictors was present, the fetal or neonatal death rate was 2%; the fetal or neonatal death rate was 4% if at least 1 predictor was present. The results of GEE analyses were identical. Analyses examining only the first pregnancy of each woman showed similar results, except that left heart obstruction had borderline significance ($P=0.05$).

A primary cardiac or neonatal event complicated 170 pregnancies (28%). The frequency of a primary cardiac or neonatal event corresponding to the absence and presence of any cardiac or neonatal risk factors was 14% and 45%, respectively. Maternal, fetal, or neonatal death occurred in 18 pregnancies (3%). The maternal, fetal, or neonatal mortality rate corresponding to the absence and presence of any of cardiac or neonatal risk factors was 2% and 5%, respectively.

PIH complicated 24 pregnancies (4%). Furthermore, in 13 pregnancies, the mothers' blood pressure was ≥140/90 mm Hg after 20 weeks gestation. PIH progressed to preeclampsia in 12 pregnancies. Nulliparity, aortic coarctation, and systemic lupus erythematosus were independent predictors of PIH. PPH complicated 19 pregnancies (3%). Use of anticoagulants in the peripartum period (used in the late prepartum period and resumed after delivery), and cyanosis were independent predictors of PPH (Table 3). GEE analyses of PIH and PPH yielded identical results. When repeated pregnancies were excluded, the results were similar to GEE except that coarctation was not predictive of PIH ($P=0.06$).

There were 2 noncardiac deaths (postpartum depression and suicide in 1 patient with an atrial septal defect and amniotic fluid embolus in another patient with a repaired atrial septal defect).

## Discussion

Our study provides a contemporary assessment of maternal and neonatal risk associated with pregnancy in women with heart disease who are receiving comprehensive prenatal care. The cardiac event rate in the present study (13%) is lower than that reported in a recent retrospective study (18%).[9] In the present study, patients referred for consultation only (likely a lower risk group) were eligible for enrollment; they were excluded in the retrospective study. Therefore, the present study population may be more representative of the total population at risk. The fetal/neonatal mortality rate (2%) and rate of preterm labor (10%) was higher than that reported in a Canadian study examining outcomes in a general obstetric population (0.3% and 4%, respectively),[17] whereas the frequency of PIH in the present study (4%) was identical.

Poor NYHA class, cyanosis, myocardial dysfunction, prior arrhythmia, and prior heart failure/stroke have been previously identified as risk factors for maternal cardiac events.[1–3,9] The present study extends the results of previous studies by quantifying these risks prospectively in a large patient group recruited across Canada. The revised risk index is simpler than the original[9] but has identical accuracy. Furthermore, it can be applied to a composite outcome that includes decline in functional class or need for urgent invasive cardiac intervention, in addition to the primary cardiac end points.

Poor NYHA class or cyanosis was predictive of neonatal events in prior studies and in the present study.[2,9] The predictive role of maternal left heart obstruction on neonatal outcome identified in this study may be mediated by inadequate placental perfusion, which then results in fetal growth retardation or premature labor. Concerns about maternal deterioration may have also led to preterm induction. Coarctation of the aorta was a predictor for PIH, reflecting abnormal response in the aorta in these patients.[18] Nulliparity and systemic lupus erythematosus have also been reported to be risk factors for PIH in the general obstetric population.[19] The association between cyanosis and PPH is likely related to the known hemostatic defects in patients with cyanotic heart disease.[20]

Pulmonary hypertension in the absence of Eisenmenger syndrome was not an independent predictor, probably because of its association with other predictors such as poor functional status or left heart obstruction. Whether reactive pulmonary hypertension resulting from mitral stenosis confers a lower mortality risk than that resulting from fixed pulmonary vascular disease remains to be determined.

In conditions with known lesion-specific risks, such as Marfan syndrome, this index will supplement lesion-specific predictors.[21] The risk associated with cardiac lesions, which were not well represented in this study (such as Fontan procedure or hypertrophic cardiomyopathy), may have been underestimated. Until additional data are available, clinical management of patients with such conditions should be based on an assumption of intermediate risk.

The strategy of combining cardiac lesions and deriving a common risk index is similar to that used in the risk stratification of patients undergoing noncardiac surgery.[22] In our study, the cohort was defined by its exposure to the cardiovascular changes of pregnancy. This strategy also allowed for the analysis of multiple cardiac lesions within the same woman. Predictors (NYHA class and ventricular function) identified in our study have also been cited as prognostic factors in lesion-specific studies.[6–8]

The selection bias associated with patient recruitment from regional centers was minimized by the fact that these centers received referrals from wide catchment areas. Because the Canadian health care system provides universal access, we expect that only patients at negligible risk would not be

referred to a regional center. Although treatment strategies were not standardized in this study, regional variation was minimized by the fact that the participating centers (part of the Canadian Adult Congenital Heart Network) used common practice guidelines.[23]

In women at high risk for cardiac events, cardiac interventions should be considered before conception if the risk-benefit ratio is favorable. Women at intermediate or high cardiac risk (risk score ≥1 or with lesion-specific risk factors) should be referred to a regional center for ongoing care. Those at low cardiac risk (risk score of 0 and without lesion-specific risk factors) can safely deliver in a community hospital. Women with risk factors for maternal cardiac or neonatal complications may require increased frequency of follow-up.

## Appendix

### Additional Investigators and Their Locations

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