Maternal Predictors of Disparate Outcomes in Children With Single Ventricle Congenital Heart Disease

Priyanka Asrani, MBBS; Nelangi M. Pinto, MD; Michael D. Puchalski, MD; Zhining Ou, MS; Robert M. Silver, MD; Erin K. Zinkhan, MD; Cara C. Heuser, MD; Amy Nance, MPH; Thomas A. Miller, DO

BACKGROUND: Significant variability in morbidity and mortality persists for children with functionally single ventricle congenital heart disease (SV-CHD) despite standardization in medical and surgical care. We hypothesized that maternal health factors may be associated with an increased risk of poor outcomes in children with SV-CHD.

METHODS AND RESULTS: This retrospective, observational, cohort study included term maternal-infant pairs with a diagnosis of SV-CHD who underwent surgical palliation from 2006 to 2015 at Primary Children’s Hospital. Pairs lacking maternal variables of interest or infant follow-up data were excluded. The association of maternal risk factors of abnormal pre-pregnancy body mass index, abnormal gestational weight gain (<7 or >20 kg), hypertensive disorders, and gestational diabetes mellitus with death/transplant and hemodynamics were analyzed using regression models. Of 190 infants, 135 (71%) maternal-infant dyads had complete data for inclusion. Death or transplant occurred in 48 infants (36%) during an average follow-up of 2.2 years (0.1–11.7 years). Abnormal gestational weight gain was associated with an increased risk of death and/or transplant in logistic regression (odds ratio, 3.22; 95% CI, 1.32–7.86; \( P = 0.01 \)), but not Cox regression (hazard ratio, 1.9; 95% CI, 1.0–3.7; \( P = 0.055 \)). Mean pulmonary artery pressures were higher in the setting of abnormal gestational weight gain (16.5±2.9 versus 14.7±3.0 mm Hg; \( P < 0.001 \)), and abnormal pre-pregnancy body mass index (15.7±3.5 versus 14.2±2.1 mm Hg; \( P < 0.001 \)) in the systemic right ventricle group.

CONCLUSIONS: Abnormal gestational weight gain (excessive or inadequate) is a novel risk factor for worse outcomes in SV-CHD. The fetoplacental environment may alter the trajectory of vascular development to impact outcomes in infants with SV-CHD.

Key Words: abnormal gestational weight gain ■ congenital heart disease ■ outcomes ■ single ventricle
Markers of fetal growth such as fetal biometry and placental dysfunction such as umbilical artery and venous Doppler assessments are routinely followed in the obstetric setting. Hypertensive disorders of pregnancy are associated with future maternal cardiovascular disease risk and mortality as well as low birth weight and preterm delivery. Preeclampsia alters long-term health outcomes for offspring, including blood pressure, body mass index (BMI), and stroke risk. Similarly, diabetes mellitus (DM) is associated with an increased risk of malformations, fetal death, and preterm delivery. Finally, gestational weight gain above and below the Institute of Medicine recommendations has been associated with a higher risk of adverse maternal and infant outcomes, suggesting that gestational weight gain also plays a role in fetal and placental development. Mechanisms for developmental programming from maternal obesity and DM for future disease in the offspring continue to be elucidated.

Given the impact of maternal health on fetoplacental vasculature, maternal risk factors may affect both the development of CHD and outcomes associated with CHD. The association between maternal risk factors of obesity, preeclampsia, and DM with CHD has been well described. There are limited data, however, regarding the impact of maternal and pregnancy health on CHD outcomes, specifically the single ventricle population. Maternal factors described above may induce changes in the vascular programming of the fetus that could potentially impact single ventricle physiology, specifically the efficiency of passive pulmonary blood flow. Further investigation into the prenatal environment may allow stratification of children who otherwise appear to have similar characteristics but continue to have variation in outcomes following single ventricle palliation. The goal of this study is to test the association of maternal and pregnancy risk factors with disparate outcomes in SV-CHD. Identifying factors that confer additional risk in CHD may enable us to institute targeted therapies or make changes in management strategies during pregnancy to improve single ventricle outcomes.

