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Blood pressure evaluation in children treated with laser surgery for twin-twin transfusion syndrome at two year follow up

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Abstract

Objective—Twin survivors of twin-twin transfusion syndrome may be at risk for early onset of cardiovascular disease. The aim of this study was to determine prevalence and risk factors for elevated blood pressure among children treated with selective laser photocoagulation of the communicating vessels.

Study Design—Data were prospectively collected from surviving children treated for twin-twin transfusion syndrome with laser surgery between 2008 and 2010. Systolic and diastolic blood pressures were obtained from 91 child survivors at age 24 months (± 6 weeks) and evaluated based on age, sex, and height percentile. Blood pressure percentiles were calculated for each patient and categorized as normal ($<95\%$) or abnormal ($>95\%$). Clinical variables were evaluated using multilevel regression models to evaluate risk factors for elevated blood pressure.

Results—Blood pressure was categorized as normal in 38%, and abnormal in 62% of twin survivors based on percentile for sex, age and height; a comparable distribution was found for diastolic blood pressure elevation. There were no differences between donor and recipient twins for absolute systolic and diastolic blood pressure or blood pressure classification. In a multivariate analysis, significant risk factors for higher systolic blood pressure included prematurity ($\beta = -0.54$, 95% Confidence Interval $[-0.99, -0.09]$; $p = 0.02$), higher weight percentile ($\beta = 0.24$, 95%

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Confidence Interval [0.05, 0.42]; $p=0.01$), and presence of cardiac disease ($\beta=0.50$, 95% Confidence Interval [0.10, 0.89]; $p=0.01$). Prematurity was also a significant risk for abnormal diastolic blood pressure (Odds Ratio=0.89, 95% Confidence Interval [0.80, 1.00], $p=0.05$).

Conclusions—Child survivors of twin-twin transfusion syndrome had elevated systolic and diastolic blood pressure measurements at 2 years of age, with no differences seen between former donor and recipient twins. Prematurity may be a risk factor for elevated blood pressure measurements in this population. Future studies are warranted to ascertain whether these cardiovascular findings persist over time.

Key Words/Phrases

cardiovascular disease; fetal interventions; fetal physiology; elevated blood pressure; twin-twin transfusion syndrome

INTRODUCTION

Twin twin transfusion syndrome (TTTS) is a severe complication that occurs in approximately 10% of monochorionic-diamniotic (MC-DA) twin pregnancies.¹ It carries a high risk of fetal death if left untreated (80–100%) and a high perinatal morbidity and mortality, including increased risks of cardiovascular (CV) changes and structural heart disease.^{1–3} In TTTS, twins are exposed to different hemodynamic conditions and environmental factors caused by an unbalanced exchange of blood through vascular communications in the monochorionic placenta with preferential shunting of blood from one twin (donor) to the other twin (recipient). Recipient twins can develop progressive volume and pressure overload, congestive heart failure, and hydrops with striking echocardiographic findings such as cardiomegaly, valve regurgitation, ventricular hypertrophy and dysfunction.^{2, 4} Donor twins have less dramatic cardiac findings, but can develop hypovolemia with hyper-dynamic left ventricular (LV) function and right ventricular (RV) diastolic impairment due to increased placental resistance.⁵

The preferred treatment for TTTS is selective laser coagulation of the communicating vessels (SLPCV), which effectively separates the twin placental circulations, normalizing the blood volume in both twins.^{2, 6–8} Fetal laser surgery has resulted in greatly improved perinatal survival as well as improved neurologic outcomes.^{9–11} As survival rates for TTTS treated with fetal laser surgery have continued to improve, the focus is shifting towards evaluation of long-term risks in this population.^{12, 13}

