Paediatrics Publications   Paediatrics Department

11-1-2015

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Maternal Cardiac Output and Fetal Doppler Predict Adverse Neonatal Outcomes in Pregnant Women With Heart Disease

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Background—The mechanistic basis of the proposed relationship between maternal cardiac output and neonatal complications in pregnant women with heart disease has not been well elucidated.

Methods and Results—Pregnant women with cardiac disease and healthy pregnant women (controls) were prospectively followed with maternal echocardiography and obstetrical ultrasound scans at baseline, third trimester, and postpartum. Fetal/neonatal complications (death, small-for-gestational-age or low birthweight, prematurity, respiratory distress syndrome, or intraventricular hemorrhage) comprised the primary study outcome. One hundred and twenty-seven women with cardiac disease and 45 healthy controls were enrolled. Neonatal events occurred in 28 pregnancies and were more frequent in the heart disease group as compared with controls (n=26/127 or 21% versus n=2/45 or 4%; $P=0.01$). Multiple complications in an infant were counted as a single outcome event. Neonatal complications in the heart disease group were small-for-gestational-age/low birthweight (n=18), prematurity (n=14), and intraventricular hemorrhage/respiratory distress syndrome (n=5). Preexisting obstetric risk factors ($P=0.003$), maternal cardiac output decline from baseline to third trimester ($P=0.017$), and third trimester umbilical artery Doppler abnormalities ($P<0.001$) independently predicted neonatal complications and were incorporated into a novel risk index in which 0, 1, and >1 predictor corresponded to expected complication rates of 5%, 30%, and 76%, respectively.

Conclusions—Decline in maternal cardiac output during pregnancy and abnormal umbilical artery Doppler flows independently predict neonatal complications. These findings will enhance the identification of higher risk pregnancies that would benefit from close antenatal surveillance. (*J Am Heart Assoc*. 2015;4:e002414 doi: 10.1161/JAHA.115.002414)

Key Words: cardiac output • heart diseases • pregnancy

Increasing numbers of women with heart disease are reaching reproductive age, attributable in large part to advances in diagnosis and treatment in early life.[1,2] In contemplating pregnancy, women with heart disease seek information not only regarding maternal, but also regarding neonatal outcomes of pregnancy. We and others have demonstrated that pregnant women with heart disease carry an increased risk of adverse maternal and neonatal outcomes. Specifically, poor functional class and left heart obstructive disease in the mother have been identified as independent predictors of neonatal compromise.[3–6]

It has been postulated that a major mechanistic link relating maternal heart disease with complications in the fetus or neonate is uteroplacental insufficiency due to inadequate maternal cardiac output.[6–9] More than 40 years ago, Ueland and colleagues measured cardiac output in a small group of women with valvular heart disease who underwent cardiac catheterization at various points during and after pregnancy.[9] Although they examined a group that was likely highly selected and antepartum data collection was incomplete, their study suggested that insufficient incremental increase in maternal cardiac output occurs in pregnant women with valvular heart disease. In contrast, a small study evaluating cardiac output using echocardiography in 29 pregnant women with congenital heart disease found that there was no statistically significant difference in cardiac output in women with hypertension and/or small-for-gestational-age offspring.[10] A systematic examination of cardiac output and its relationship to pregnancy outcomes in a sizable population of

women with a spectrum of heart disease has not been performed. Nevertheless, indirect evidence suggests that a relationship may exist between impaired maternal cardiac output and offspring outcomes in women with cardiac disease. In women with structurally normal hearts, lower maternal cardiac output, determined echocardiographically, has been associated with intrauterine growth restriction.[11] Some pregnant women with obstructive left heart disease do not display the increase in transvalvular gradients on echocardiography that would be expected with advancement of pregnancy if anticipated augmentation of cardiac output by 30% to 50% were actually occurring in those women.[12,13] Furthermore, there is an established association between cardiac conditions that limit cardiac output including severe left heart valvular stenosis and cardiomyopathy, and increased frequency of neonatal complications.[7,14,15]

Although maternal cardiac hemodynamics have not been adequately characterized in pregnant women with heart disease, uteroplacental Doppler flow patterns have recently been described in women with congenital heart disease. Pieper and Balci and colleagues reported abnormal umbilical artery and uterine artery Doppler waveforms in women with congenital heart disease, as well as its association with complications in offspring.[16] While direct measurements of maternal cardiac output were not provided, they reported that markers of impaired ventricular function and cardiovascular adaptation were associated with abnormal umbilical artery indices.[16] These observations extend previous findings that neonatal event rates in women with cardiovascular risk factors for such events are highest in those women who also have preexisting obstetric (noncardiac) risk factors.[4]

To address current deficiencies in knowledge, specifically the relationship between maternal cardiac output, uteroplacental flow characteristics, and pregnancy outcomes, we prospectively and serially characterized maternal cardiac output and Doppler flow patterns at umbilical and uterine arteries in pregnant women with heart disease. We hypothesized that insufficient maternal cardiac output and fetal flow abnormalities would be predictive of complications in offspring.

Methods

Study Design and Patient Population

This prospective study enrolled women with heart disease referred to Mount Sinai Hospital in Toronto, Ontario, Canada for obstetric care. Heart disease was defined as the presence of structural cardiac abnormalities (excluding mitral valve prolapse with ≤mild regurgitation) and/or symptomatic cardiac arrhythmia requiring treatment prior to pregnancy. We excluded women who presented after 22 weeks gestation

because their relatively late stage in pregnancy would preclude establishment of cardiac output prior to peak changes in cardiac output that are anticipated early in the third trimester.[9] We also excluded women transferred for inpatient care, those referred for termination of pregnancy, and those unwilling/unable to give informed consent.