**METHODS**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Study Design and Population**

This retrospective, observational cohort study included all maternal-infant dyads for infants born after 37 0/7 weeks’ gestational age with a diagnosis of SV-CHD who underwent surgical palliation between 2006 and 2015 at Primary Children’s Hospital identified by surgical database records. We excluded infants who were lost to follow-up or transferred their care to another institution within the first year of life. We also excluded any individuals for whom the minimal maternal variables of pre-pregnancy BMI, DM, or hypertension were not available. The study was approved by the institutional review boards of the University of Utah and Primary Children’s Hospitals, as well as the Utah Department of Health. A waiver for consent was obtained from the review boards.

**Maternal and Pregnancy Variables**

Prenatal variables were obtained via abstraction of maternal and infant medical records, as well as query of the Department of Health’s Utah Birth Defect Network, which has monitored all major birth defects reported in the state since 1999. The Utah Birth Defect Network records include maternal variables including maternal pre-pregnancy weight, maternal delivery weight, gestational weight gain, maternal

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**CLINICAL PERSPECTIVE**

**What Is New?**

- Abnormal gestational weight gain is a novel and potentially modifiable risk factor that may contribute to worse outcomes in single ventricle congenital heart disease.
- The association of higher vascular pressures measured invasively with maternal risk factors raises the possibility that altered vascular development and trajectory may be one mediator of increased risk.

**What Are the Clinical Implications?**

- Identifying factors that confer additional risk in congenital heart disease may enable changes in management strategies that impact developmental programming during pregnancy to improve single ventricle outcomes.

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**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Description                        |
|--------------|------------------------------------|
| BMI          | body mass index                    |
| CHD          | congenital heart disease           |
| DM           | diabetes mellitus                  |
| PA           | pulmonary artery                   |
| SV-CHD       | single ventricle congenital heart disease |
hypertension during pregnancy, and maternal DM during pregnancy.

Four primary maternal conditions were analyzed and defined as follows:

1. Maternal hypertensive disorder was a composite variable and was considered present if there was chronic hypertension in pregnancy, gestational hypertension, or preeclampsia. Chronic hypertension was defined as blood pressure exceeding 140/90 mm Hg before pregnancy or before 20 weeks’ gestation. Gestational hypertension was defined as hypertension with onset in the latter part of pregnancy (>20 weeks' gestation) without any other features of preeclampsia and followed by normalization of the blood pressure postpartum. Preeclampsia was clinically defined by hypertension and proteinuria, with or without pathologic edema during pregnancy.

2. DM during the study period was defined as anyone with DM during pregnancy (preexisting or gestational) using the Carpenter-Coustan 2-step method promoted by the American College of Obstetricians and Gynecologists and the National Institutes of Health.

3. Given that our cohort contains children before and after the Institute of Medicine guideline change in 2009 regarding weight gain during pregnancy based on pre-pregnancy BMI, we defined excessive weight gain as >20 kg and inadequate weight gain as <7 kg during pregnancy, calculated from the pre-pregnancy weight and the weight at the time of delivery.

4. Abnormal pre-pregnancy BMI is defined as BMI outside the range of normal adult BMI (18.5–24.9) as defined by the Centers for Disease Control and Prevention.

5. Smoking was defined as positive if there was any positive self-report of smoking during pregnancy.

Outcome and Covariate Definitions
Postnatal data from neonatal hospitalization, stage II and III preoperative evaluation and operative hospitalization, along with data from last follow-up were abstracted from medical records. The primary outcome was time to death or receipt of a heart transplant. Secondary outcomes such as mean pulmonary artery (PA) pressures, pulmonary vascular resistance, and ventricular end-diastolic pressures were collected at the time of routine cardiac catheterization performed before their Fontan surgery.

Statistical Analysis
Descriptive analyses of prenatal exposures (maternal and fetal factors) were summarized using count and percentage for categorical variables, mean (±SD) or median (interquartile range) for continuous variable as appropriate. The primary prenatal exposures of the study were gestational weight gain, maternal pre-pregnancy BMI, maternal DM, maternal hypertension, and smoking. Univariate and multivariate logistic regression was conducted using maternal and neonatal variables including abnormal gestational weight gain, abnormal BMI, maternal hypertension, maternal DM, smoking, insurance status, maternal age, and birth weight and sex of the baby to evaluate the association between the event time (composite outcome of death or transplant) and exposures in the entire cohort. Kaplan–Meier curve of time to death or transplant was generated using a multivariate Cox proportional hazards method including the variables of gestational weight gain, maternal pre-pregnancy BMI, maternal DM, and maternal hypertension and smoking. Schoenfeld residuals from the Cox models were examined to assess possible departures from the proportional hazards model assumption. There was no significant departure from that assumption for any model (all well over P>0.05). An additional post hoc subgroup analysis of the systemic right ventricular cohort was performed studying the association of prenatal exposures on mean PA pressures, ventricular end-diastolic pressures, and pulmonary vascular resistance at the time of the pre-Fontan catheterization using the unpaired t-test method. The significance level was considered 0.05. All statistical analysis was conducted using StataMP 14 and R v. 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). The principal investigator has full access to all the data in the study and is responsible for its integrity and the data analysis.