Previous reports provide evidence that prenatal disease states with abnormal flow patterns, volume loading and afterloading conditions can lead to permanent CV changes that persist after birth. One such example is adult survivors of neonatal coarctation repair who develop early onset of systolic hypertension due to presumed abnormalities in vascular reactivity, arterial distensibility and baroreceptors reflex function.^{14–17} In another example, adults with a single umbilical artery were found to have structural and functional differences between their upper and lower extremity arteries, suggesting permanent changes in arterial structure from altered prenatal flow patterns.¹⁸

In TTTS, the cardiomyopathy seen in recipient twins is due to a combination of increased afterload, hypervolemia, and exposure to increased levels of circulating vaso-constrictive substances.^{1, 6, 19} The immediate impact of SLPCV in the recipient twin has been improved ventricular function, normalization of peripheral Doppler's, decreased valve regurgitation, and improved flow across the pulmonary valve.^{20–22} However, it is possible that altered fetal hemodynamics in the recipient twin prior to SLPCV may cause lasting CV changes that predispose to early childhood hypertension. The donor twin can have a transient hydrops phenomenon after SLPCV, possibly secondary to acute increases in volume and afterload resulting in transient cardiac dysfunction.^{23, 24} Former donor twins have been shown to have CV changes that persist even after SLPCV, such as increased cardiothoracic ratio.²⁵ Thus, donor twins have a different set of hemodynamic stressors that may put them at risk for permanent CV changes.

Recent long term TTTS follow up studies have been more encouraging, showing normalization of cardiac function in the majority of child survivors 10 years after successful fetal laser surgery for TTTS despite severe prenatal cardiac findings.^{26–29} However, there are also many characteristics of TTTS survivors, including low birth weight, small for gestational age (SGA), and prematurity that are associated with increased risk for CV changes in neonates.^{30, 31} We suspect these additional risk factors combined with the prenatal hemodynamic stressors of TTTS may increase the risk for CV changes such as hypertension.

The goal of our study was to assess the prevalence and risk factors for elevated blood pressure (BP) among children treated with SLPCV for TTTS who survived to age 2 years old. We hypothesized that surviving twins would be at increased risk for elevated BP based on their in-utero exposure to the hemodynamic changes seen in TTTS. Furthermore, we compared former donor and recipient twins directly to look for differences suggesting one population may be more at risk for CV changes.

MATERIALS AND METHODS

Study population

As part of a neurodevelopmental outcome study, all consecutive patients treated for TTTS between December 2007 and May 2010 were considered eligible and contacted for this study. TTTS was diagnosed at initial assessment at Los Angeles Fetal Therapy (University of Southern California, USC) if the MC-DA gestation had a maximum vertical pocket of fluid 8 cm in the recipient's sac and 2 cm in the donor's sac. Each case was classified prospectively according to the Quintero staging system.¹⁹ All patients were given the options of expectant treatment, pregnancy termination, amnioreduction, laser surgery (SLPCV), or selective reduction (at another center). Patients were not offered SLPCV if preoperative ultrasound scans revealed gross abnormalities of intracranial anatomy. Cases were treated exclusively by SLPCV with or without sequential technique, as described in detail previously.^{12, 13}

A study nurse, who was blinded to the predictors, contacted all consecutive laser-treated TTTS patients during the study period before the time their child was to reach 2 years old

and invited them to participate. There were no exclusion criteria. All subjects were evaluated in the Southern California Clinical Translational Science Institute's Clinical Trials Unit at Children's Hospital Los Angeles (CHLA). Families were given an incentive per child of \$25 for their participation. There was no travel budget. This study was approved by the Institutional Review Boards of the Health Sciences Campus of the USC and CHLA.