A concurrent control group of women without heart disease was recruited from the general obstetric program at the same hospital, which is co-located with the maternal cardiac clinic and in which the same obstetricians provided care for both the study and the control cohorts, in order to ensure consistency in clinical practice and data collection among all women. Control women were included if they presented for obstetric care prior to 22 weeks gestation and were deemed "low risk" (ie, absence of identifiable obstetric risk factors or medical conditions). We applied the same exclusion criteria as for the study group. If a woman recruited into the control group was found to have structural heart disease or another significant medical condition, or if a fetal abnormality was identified on obstetrical ultrasound, she was withdrawn from the study and was referred for medical care as appropriate. This study protocol received institutional research ethics approval and all subjects gave informed written consent.

Demographic and obstetric data collected in both heart disease and control groups included the following: age, baseline weight, height, gestational age, parity status, maternal smoking and/or alcohol consumption, and the presence of obstetric risk factors for complications in offspring (history of premature delivery or rupture of membranes, incompetent cervix, cesarean section, antepartum bleeding >12 weeks gestation, febrile illness, and/or uteroplacental abnormalities).[4] In the heart disease group, the following data were also recorded: type of cardiac lesion, past history of stroke, heart failure, or arrhythmia, prior cardiac surgery or interventions, baseline New York Heart Association (NYHA) functional class, and nature of cardiovascular medications and cyanosis (oxygen saturation <90%). Comorbid conditions (ie, pulmonary disease, thyroid dysfunction, hypertension, diabetes mellitus, and/or systemic lupus erythematosus)[6] were documented if present and were screened for with the same rigor in control and study patients.

Maternal Echocardiography

All subjects underwent echocardiographic studies at 3 defined time points using an iE33 echocardiography machine (Philips Medical Systems, Bothell, WA): (1) a baseline study ≤26 weeks gestation (prior to expected peak augmentation of cardiac output), (2) a third-trimester study ≥27 weeks gestation (corresponding to the anticipated peak in cardiac output), and (3) a postpartum study at least 6 weeks following

delivery (at which point the majority of the hemodynamic changes related to pregnancy are anticipated to have returned to baseline).[17] Ventricular and valvular function were evaluated according to standardized guidelines.[18–20] A single dedicated cardiac research sonographer (CSL) blinded to patient characteristics and study order performed off-line echocardiographic analysis. To calculate stroke volume and cardiac output, pulse wave Doppler imaging with the highest left ventricular outflow tract (LVOT) velocity from either the apical or suprasternal views was recorded and LVOT diameter was measured from the parasternal long axis view during systole.[21] If LVOT pulse wave Doppler was not feasible due to elevated subaortic velocities (present in 12 patients with valvular aortic stenosis and/or LVOT obstruction related to hypertrophic cardiomyopathy), then the pulse wave Doppler profile was recorded at the pulmonary valve and pulmonary annulus diameter was measured from the parasternal short axis view. For each measured parameter, 5 consecutive cardiac cycles were recorded (10 consecutive cardiac cycles in the presence of atrial fibrillation or frequent ectopics). The same observer remeasured cardiac output in a random sample of 12 studies to establish intraobserver variability, which was defined as the percentage error between paired measurements (percentage error=[SD between 2 measurements$\times$100%]/[mean of the 2 measurements])[22]; a decrease in cardiac output was therefore considered significant if values exceeded established intraobserver measurement variability (percentage error was 9% and 23% for the aortic and pulmonary valve cardiac output, respectively).

Significant left heart obstructive disease was defined as mitral valve area <2.0 cm^2, aortic valve area <1.5 cm^2, or peak LVOT gradient >30 mm Hg in the case of subaortic stenosis, as previously described.[6] Significant pulmonary stenosis was defined as a maximum instantaneous gradient >3 m/s and significant tricuspid stenosis as a mean gradient >5 mm Hg.[20] Moderate or severe valvular regurgitation was considered significant.[19] Systemic ventricular ejection fraction was calculated using biplane method of disks for morphologic left ventricles and was estimated visually for morphologic right ventricles; ejection fraction$<40\%$ was considered significant systolic dysfunction.[6,18,23]

Fetal and Uteroplacental Ultrasonography

Fetal ultrasound imaging was performed by certified obstetrical sonographers on 2 occasions during the antepartum period (early, ≤26 weeks gestation and late, ≥27 weeks gestation) using an iU22 ultrasound system (Philips Medical Systems). On all ultrasound studies, pulsed Doppler profiles of the free loop of the umbilical arteries and the proximal uterine arteries were obtained and pulsatility index was calculated [PI]; for the uterine artery waveforms, the presence or absence of early diastolic notching was also recorded.[24,25] Umbilical artery recordings were performed in the absence of fetal breathing or fetal movements according to accepted standards of practice.[26] The proximal uterine arteries were located at their crossover point with the external iliac arteries, using color flow mapping. Doppler waveforms were analyzed from 3 consecutive beats and care was taken to ensure that the angle of insonation did not exceed $30°$. Details of the protocol employed at our institution for obstetric flow analyses have been previously published.[27]