RESULTS
Patient Cohort
Of the 190 neonates with SV-CHD identified who underwent surgical palliation between 2006 and 2015, 135 (71%) maternal-infant dyads had complete data for inclusion. All pregnancies were singleton. This cohort was split into systemic right ventricular morphology (69%) and systemic left ventricular morphology (31%). Anatomic diagnoses in the systemic right ventricular group included hypoplastic left heart syndrome (90%), unbalanced right dominant atrioventricular canal (5%), and others (4%). The anatomic diagnoses in the systemic left ventricular group included tricuspid atresia (48%), pulmonary atresia (24%), and others (28%). Initial surgical palliation consisted of Norwood with Sano/Blalock-Taussig shunt in 95 (70%) of the entire cohort, with 89 (96%) in the systemic right ventricular group. Demographics and characteristics of the analytic cohort are outlined.
Abnormal gestational weight gain was recorded in 34 (25%) mothers, of which 24 (71%) had excessive (>20 kg) and 10 (29%) had inadequate (<7 kg) weight gain; 53% had an abnormal pre-pregnancy BMI, 10% had DM, 6% had maternal hypertensive disorder, and 8% self-reported smoking.

Survival
Death or transplant occurred in 48 (36%) infants during an average follow-up period of 2.2 years (0.1–11.7 years). Multivariable logistic regression analysis using maternal and neonatal variables suggested abnormal gestational weight gain was independently associated with an increased risk of death or transplant in an offspring with SV-CHD (odds ratio, 3.22; 95% CI, 1.32–7.86; P=0.01) cohort in its entirety and within the subset of the cohort with a systemic right ventricle (odds ratio, 4.46; 95% CI, 1.32–15.12; P=0.01). None of the other factors included in the regression conferred an increased risk of death or transplant in this cohort. The impact of abnormal gestational weight gain, however, was not significant with Cox regression analyses (Table 2). Kaplan–Meier survival curve (Figure 1) demonstrates that the hazard of death or transplant for those with abnormal maternal weight gain was 1.9 times (adjusted hazard ratio, 1.9; 95% CI, 1.0–3.7; P=0.055) relative to those with normal weight gain; however, this did not reach significance.

Hemodynamics
Given that the increased risk of death or transplant appeared to continue over time, as well as being more pronounced in the systemic right ventricle cohort as noted in a post hoc analysis of the cohort, we performed further subanalysis of invasive hemodynamic data in the systemic right ventricle cohort that underwent pre-Fontan cardiac catheterization (n=63). Comparison of mean PA pressures at the time of the pre-Fontan cardiac catheterization by maternal predictors (Figure 2) showed that pressures were higher in those with abnormal gestational weight gain (16.5±2.9 versus 14.7±3.0 mm Hg; P<0.001), maternal hypertension (18.2±4.0 versus 14.8±2.9 mm Hg; P=0.022), and those with an abnormal maternal pre-pregnancy BMI (15.7±3.5 versus 14.2±2.1 mm Hg, P<0.001). In addition, the pulmonary vascular resistance was statistically higher in those with abnormal gestational weight gain (2.2±0.9 versus 1.6±0.7, P<0.001), hypertension (2.6±1.6 versus 1.7±0.7, P=0.005), DM (2.0±1.2 versus