Measures

A single research study nurse measured weight and height for each patient and then used an automated BP machine that employs the oscillometric method for determining non-invasive BP with a reported mean error of 5 mmHg and standard deviation of 8 mmHg (Dinamap Procare, GE Healthcare; Milwaukee, WI). Measurements were made using a child cuff appropriate to the size of the child (Critikon Soft-Cuf, GE Healthcare; Milwaukee, WI). A single measurement for systolic BP (SBP) and diastolic BP (DBP) was recorded for each patient on a random arm and multiple attempts were made if the machine was unable to register. The children were sitting while BP measurements were taken, and had sedentary play prior to BP measurements. The subjects also underwent developmental testing as a separate part of the study.³² Height, weight and body mass index (BMI) percentiles and Z-scores for age and sex were calculated for each subject using published normative values.³³ The chronologic age of the child was used to generate normative parameters, as children in the study sample had reached age 2 years old at which time catch-up growth is to be expected and correction for prematurity is no longer the standard. The raw measurements were used along with uncorrected age and height percentile to calculate a SBP and DBP percentile for each child using published normative values.³³ Subjects were classified as having either abnormally elevated BP (≥95%) or normal BP (<95%) based on their calculated BP percentile.

Additionally, we evaluated and recorded prenatal, neonatal, and current childhood risk factors potentially associated with elevated BP classification including: 1) prenatal risk factors: donor/recipient status (donor=1, recipient=0), Quintero stage (1–4), gestational age (GA) at surgery (weeks), in-utero growth restriction (IUGR) status prior to surgery (yes=1, no=0), and cardiomyopathy status (yes=1, no=0); 2) neonatal risk factors: raw birth weight (kg), SGA status (yes=1, no=0), and estimated GA at birth (weeks); and 3) current risk factors: raw height, height percentile, raw weight, weight percentile and Z-score, BMI percentile and Z-score, and concurrent cardiac or renal disease. In-utero growth restriction (IUGR) was designated as < 10% expected fetal weight for estimated GA.³⁴ SGA was defined as < 10% for weight at birth for estimated GA.³⁵

Recipient twin cardiomyopathy was defined as having mild or greater than mild findings in at least 2 of the following categories on fetal echocardiography: cardiac enlargement, ventricular dilation or hypertrophy, ventricular dysfunction, and valve regurgitation of the mitral or tricuspid valve. Fetal echocardiography was performed in accordance with the AIUM/ISUOG published guidelines.³⁶ Associations between renal disease and outcomes were not assessed due to low prevalence in this sample.

Statistical analyses

Descriptive statistics were produced with IBM SPSS Statistics software (version 21; SPSS Inc, Chicago, IL). Paired T tests and McNemar exact tests were used to evaluate twin pairs. Multilevel linear and logistic regression analyses were conducted in Mplus software (version 7.2; Muthén & Muthén, Los Angeles, CA), with twins grouped or nested within pregnancy.³² All prenatal, neonatal, and current risk factor measures (see Table 3) were tested for association with absolute and elevated SBP and DBP. Risk factors that potentially differed between twins (e.g., weight, presence of cardiac or renal disease) were modeled as within-subjects predictors; risk factors shared by twins of the same family (e.g., GA) were modeled as between-subjects factors. To examine the robustness of the effects on absolute SBP, all significant or nearly significant ($p < 0.10$) risk factors were entered simultaneously into a multivariate regression model, and non-significant factors were removed to arrive at a more parsimonious final model. A p-value of 0.05 was used for determining statistical significance.