Outcome Events

A study coordinator blinded to imaging results recorded and verified all clinical outcome events using delivery records, clinic charts, and hospital health records. The primary study outcome consisted of fetal or neonatal complications defined as low birth weight (small-for-gestational-age if birthweight was <10th percentile for gestational age or if absolute birthweight was <2500 g), premature delivery (delivery <37 weeks gestation), respiratory distress syndrome, intraventricular hemorrhage, fetal demise (death >20 weeks gestation), or neonatal death (death within 30 days of delivery). Cranial ultrasound scans for the diagnosis of intraventricular hemorrhage are routinely performed at our center on infants <1500 g at birth, on those with documented abnormalities on antenatal ultrasound scan, and on infants in whom neurologic abnormalities are identified after birth.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (Version 22.0; IBM Corp, Armonk, NY). Data were presented as means$\pm$SD or proportions; if data were not normally distributed, median values with ranges were provided. For non-normally distributed data, variance-stabilizing transformation was utilized prior to statistical testing. Two-tailed P values were calculated and level of significance was set at 0.05, unless otherwise specified.

Univariate analyses of potential predictors of the primary outcome in the heart disease group were performed using Student t, χ^2, and Fisher Exact tests, wherever appropriate. Candidate variables included baseline demographics (age, parity, obstetric risk factors), smoking history, comorbid conditions (thyroid, pulmonary, systemic lupus erythematosus, hypertension, or diabetes mellitus), cardiovascular complications prior to or during current pregnancy (stroke, transient ischemic attack, pulmonary edema/heart failure, sustained arrhythmia requiring treatment), NYHA functional class, nature of cardiac medications, echocardiographic indices of stenosis and/or regurgitation, any ventricular systolic dysfunction, maternal cardiac output, Doppler-derived

PI at the umbilical/uterine arteries as well as presence/ absence of bilateral notching, and changes in cardiac output between baseline and third trimester. Serial change in cardiac output during pregnancy was expressed in 2 ways: (1) Δ cardiac output over time (slope) was an expression of change in cardiac output (L) divided by the time interval between measurements (weeks) (ie, [cardiac output third trimester−cardiac output baseline]/number of intervening weeks), and (2) frequency (%) of pregnancies with a decline in cardiac output between baseline and third trimester. A decline in cardiac output was designated as a decrease in cardiac output that exceeded the observer variability as delineated by percentage error between the 2 measurements of cardiac output. Umbilical or uterine Doppler parameters were classified as abnormal, signifying increased vascular resistance, if the PI exceeded the 95% confidence limits for gestational age or if bilateral systolic notching of the Doppler spectrum was evident.[24,25]

Candidate variables with a level of significance $P<0.10$ on univariate analysis were entered into a multivariable logistic regression model examining the heart disease group. A stepwise backwards elimination algorithm was utilized and a significance level $P<0.05$ was chosen for inclusion in the multivariable model. After independent predictors were identified, these were then cross-validated in the heart disease group by bootstrapping (Stata version 8.2, College Station, TX) and were subsequently incorporated into a risk index using previously described methodology.[6] To calculate the expected event rates, we determined the odds of occurrence of a neonatal complication for each woman. This was calculated using the logistic regression model derived from our data. In our model, the beta coefficient for each predictor was rounded off in order to give equal weighting to each predictor. The odds were then converted into an expected risk of neonatal complications for each woman. The number of women in each risk category (0, 1, and >1 predictors) expected to have complications was then calculated. Discrimination (C-statistic) and calibration (Hosmer-Lemeshow goodness of fit) statistics were calculated. A multivariable linear regression analysis examining possible predictors of umbilical or uterine artery PI was also performed.

Results

Study Population

Consecutive women with heart disease were approached if eligibility criteria were met. A total of 127 women with heart disease and 45 healthy controls were enrolled and completed the study. During the study period, 309 pregnant women with heart disease were followed at our hospital, 171 were excluded because they did not meet inclusion criteria, 7

women chose not to participate, and 4 women were withdrawn from the study (fetal demise before 20 weeks gestation in 3 women and pregnancy termination due to trisomy 21 in 1 woman). Baseline demographic characteristics are summarized in Table 1. Cardiac conditions of the study population are listed in Table 2. According to the modified World Health Organization classification of maternal cardiac risk in pregnancy, 17 (13%), 71 (56%), 36 (28%), and 3 (2%) women were in modified World Health Organization categories I, II, III, and IV, respectively.[28] None of the women studied were cyanotic. Forty-three women (34%) had significant valvular stenosis or regurgitation. There were no women in this study with severe tricuspid stenosis or severe pulmonary stenosis.[20] In women with mixed valve disease, classification was based on the most hemodynamically relevant lesion. In total, 64% (n=81/127) had congenital disease as their primary lesion. In 57% (n=72/127), the mother had undergone prior intervention on the primary cardiac lesion, consisting of the following: closure of an intracardiac shunt (n=12), valve replacement or repair (n=31, of which 10 patients had a mechanical valve prosthesis inserted), repair of complex congenital lesion (n=21), ablation or implantable cardioverter defibrillator for ventricular tachycardia (n=3), pacemaker implantation (n=4), or coronary stenting (n=1). Significant left or right ventricular systolic dysfunction was present in 9 pregnancies (7% of heart disease group).