| Table 1. Demographics |
|-----------------------|
|                      |
| All (N=135)          |
| Systemic Right Ventricle (N=93) | Systemic Left Ventricle (N=42) |
| Maternal age, y 27.5±4.9 | 27.7±5.5 | 26.9±4.9 | 0.42 |
| Advanced maternal age ≥35 y, n (%) 13 (9.6) | 9 (9.7) | 4 (9.5) | 0.98 |
| Medicaid, n (%) 37 (27.4) | 18 (19.4) | 19 (45.2) | 0.018 |
| Abnormal gestational weight gain, n (%) 34 (25) | 19 (20) | 15 (36) | 0.06 |
| Abnormal pre-pregnancy BMI, n (%) 71 (52.6) | 48 (51.6) | 23 (55) | 0.72 |
| Diabetes mellitus, n (%) 14 (10.4) | 7 (7.5) | 7 (16.7) | 0.11 |
| Hypertension, n (%) 8 (5.9) | 5 (5.4) | 3 (7.1) | 0.69 |
| Smoking, n (%) 11 (8.2) | 5 (5.4) | 6 (14.3) | 0.08 |
| Pre-pregnancy BMI 25.7±6.3 | 25.4±5.5 | 26.3±7.7 | 0.44 |
| Cesarean section, n (%) 36 (26.8) | 24 (25.8) | 12 (28.6) | 0.73 |
| Tertiary care delivery, n (%) 107 (79.3) | 75 (80.6) | 32 (76.2) | 0.55 |
| Prenatal diagnosis, n (%) 111 (82.2) | 77 (82.8) | 34 (80.9) | 0.79 |
| Birth weight, kg 3.08±0.6 | 3.14±0.5 | 2.97±0.8 | 0.13 |

Comparison of maternal risk factors and other demographics between the systemic right ventricle and systemic left ventricle cohort. BMI indicates body mass index.
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1.7±0.7, \( P=0.011 \), smoking (2.1±0.4 versus 1.7±0.8, \( P=0.001 \)), and abnormal maternal pre-pregnancy BMI (1.9±0.8 versus 1.5±0.5, \( P=0.002 \)). However, the mean pulmonary vascular resistance was <3.0 Woods units in all groups. Those with abnormal gestational weight gain and abnormal maternal pre-pregnancy BMI also had higher right ventricular end-diastolic pressures at the time of the pre-Fontan cardiac catheterization (11.7±3.1 versus 10.4±2.3 mm Hg, \( P=0.002 \); and 11.4±2.6 versus 9.6±2.1 mm Hg, \( P<0.001 \)) respectively (Figure 3). No other maternal predictors were associated with a difference in right ventricular end-diastolic pressure. No differences in systemic arterial pressure measured invasively at the time of the pre-Fontan cardiac catheterization were found based on maternal predictors.

**DISCUSSION**

We found a possible novel association between abnormal weight gain in pregnancy and death or transplant in SV-CHD. While there is increasing interest regarding the impact of the in-utero environment on outcomes in CHD, to our knowledge this is the first report of a potentially modifiable maternal health metric that may impact outcomes in offspring with CHD. The association of higher vascular pressures as measured invasively at the time of the pre-Fontan hemodynamic evaluation with abnormal gestational weight gain, abnormal maternal pre-pregnancy BMI and maternal hypertensive disorders raise the possibility that altered vascular development and trajectory may be one mediator of increased risk.

**Figure 1. Event-free survival.**

Kaplan–Meier survival curve showing that the hazard of death or transplant for those with abnormal gestational weight gain was 1.9 times (hazard ratio, 1.9; 95% CI, 1.0–3.7) relative to those within the range of normal weight gain. \( P=0.055 \).

**Table 2. Cox Regression Analysis for Event-Free Survival**

| Variables                  | Univariable          | Multivariable         |
|----------------------------|----------------------|-----------------------|
|                            | HR (95% CI)          | \( P \) Value | HR (95% CI) | \( P \) Value |
| Abnormal gestational weight gain | 1.6 (0.9–2.9)       | 0.13            | 1.9 (1.0–3.7) | 0.055         |
| Hypertension               | 1.4 (0.5–3.8)        | 0.54            | 1.4 (0.5–4)  | 0.53          |
| Diabetes mellitus          | 1.3 (0.6–3.1)        | 0.54            | 1.4 (0.5–3.4) | 0.52          |
| Smoking                    | 0.7 (0.2–2.3)        | 0.59            | 0.8 (0.2–2.6) | 0.67          |
| Abnormal pre-pregnancy BMI | 0.9 (0.5–1.6)        | 0.68            | 1.0 (0.5–1.9) | 0.96          |
| Government insurance       | 0.9 (0.4–1.6)        | 0.64            | 0.7 (0.3–1.4) | 0.31          |

BMI indicates body mass index; and HR, hazard ratio.