RESULTS

One hundred thirty consecutive TTTS cases were treated by SLPCV between December 2007 and May 2010, and fifty-seven families comprising 100 eligible children were initially enrolled in the study.³² Reliable BP measurements could not be obtained in 9 subjects due to poor patient cooperation after multiple attempts, and these patients were excluded from the study. The final study cohort comprised 91 patients from 54 families. Table 1 presents shared risk factors and family characteristics. Approximately one-third of patients delivered < 33 weeks GA (33%), and overall average GA at birth was 33 weeks comparable with expected rate of prematurity after laser surgery.³⁷ Table 2 presents child risk factors and individual child characteristics with no significant differences seen for child demographics. In the cohort 29% met criteria for IUGR (estimated fetal weight less than the 10th percentile) at the time of TTTS diagnosis and at birth 42% met criteria for SGA (birth weight less than the 10th percentile). Only 10% of recipient twins met our criteria for significant cardiomyopathy, but this was only formally evaluated by fetal echocardiography in 40 patients (44%) so it is likely underestimated. In follow up, 9 patients (10%) were confirmed to have congenital heart defects including atrial and ventricular septal defects, aortic stenosis, pulmonary stenosis, tetralogy of Fallot and pulmonary atresia with hypoplastic right ventricle; and 4 patients (4%) were found to have renal disease including hydronephrosis, nephrocalcinosis, pyelectasis and acute renal failure. Although most children in the study had normal growth parameters, 6 patients (6.6%) were underweight (BMI < 5%) and 13 patients (14.3%) were overweight (BMI > 85%). However, only 2 patients had BMIs falling outside the LMS parameters (<3% or >97%).

Overall 62% of subjects' met criteria for elevated SBP (< 95%) and 63% had evidence of elevated DBP (< 95%). The unadjusted intra-class correlations for absolute SBP and DBP were 0.258 and 0.056, respectively, indicating that over a quarter of the variation in SBP, but only about 5% of the variation in DBP, is attributable to shared pregnancy, genetic, or environmental characteristics rather than unique child-level factors. Paired T tests performed on 37 twin pairs showed no difference between donor and recipient for absolute SBP

($p=0.46$) or absolute DBP ($p=0.81$). McNemar exact test (37 twin pairs) also showed no difference between donor and recipient for SBP category ($p=0.77$) or DBP category ($p>0.99$). Univariate regression results are presented in Table 3. Being small for GA ($\beta=-0.42$, 95% CI $[-0.81, -0.02]$; $p=0.04$) and later GA at birth ($\beta=-0.43$, 95% CI $[-0.85, 0.00]$; $p=0.05$) were associated with lower absolute SBP. Nearly significant risk factors for higher absolute SBP included higher weight percentile ($\beta=0.19$, 95% CI $[-0.01, 0.40]$; $p=0.06$), weight Z-score ($\beta=0.17$, 95% CI $[-0.02, 0.36]$; $p=0.07$), and presence of cardiac disease ($\beta=0.38$, 95% CI $[-0.03, 0.78]$; $p=0.07$). No risk factors in the univariate analyses were significantly associated with absolute DBP or elevated SBP classification. However, lower GA at birth was a significant risk for elevated DBP classification (OR=0.89, 95% CI $[0.80, 1.00]$, $p=0.05$).

Significant risk factors for higher SBP comprising the final multivariate model included lower GA at birth ($\beta=-0.54$, 95% CI $[-0.99, -0.09]$; $p=0.02$), higher weight percentile ($\beta=0.24$, 95% CI $[0.05, 0.42]$; $p=0.01$), and cardiac disease ($\beta=0.50$, 95% CI $[0.10, 0.89]$; $p=0.01$). R-square values for this model were 0.07 on the within level and 0.29 at the between level, suggesting that GA at birth explains 29% of the variation in SBP, while weight percentile and cardiac disease explains only 7% of the variation in SBP.

COMMENT

Child survivors of fetal laser surgery for TTTS were found to have elevated systolic and diastolic BP measurements at 2 years of age in our study. Despite very different in-utero CV exposures for donor and recipient twins prior to and after SLPCV for TTTS, there were no differences observed between surviving donor and recipient twins for absolute systolic and diastolic BP or elevated BP classification. Thus, it appears that in this cohort both donor and recipient twin survivors are equally at risk for elevated blood pressure measurements.

Higher SBP was most highly associated with prematurity, higher current weight percentile, and presence of congenital heart disease. Prematurity was also found to be associated with elevated DBP classification. In our linear regression model, gestational age explained 29% of the variation in SBP likely attributable to shared biological or environmental effects, while the combination of weight percentile and congenital heart disease explained only 7% of the variation in SBP with the remainder likely attributable to individual child factors. These results suggest that prematurity may be a primary risk factor for elevated BP measurements at two years of age in this population.