Cardiac and Obstetric Imaging

All subjects (n=172) underwent cardiac output determination at baseline (mean 13±4 weeks, range 6–25 weeks,

Table 1. Baseline Characteristics of Women With Heart Disease and Healthy Controls

	Heart Disease (n=127)	Controls (n=45)	P Value
Singleton pregnancies	124 (98%)	45 (100%)	0.57
Maternal age (mean±SD), y	30±5	34±5	<0.001
Maternal age (18–35 y)	108 (85%)	29 (64%)	0.003[‡]
Obstetric risk factors*	29 (23%)	13 (29%)	0.42
Nulliparous	64 (50%)	23 (51%)	0.93
Smoking	10 (8%)	0	0.065
Comorbidities[†]	18 (14%)	0	0.004
Body surface area, mean±SD	1.73±0.25	1.69±0.15	0.21
Hemoglobin, g/L	124±9	126±8	0.22

*History of previous premature delivery or rupture of membranes, incompetent cervix, cesarian delivery in a previous pregnancy; or presence of antepartum bleeding >12 weeks gestation, febrile illness, premature labor, or uterine/placental abnormalities during the current pregnancy.[4]
[†]Diabetes mellitus, hypertensive, thyroid disorders, pulmonary disorders, or systemic lupus erythematosus.[6]

Table 2. Antepartum Characteristics of Women With Heart Disease (n=127)

Primary Cardiac Lesion	n (%)	Prior Repair or Intervention	Prior Cardiac Events	Baseline NYHA ≥2	Significant AS, MS, or PS*	Significant AR, MR, PR or TR
Intracardiac shunts	17 (13)	12	4	3	2	3
Valvular	47 (37)					
Mitral/aortic	38	26	6	3	16	7
Pulmonic	9	5	1	1	—	2
Complex congenital	32 (25)					
TOF/DORV	17	17	2	—	1	7
Complete TGA or ccTGA†	10	4	1	—	1	4
Ebstein	5	—	2	—	—	4
Myocardial/coronary	20 (16)					
DCM/CAD, or HCM	20	1	10	3	2	—
Arrhythmia	11 (9)					
SVT or VT	7	3	7	—	—	—
Bradycardia	4	4	4	—	—	—

AR indicates aortic regurgitation; AS, aortic stenosis; ccTGA, congenitally corrected transposition of the great arteries (6 women); Complete TGA, complete or classic transposition of the great arteries (4 women); DCM/CAD, dilated cardiomyopathy or coronary artery disease (17 women); DORV, double outlet right ventricle; HCM, hypertrophic cardiomyopathy (3 women); MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PR, pulmonary regurgitation; PS, pulmonary stenosis; SVT, supraventricular tachycardia (4 women); TOF, tetralogy of Fallot; TR, tricuspid regurgitation; VT, ventricular tachycardia (3 women).
*Moderate pulmonary stenosis observed in 2 women, 1 post Ross procedure within the homograft and 1 post arterial switch procedure; there were no women with severe pulmonary or important tricuspid stenosis.
†Rastelli procedure in 2 women and Jatene procedure in 2 women (women had complete TGA).

interquartile range 11–15 weeks gestation), and again during the third trimester (mean 32±3 weeks, range 27–39 weeks, interquartile range 29–34 weeks gestation); postpartum echocardiography was completed in 145 women (84% of total) (mean 4±3 months, range 2–15 months, interquartile range 3–8 months following delivery). Twenty-seven women with heart disease did not return for postpartum echocardiography.

Baseline obstetric ultrasound data (mean 20±1 weeks gestation) were available in 160 women (12 women with heart disease unable to return during the specified time interval) and third trimester data (mean 32±1 weeks gestation) were available in 164 women (8 women with heart disease unable to return during specified time interval). Of these, 151 studies (94%) ≤26 weeks and 156 studies (95%) ≥27 weeks had complete data for umbilical and uterine artery analyses. Overall, of the women with heart disease, 111 (87%) had complete data sets for analysis; baseline characteristics, frequency of decline in cardiac output, and occurrence of neonatal complications were not statistically different in those with and without missing data.

Maternal Outcomes: Cardiovascular and Obstetric

Cardiovascular complications occurred in 18 women with heart disease (14%) but did not occur in any of the controls (*P*=0.004). These 18 women experienced 20 complications consisting of the following: sustained tachyarrhythmia (supraventricular n=9 and ventricular n=1), NYHA functional classification decline ≥2 classes or progression to NYHA class 4 disability (n=6), transient ischemic attack (n=2), myocardial infarction attributed to spontaneous right coronary artery dissection (n=1), and endocarditis (n=1). Two women had multiple cardiovascular events complicating the same pregnancy: 1 woman experienced a supraventricular tachyarrhythmia with concomitant worsening of NYHA class and a second woman had atrial flutter in addition to endocarditis. Sixteen of the 20 cardiovascular complications occurred in the antepartum period. Obstetric complications occurred in 15 women, consisting of gestational hypertension/preeclampsia in 9 women and premature rupture of membranes in 6 women; obstetric event rates were not statistically significant between women with heart disease (n=11, 9%) and controls (n=4, 9%). Frequency of gestational hypertension/preeclampsia was not statistically different in women with and without neonatal complications.