\( \text{TOTAL N}=135 \)

\( \text{TOTAL N}=93 \)

Abnormal weight gain
Normal weight gain
Abnormal vs normal weight gain \( P=0.055 \)

Abnormal weight gain
Normal weight gain
Abnormal vs normal weight gain \( P=0.061 \)
While there has been increasing interest in the impact of structural heart disease on endothelial function in the systemic vasculature of adults with CHD as well as increasing understanding of the mediators of pulmonary vascular physiology in SV-CHD, the developmental trajectory of the vasculature in CHD is poorly understood. The potential for an intrauterine insult that may alter the developmental trajectory in CHD remains a promising hypothesis given the associations of fetal growth restriction and later cardiovascular disease.

Maternal nutrition and weight have also been associated with systemic hypertension in the offspring. We have previously demonstrated in a rat model that a maternal high-fat diet in addition to fetal growth restriction alters the systemic blood pressure and compliance along with elastin and collagen morphometry in juvenile

Figure 2. Mean pulmonary artery (PA) pressures.
Pre-Fontan mean PA pressures stratified by maternal predictors for the systemic right ventricle cohort (N=93). The pressures were higher in those with abnormal gestational weight gain, maternal hypertension during pregnancy and abnormal maternal pre-pregnancy BMI. BMI indicates body mass index; and HLHS, hypoplastic left heart syndrome.

Figure 3. Right ventricular pressures.
Pre-Fontan right ventricular end-diastolic pressures (EDP) stratified by maternal predictors for the systemic right ventricle cohort (N=93). The pressures were higher in those with abnormal gestational weight gain and abnormal maternal pre-pregnancy BMI. BMI indicates body mass index; and HLHS, hypoplastic left heart syndrome.
offspring.\textsuperscript{31,32} A similar model of fetal growth restriction has also been shown to alter elastin content (decrease) contributing to reduced lung compliance of the pulmonary vasculature.\textsuperscript{33} Developmental programming of adult cardiovascular disease, however, goes beyond the vasculature, as growth restriction has also been associated with cardiac remodeling, in the absence of CHD.\textsuperscript{34,35} Further investigation is required to determine if the differences in right ventricular end-diastolic pressure found in our cohort are related to intrinsic myocardial changes from oxidative stress, inflammation, or hypoxia; or potentially secondary to changes in systemic vascular compliance and resistance despite similar pressures.

Although there are fewer data on the impact of the in-utero environment on CHD outcomes, the findings to date support the underlying developmental origins hypothesis. We have previously shown that Doppler indices of worse placental health are associated with worse postnatal growth and decreased ventricular performance in hypoplastic left heart syndrome.\textsuperscript{18} A composite variable for impaired maternal-fetal environment as defined by the presence of preeclampsia, small for gestational age, and preterm birth has also been associated with a lower survival at 36 months in those infants who underwent cardiac surgery and also specifically for infants with hypoplastic left heart syndrome.\textsuperscript{19} The possible association between abnormal gestational weight gain during pregnancy and transplant-free survival in this study, continues to support the concept that variations in maternal health markers during pregnancy may initiate differing cascades in fetal development that contribute to the heterogeneity in outcomes in CHD. Such heterogeneity is most pronounced in the SV-CHD population, perhaps because of the dependence on vascular function in the lungs with passive pulmonary perfusion.