Prematurity (including both late preterm and extremely preterm infants) has been shown by multiple long-term studies to be associated with higher blood pressures in surviving children and adolescents.^{38–40} One study even demonstrated significantly elevated carotid intima-medial thickness along with elevated blood pressure in extremely preterm adolescents, as compared with age-matched controls.³⁹ It has also been reported that children who were SGA at birth have a higher percentage of body fat which may predispose such children to develop metabolic syndrome as adults.⁴¹ We found that at age two years the weight percentile (regardless of height) was significantly associated with increased SBP, which may suggest obesity as a risk factor for elevated BP classification. However, after dichotomizing

for BMI percentile the numbers were too small for further analysis as only 13 patients (14.3%) were overweight (BMI > 85%). Low birth weight infants have been associated with higher SBP later in life as compared to infants born at term,³⁰ and one meta-analysis even demonstrated an inverse linear relationship between birth weight and SBP later in life.³¹ We did not find that fetal growth restriction or birth weight to be significant risk factors for increased absolute BP or elevated BP classification.

Twin survivors in a current 10-year follow up study had a positive impact of fetal laser surgery on postnatal cardiac performance with no lasting CV changes such as hypertension noted.²⁶ Furthermore, a recently published comparison of cardiac function at 10 years of age between MC-DA twin pairs without TTTS and those treated for TTTS with either laser surgery or amnioreduction showed normal cardiac measurements for all groups with no significant within-twin-pair and intergroup differences in current size, heart rates, strain or strain rate.²⁸ While there were some within-twin-pair differences seen in the amnioreduction treated group, including reduced rotation and diastolic function in the ex-recipient compared to the ex-donor, these variables still measured within the normal range. Despite these studies findings, there still may be subtle underlying CV changes and renal pathology that predisposes to elevated BP classification in this population that are not fully appreciated.^{42–45} It is also possible that CV abnormalities seen in the neonate and young child continue to resolve with age, just as the dramatic cardiac findings seen in TTTS tend to improve and resolve during gestation after SLPCV. While our results are provocative, they give an incomplete picture of the CV change risk profile in these patients and require further long-term investigation.

Limitations

There are several important limitations to this study. First, there was a selection bias of patients who lived locally to participate due to limited travel budget resources, and this limited recruitment. Thus patients who lived far from the study center were significantly less likely to participate. These concerns were addressed in a prior publication on neurodevelopmental outcomes in this same cohort.³² Second, a larger sample size may have detected additional statistically significant findings. Third, this cohort had a fixed follow up period of 2 years, and it is unknown whether these findings will persist over time. Fourth, measurements errors may be a factor given the difficulty of obtaining an accurate BP in a toddler. Furthermore, these were onetime BP measurements and may not denote a true persistent hypertensive state. It is our hope to bring this same cohort of patients back at age 5 and 10 years old for further evaluation of CV risks. Lastly, several of the data points were incomplete such as the cardiomyopathy evaluation, which may have resulted in an under-estimate of true effect. Further study is needed in this area to determine if long-term CV risks in this population will increase or resolve with time, which will become increasingly important as treatment with SLPCV continues to improve outcomes and create a larger cohort of TTTS survivors.

Conclusions

Child survivors of TTTS had elevated systolic and diastolic BP measurements at 2 years of age that met criteria for elevated SBP in 62% and elevated DBP in 63%, with no differences

seen between surviving donor and recipient twins. Prematurity may be a risk factor for elevated BP in this population. Future studies are warranted to ascertain whether these CV findings persist over time.