Fetal and Neonatal Outcomes

There were no fetal or neonatal deaths in this cohort. Neonatal complications occurred in 28 pregnancies (16%) and were more frequent in women with heart disease as
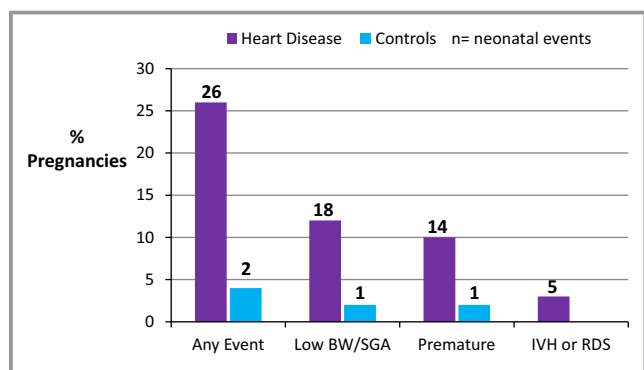
Figure 1. Neonatal complication rates in women with heart disease compared with healthy controls. Number of neonatal events (n) are shown. BW indicates birthweight; IVH, interventricular hemorrhage; RDS, respiratory distress syndrome; SGA, small-for-gestational-age birthweight.

compared with controls (n=26 or 21% versus n=2 or 4%, *P*=0.01) (Figure 1). Neonatal complications in women with heart disease were low birthweight/small-for-gestational-age (n=18), prematurity (n=14), and respiratory distress syndrome/intraventricular hemorrhage (n=5). Neonatal complications in control women were low birthweight (n=1) and prematurity (n=1). Multiple complications in a single infant were counted as a single outcome. The neonatal event rate in the 10 mothers with mechanical valves was 40% (n=4) compared with a neonatal event rate of 19% in the remainder of the heart disease group; this difference was not statistically significant (*P*=0.12). On univariate analysis, women in the heart disease group with neonatal complications were more likely to have obstetric risk factors, to have a multiple gestation, or to be on anticoagulation/antiplatelet medications (Table 3). All women with congenital cardiac disease underwent fetal echocardiography; 1 fetus was diagnosed with a ventricular septal defect antenatally and an additional 4 children were diagnosed with shunt lesions on pediatric echocardiography postnatally. Maternal cardiac World Health Organization classification was not associated with adverse neonatal outcomes (*P*=0.43).

Table 3. Characteristics of Heart Disease Group With and Without Neonatal Complications (n=127)

	Neonatal Complications (n=26)	No Neonatal Complications (n=101)	P Univariate	P Multivariable
Multiple gestation	3 (12%)	0	0.008*	—
Maternal age, y	30±5	30±5	0.92	—
Maternal age (18–35 y)	22 (85%)	86 (85%)	0.95	—
Obstetric risk factor[†]	11 (43%)	18 (18%)	0.008*	0.003
Nulliparity	16 (62%)	48 (48%)	0.20	—
Smoking	4 (15%)	6 (6%)	0.12	—
Comorbidity	4 (15%)	14 (14%)	0.76	—
Prior cardiovascular events[‡]	9 (35%)	28 (28%)	0.49	—
Baseline NYHA >1	4 (15%)	6 (6%)	0.12	—
Baseline cardiovascular meds	6 (23%)	16 (16%)	0.39	—
ASA/warfarin/heparin	8 (31%)	15 (15%)	0.06*	—
Valve dysfunction at baseline[§]	12 (46%)	34 (34%)	0.24	—
Stenosis (AS, MS, or PS)	7 (27%)	15 (15%)		
Regurgitation (any valve)	5 (19%)	22 (22%)		
Baseline LV or RVEF <40%	2 (8%)	7 (7%)	1.00	—
Antepartum cardiovascular event	5 (19%)	10 (10%)	0.19	—
Hemoglobin in 3rd trimester				
Absolute, g/L	118±10	118±12	0.69	
Frequency (%) <100 g/L	1 (4%)	7 (7%)	1.0	

AS indicates aortic stenosis; ASA, aspirin; EF, ejection fraction; LV, left ventricular; MS, mitral stenosis; NYHA, New York Heart Association; PS, pulmonary stenosis; RV, right ventricular.
*Univariate predictors entered into the multivariable model.
[†]History of previous premature delivery or rupture of membranes, incompetent cervix, cesarian delivery in a previous pregnancy; or antepartum bleeding >12 weeks gestation, febrile illness, premature labor, or uterine/placental abnormalities during the current pregnancy.[4]
[‡]Cardiovascular event defined as pulmonary edema, stroke, sustained arrhythmia, death, reduction in NYHA by >2 function classes, or class 4 NYHA symptoms.[6]
[§]Moderate or severe valve dysfunction.

Maternal Cardiac Output

There were significant within-group differences in cardiac output measured at baseline versus third trimester in both heart disease group (*P*<0.001) and controls (*P*=0.007). However, there were no statistically significant differences in maternal cardiac output between heart disease and control groups during or after pregnancy (baseline 5.3 versus 4.7 L/min, *P*=0.083; third trimester 5.8 versus 5.1 L/min, *P*=0.17; postpartum 4.6 versus 4.1 L/min, *P*=0.96); indexing cardiac output to body surface area at baseline assessment also did not reveal significant differences between women with heart disease and controls.

In the heart disease group, when absolute and indexed cardiac output measurements were compared between women with and without neonatal complications of pregnancy, no statistically significant differences were noted, as demonstrated in Table 4. However, when cardiac output measurements were expressed as a change over time, statistically significant differences in cardiac output were observed between those women with and without neonatal complications. Specifically, negative Δ cardiac output with progression of pregnancy was evident in those with eventual neonatal complications, in keeping with a decrease in cardiac output despite advancing gestation, as compared with positive or flat Δ cardiac output in those without neonatal complications, as shown in Table 4. Overall, a decline in cardiac output was observed in one third of women with neonatal complications. Change in heart rate was not significantly different in women with neonatal events as compared to those without (7±14 versus 9±9 bpm, *P*=0.22; change in stroke volume was of borderline statistical significance (−4.4±15.5 versus 2.3±14.7 mL/beat, *P*=0.053).