Subanalysis of the systemic right ventricle group demonstrated higher mean PA pressures at the time of the pre-Fontan catheterization in those with a history of abnormal gestational weight gain, abnormal pre-pregnancy BMI, and maternal hypertension. The potential role of the placenta in these associations should be further investigated. Maternal risk factors, such as obesity during pregnancy, have an adverse impact on the in-utero environment and are associated with placental vascular dysfunction in concert with metabolic changes at the fetoplacental microvascular and macrovascular endothelium.\textsuperscript{36} The placenta in pregnancies with CHD is different than unaffected pregnancies from a structural, functional, and transcriptional standpoint,\textsuperscript{37-40} but the mechanistic basis of the relationships between the placenta, fetal heart development, and later risk of cardiac dysfunction have not been fully elucidated. Animal studies using environmental exposures and gene manipulations are providing insights into the pathways involved.\textsuperscript{41} In conditions of placental insufficiency, reduced oxygen and nutrients may directly affect cardiomyocytes and increase cardiac afterload attributable to increased placental resistance to blood flow resulting in a more spherical shape of the fetal heart to reduce wall stress and better tolerate pressure overload. These changes also persist postnatally.\textsuperscript{35} In addition to placental health, there is also evidence that prenatal exposures such as smoking and polyunsaturated fatty acids impact pulmonary vasculature in persistent pulmonary hypertension; however, this has not been studied in the CHD population.\textsuperscript{42} Separating the contribution of myocardial as opposed to vascular pathology on later outcomes is difficult with our limited cohort. The interactions are likely complex, as evidenced by elevated mean PA pressures in the abnormal gestational weight gain, abnormal pre-pregnancy BMI, and maternal hypertensive groups, but the presence of elevated right ventricular end-diastolic pressure only in the first 2 groups but not the latter.

The offspring of those mothers with hypertensive disorders had significantly higher mean PA pressures, despite no association with an increased risk of death or transplant. The significant signal in the invasive measurements despite the lack of association with the primary outcome may suggest these groups remain at higher risk, but that risk was not uncovered in our follow-up time frame. In addition, whether there are additional secondary postnatal hits related to their cardiac course, surgical interventions as well as a prolonged period of hypoxemia as is the nature of their initial physiology is also unclear. Regardless, abnormal gestational weight gain, abnormal pre-pregnancy BMI, and maternal hypertension likely contribute to cardiovascular programming in fetal life that may lead to potentially deleterious long-term consequences for the SV-CHD patient.

As a retrospective single-center study, this study had some important limitations. With time-to-outcome data, the Cox regression is the preferred model, and therefore the findings of the logistic regression may be considered invalid. Given our borderline findings in the Cox model, however, combined with our risk of type II error with the sample size and number of events, we also performed a logistic regression. Because the largest signal was with the risk factor of “abnormal gestational weight gain” in both models, we found the findings worth reporting. There was selection bias since we excluded those patients who did not undergo any surgical palliation and chose comfort care, which included some extremely high-risk patients who may have delivered early because of growth restriction or maternal hypertensive disorders. These infants may have provided additional insight into the impact of more profound in-utero insults. We did not find any associations between maternal DM and hypertension with increased risk of death or transplant in this study; however, the number of mothers who
had any kind of DM or hypertension during pregnancy in this cohort were very small, thereby increasing the risk of type II error in this study. We were also limited in the total number of maternal risk factors and did not have information on some potentially relevant factors such as use of assisted fertilization, which may also impact vascular development. There may also be the potential for residual confounding attributable to unmeasured characteristics in the study. Regardless of these limitations, the findings of this study provide further insight into the impact of maternal health, especially adequate gestational weight gain on the outcomes for children undergoing palliative surgery. The findings support ongoing encouragement of an overall healthy lifestyle during pregnancy. Future studies should consider the link between carrying a pregnancy with CHD, and how variations in the associated placental and maternal health during that gestation may impact both CHD outcomes and long-term maternal cardiovascular health.

CONCLUSIONS

Our findings suggest that abnormal gestational weight gain is a novel and potentially modifiable risk factor that may contribute to worse outcomes in SV-CHD. In addition, our data suggest that other factors such abnormal maternal pre-pregnancy BMI and hypertension may also play a role in altering the fetoplacental vasculature, specifically the pulmonary vascular development in this population, which may in turn lead to a higher risk vascular profile. These data promote developmental programming as an explanation for some disparity in the outcomes in SV-CHD, but larger studies are required to assess the impact of other maternal, genetic, and environmental influences on fetoplacental vasculature and the myocardium in the CHD population.

ARTICLE INFORMATION

Received September 19, 2019; accepted April 13, 2020.

Affiliations

From the Divisions of Pediatric Cardiology (P.A., N.M.P., M.D.P., T.A.M.) and Neonatology (E.K.Z.), Department of Pediatrics, and Center for Clinical and Translational Science Study Design and Biostatistics Center (Z.O.), and Division of Maternal-Fetal-Medicine, Department of Obstetrics and Gynecology (R.M.S., C.C.H.), University of Utah, Salt Lake City, UT; Utah Birth Defect Network, Utah Department of Health, Salt Lake City, UT (A.N.).

Disclosures

None.

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