Uteroplacental Doppler Flow Patterns

Baseline Doppler flow abnormalities were present within the umbilical arteries in 7% (n=9/131) or uterine arteries in 13% (n=19/149) of pregnancies. A statistically significant decline in mean PI for uterine arteries (*P*=0.001) and umbilical arteries (*P*<0.001) was observed from baseline to third trimester in both heart disease and control groups. When comparing women with heart disease to controls, third trimester mean PI values were significantly different at the uterine artery (0.87±0.23 versus 0.79±0.19, *P*=0.038) but not at the umbilical artery (1.08±0.20 versus 1.02±017, *P*=0.14); baseline mean PI values did not differ significantly between the groups at either artery (uterine artery 1.06±0.30 versus 1.00±0.26, *P*=0.28; umbilical artery 1.37±0.20 versus 1.32±0.20, *P*=0.23).

However, when pregnancies in the heart disease group were grouped according to presence or absence of neonatal complications, umbilical artery flow abnormalities were more frequent in the third trimester in pregnancies where adverse events in offspring occurred, as detailed in Table 5. Independent predictors of third trimester umbilical artery PI were NYHA functional class ≥2 at baseline and Δ cardiac output with progression of pregnancy; ≥moderate aortic or mitral stenosis had borderline statistical significance (Table 6). As both umbilical PI and Δ cardiac output are continuous variables and inversely related, negative Δ cardiac output (ie, reduction in cardiac output with advancing pregnancy) corresponded to a higher (ie, more likely to be abnormal) umbilical artery PI.

Prediction Rule for Neonatal Complications

Univariate candidate predictor variables of neonatal complications in the heart disease group (shown in Tables 3 through

Table 4. CO in Heart Disease Group With and Without Neonatal Complications (n=127)

	Neonatal Complications (n=26)	No Neonatal Complications (n=101)	*P* Univariate	*P* Multivariable
CO: baseline, L/min	5.76±2.20	5.14±1.57	0.27	—
CO: 3rd trimester, L/min	5.74±2.40	5.84±1.79	0.65	—
CO: postpartum, L/min	4.68±2.29 (n=23)	4.51±1.31 (n=77)	0.66	—
CI: baseline, L/min per m^2	3.29±1.17	3.00±0.86	0.26	—
CI: 3rd trimester, L/min per m^2	3.28±1.26	3.42±1.05	0.50	—
CI: postpartum, L/min per m^2	2.71±1.23 (n=23)	2.62±0.69 (n=77)	0.45	—
Δ CO per unit time, L/week	−0.01±0.10	0.04±0.09	0.032*	0.037
Δ CO absolute, L	−0.03+1.59	0.69+1.42	0.048*	0.039
Decline in CO, n (%)	9 (35%)	17 (17%)	0.045*	0.017

CI indicates cardiac index; CO, cardiac output.

*Variables entered into multivariable model.

Table 5. Abnormal Uteroplacental Flow Patterns in the Heart Disease Group With and Without Neonatal Complications

Parameter	Timing of Study	Pregnancies With Neonatal Complications (%)[†]	Pregnancies Without Neonatal Complications (%)[†]	P Univariate	P Multivariate
Abnormal uterine artery flow*	≤26 weeks	4/23 (17%)	10/81 (12%)	0.51	—
	≥27 weeks	1/19 (5%)	8/81 (10%)	1	—
Abnormal umbilical artery flow*	≤26 weeks	3/19 (16%)	4/69 (6%)	0.17	—
	≥27 weeks	9/23 (39%)	8/88 (9%)	0.001[†]	<0.001

*Abnormal flow patterns in the umbilical and uterine arteries defined by presence of abnormal pulsatility index or bilateral notching on Doppler flow interrogation.
[†]Variables entered into multivariable model.

5) were entered into a multivariable logistic regression model. The following 3 factors were found to be independent predictors of neonatal complications: (1) any obstetric risk factor (odds ratio 6.2, 95% CI 1.8–21.3, $P=0.003$), (2) decline in cardiac output (odds ratio 4.3, 95% CI 1.3–14.6, $P=0.017$), and (3) abnormal third trimester umbilical artery Doppler (odds ratio 12.3, 95% CI 3.1–48.9, $P<0.001$). Exclusion of the 3 women with multiple gestation pregnancies did not result in a change to the aforementioned predictors of adverse neonatal outcomes (the odds ratio associated with the third trimester umbilical artery Doppler variable did increase, however, to 17.6 with multiple gestation pregnancies excluded). As Δ cardiac output (L/week) between baseline and third trimester correlated highly with decline in cardiac output, only one of these could be evaluated in the same model. However, when Δ cardiac output as a continuous variable, either as an absolute change or corrected for time interval between baseline and third trimester studies, was evaluated in the multivariable model in place of dichotomous decline in cardiac output, Δ cardiac output was also an

Table 6. Predictors of Abnormal Umbilical Artery Pulsatility Index in Heart Disease Group (≥27 Weeks Gestation)

Maternal Characteristic	Pregnancies With Characteristic		Pregnancies Without Characteristic		P* Univariate	P Multivariable
	n	Pulsatility Index (mean±SD)	n	Pulsatility Index (mean±SD)		
Multiple gestation	3	0.87±0.25	105	1.09±0.20	0.15	—
Maternal age (18–35 y)	89	1.09±0.21	19	1.04±0.16	0.29	—
Obstetric risk factor[4]	26	1.09±0.16	82	1.08±0.22	0.49	—
Nulliparity	52	1.11±0.24	56	1.05±0.16	0.094*	—
Smoker	8	1.08±0.18	100	1.08±0.21	0.98	—
Comorbidity	16	1.13±0.28	92	1.07±0.19	0.47	—
Prior cardiovascular events[6]	29	1.10±0.23	79	1.07±0.19	0.56	—
NYHA ≥2 at baseline	10	1.22±0.29	98	1.07±0.18	0.12*	0.03
Baseline cardiovascular medications	19	1.12±0.29	89	1.07±0.18	0.77	—
Antiplatelet/anticoagulant	22	1.11±0.24	86	1.07±0.19	0.68	—
≥Moderate AS or MS	13	1.17±0.28	95	1.06±0.19	0.12*	0.052
≥Moderate AR or MR	3	1.00±0.10	105	1.08±0.21	0.49	—
≥Moderate PR or TR	14	1.01±0.20	94	1.09±0.20	0.25	—
LV or RVEF <40%	8	1.04±0.22	100	1.08±0.19	0.37	—
Antepartum cardiovascular event[6]	12	1.09±0.28	96	1.08±0.19	0.25	—
Δ Cardiac output[†]					0.039*	0.008

AR indicates aortic regurgitation; AS, aortic stenosis; EF, ejection fraction; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation.
*Univariate predictors entered into the multivariable model.
[†]Pulsatility index=[−0.4×Δcardiac output]+1.1; SD of regression=0.21, $P=0.039$.

independent predictor of neonatal complications (Table 4). The 3 aforementioned binary predictors (presence of obstetrical risk factors, decline in cardiac output, and abnormal third trimester umbilical artery Doppler) were incorporated into a risk index to predict the likelihood of neonatal complications (Figure 2). Expected and observed event rates were as follows: 0 predictors 5% expected and 7% observed, 1 predictor 30% expected and 24% observed, and >1 predictor 76% expected and 80% observed. The discrimination and calibration statistics were 0.77 and $P=0.26$, respectively. The above 3 binary independent predictors were cross-validated using bootstrapping; the resultant odds ratios and discriminative statistics were similar to the original analysis. No statistically significant differences were found between mothers with and without a mechanical valve with respect to obstetric risk factors (40% versus 21%, $P=0.24$), decrease in cardiac output with progression of pregnancy (40% versus 19%, $P=0.12$), or frequency of abnormal umbilical artery Doppler waveforms in the third trimester (20% versus 15%, $P=0.65$).

Discussion

Through analysis of maternal and uteroplacental flow patterns at various stages of pregnancy, our study provides new insights into the mechanistic underpinnings that contribute to the development of adverse neonatal outcomes in pregnant women with underlying heart disease. Importantly, we demonstrated that inadequate augmentation of cardiac output during pregnancy and abnormalities in umbilical artery Doppler flow in the third trimester independently predicted

Figure 2. Observed adverse neonatal event rates following pregnancy. Independent predictors of adverse neonatal events (rates, %) are as follows: (1) any obstetrical risk factor, (2) decline in cardiac output during pregnancy, and (3) abnormal umbilical artery Doppler pattern in the third trimester. Ten women had >1 predictor, specifically: 1 woman had all 3 predictors, 5 women had reduction in cardiac output along with an obstetric risk factor, and 4 women had reduction in cardiac output in addition to an abnormal umbilical artery Doppler flow.

neonatal complications. Furthermore, this study highlights the utility of serial measurements of cardiac output to help differentiate those women at risk for neonatal complications from those who will have no major adverse events in offspring. This study is also the first to incorporate sequential cardiac output measurements and umbilical artery Doppler assessment into a risk index to stratify pregnant women with heart disease into those at low, medium, or high risk for neonatal complications.

Although inadequate cardiac output response has been implicated as the mechanism responsible for the relationship between poor maternal function class, left heart obstruction, and fetal/neonatal complications in the population of pregnant women with heart disease,[4,6,7] there have been no prior studies examining antepartum and postpartum cardiac output in this population. One of the key findings of our study is the demonstration that inadequate augmentation of cardiac output in pregnancies predicts neonatal complications, thereby defining one potential link in the pathophysiology of adverse outcomes in women with heart disease. Importantly, cardiac output paradoxically decreased from baseline to third trimester in one third of the group with neonatal complications, in contrast to the expected increase in maternal cardiac output of 30% to 50% by the beginning of the third trimester.[13] Our study demonstrates that 2 measurements of maternal cardiac output early and late in pregnancy can be used to detect those who are at increased risk for neonatal complications, unlike measurements at a single time point early or late in pregnancy, which were not found to be of statistical significance (Table 4). We attributed the absence of between-group differences in baseline cardiac output to the nature of our study group, wherein those with symptomatic or severe cardiac conditions generally will have undergone cardiac interventions prior to pregnancy, and women at very high risk are counseled to avoid pregnancy altogether.

The complex interplay between abnormalities in placentation, maternal vascular health, and suboptimal fetal growth has been well studied in the general population.[29] Specifically, placental disease has been implicated in the development of preeclampsia and intrauterine growth restriction.[30] However, the relationship between placental abnormalities and neonatal complications in women with heart disease has been only recently described.[16] Pieper and Balci and their colleagues reviewed 209 women with congenital heart disease and found that abnormalities in uteroplacental flow patterns (measured at the uterine and umbilical arteries) were more commonly seen in pregnancies associated with adverse events in offspring. Independent predictors of abnormal umbilical artery resistance index at 32 weeks included tricuspid annular plane systolic excursion, systemic atrioventricular valve regurgitation, and pulmonary atrioventricular valve regurgitation. Our study extends their findings by demonstrating that third
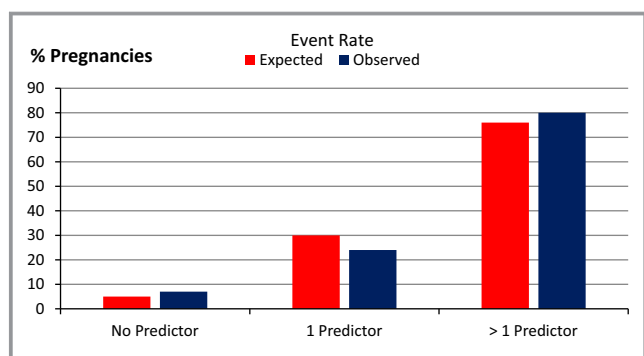
trimester umbilical artery PI are associated with Δ cardiac output, an important parameter that was difficult to reliably quantify in a multicenter study.[16] In contrast to the study by Pieper and Balci, where flow abnormalities in both umbilical and uterine arteries were related to complications in offspring, we observed abnormal Doppler flow in the umbilical arteries alone. Our findings are in keeping with the belief that umbilical artery flows are the more direct reflection of compromised fetal health, as compared with uterine artery flows, particularly when disease within the gas-exchanging placental villi is present.[31]

Beyond the establishment of decline in cardiac output as an independent predictor of adverse neonatal outcomes, our study provides a unifying concept that integrates maternal, placental, and fetal factors in determining pregnancy outcomes.[32] To date, published literature examining the relationship between maternal cardiac output and placental blood flow has been limited to women with structurally normal hearts.[11,33] Our study focuses on cardiac output in women with preexisting heart disease, thereby expanding the existing knowledge base. Our observations support the notion that "upstream" abnormalities in maternal cardiac output can mediate "downstream" abnormalities in fetal flow patterns, and each of these factors is independently predictive of complications in offspring. Specifically, we found that independent cardiovascular predictors of abnormal umbilical artery flow patterns included NYHA functional class ≥2, significant aortic or mitral stenosis, and inadequate augmentation of cardiac output.

In a recent review of established models to predict outcomes of pregnancy (including the ZAHARA, CARPREG, and World Health Organization risk scores), the authors concluded that although maternal cardiovascular risk could be accurately determined using validated scoring systems, the known incremental risk in offspring could not be adequately predicted with existing models.[34] In contrast to previous studies that have utilized baseline parameters at a single point in time to predict adverse outcomes of pregnancy, our study reveals that serial measurements at 2 time points during the antepartum period are necessary to evaluate maternal–fetal interactions and the effect of these on neonatal outcome. The obstetric risk factors, maternal cardiac output measurements, and umbilical flow patterns found to be independent predictors of neonatal complications in our cohort can be easily determined in clinical practice and, pending further validation, may at some point be incorporated into routine maternal care. Technology is now emerging to allow for continuous noninvasive assessment of cardiac output at the bedside without the need for echocardiography; although these applications may have tremendous clinical benefit, they have yet to be studied in pregnant women with cardiac disease.[35]

Study Limitations

Although a single-center study can optimize reproducibility and accuracy, the present study was not powered to examine cardiac output and its effect on neonatal outcomes in the context of specific lesions. On the other hand, we would suggest that the generalizability of our study results is enhanced by the prospective enrollment of a relatively large population of women with heart disease. Despite its prospective design with specific time points prescribed for completion of study examinations, some patients were not able to return to our center for specified antepartum and postpartum imaging. Establishing baseline cardiac output within the first trimester of pregnancy was difficult to ascertain, given the usual timing for the first obstetric visit (often after completion of the first trimester). Although reported to be useful by others,[16] resistance index in the uterine and umbilical arteries was not utilized for our study cohort because PI, a more widely utilized marker of placental function, measures the entire waveform, and is the parameter routinely measured at our center.[31] Finally, we acknowledge that measurements of cardiac output and umbilical artery Doppler interrogation in the third trimester afford a relatively narrow window of opportunity for intervention between identification of the high risk pregnancy and diagnosis of complications in the neonate.

Implications for Clinical Practice and Future Directions

We propose that surveillance in pregnancy be intensified in those designated as "high risk" through this prediction model in an attempt to mitigate adverse neonatal outcomes; the clinical utility of this strategy, however, awaits further study. Validation of our prediction model in larger populations and in specific high risk subgroups would be of value and may uncover additional relationships between maternal cardiac adaptations and outcomes of offspring. Finally, further study into the cost-effectiveness of our proposed model and the possible utility of novel, noninvasive, bedside measurement of cardiac output[36] would likely be of interest.

Sources of Funding

Disclosures

None.

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