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Abbreviations

BMI	body mass index
BP	blood pressures
CVD	cardiovascular disease
CI	confidence interval
DBP	diastolic blood pressure
GA	gestational age
IUGR	In-utero growth restriction
LV	left ventricles
MC-DA	monochorionic-diamniotic
RV	right ventricle
SGA	small for gestational age
SLPCV	Selective Laser Photocoagulation of Communicating Vessels
SBP	systolic
TTTS	twin-twin transfusion syndrome

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Table 1

Shared Risk Factors and Family Demographics (N=54)

Prenatal Risk Factors	N (%) or Mean (SD)
Quintero stage:	
I	10 (18.5%)
II	12 (22%)
III	28 (52%)
IV	4 (7%)
Neonatal Risk Factors	
GA ^a at surgery: (range: 16.4–26.0 wks)	20.56 (2.67)
GA ^a at delivery: (range: 24.3–38.7 wks)	32.99 (3.43)
Prematurity (<32 weeks)	18 (33.3%)
Family Demographics	
Married	39 (72%)
Maternal age (range: 21–45)	32.02 (6.44)
Paternal age (range: 22–52)	35.46 (7.85)
# adults in home (range: 1–5)	2.31 (0.84)
# children in home (range: 0–6)	2.85 (1.34)

^a Gestational Age

Table 2**Child Risk Factors and Demographics (N=91)**

Prenatal Risk Factors	Overall N (%) or Mean (SD)
Donor (vs. recipient) status	47 (52%)
IUGR ^a status	26 (29%)
Preoperative cardiomyopathy ^b	9 (10%)
Neonatal Risk Factors	
SGA ^c status	38 (42%)
Donor (Elevated systolic BP)	27 (15, 55%)
Recipient (Elevated systolic BP)	11 (7, 63%)
Birth weight (kg; range 0.54–3.82)	1.81 (0.70)
Current Risk Factors	
Weight (kg; range 9.0–17.7)	12.10 (1.59)
Weight percentile, median (IQR) (range 0.1–99.6) ^d	27.27 (8.73–56.56)
Weight Z-score (range –3.25–2.68)	–0.55 (1.10)
Height (cm; range 75–96)	85.26 (3.71)
Height percentile, median (IQR) (range 0.1–99.6) ^d	28.65 (12.50–51.80)
Height Z-score (range –3.25–2.68)	–0.55 (1.03)
Absolute systolic BP, median (IQR) (range 76–150)	97.50 (86.75–100.00)
Absolute diastolic BP, median (IQR) (range 44–107)	97.00 (89.00–99.00)
Systolic BP status ^{f,47}	
Normal	35 (38%)
Elevated	56 (62%)
Diastolic BP status ^{f,47}	
Normal	34 (37%)
Elevated	57 (63%)
Congenital heart disease	9 (10%)
Renal disease	4 (4%)
Child Demographics	
Male sex	51 (51%)
Race	
White	43 (43%)
Hispanic	37 (37%)
Asian	11 (11%)
Black	5 (5%)
Other/decline to state	4 (4%)

^aIntrauterine growth restriction;

^b Among N=40 children who could be categorized for cardiomyopathy status;

^c Small for gestational age;

^d Based on LMS Parameters for Boys and Girls: Weight for Age. National health and nutrition survey (NHANES), CDC/National Center for Health Statistics;

^e Based on LMS Parameters for Boys and Girls: BMI for Age. National health and nutrition survey (NHANES), CDC/National Center for Health Statistics;

^f Based on LMS Parameters for Boys and Girls: Height for Age. National health and nutrition survey (NHANES), CDC/National Center for Health Statistics.

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Table 3
Risk factors for elevated absolute blood pressure and elevated blood pressure classification

	Absolute Systolic BP		Absolute Diastolic BP		Elevated Systolic BP		Elevated Diastolic BP	
	β	95% CI	β	95% CI	OR	95% CI	OR	95% CI
<i>Prenatal Risk Factors</i>								
Donor status	0.14	[-0.30, 0.58]	0.04	[-0.39, 0.46]	1.32	[0.45, 3.82]	0.90	[0.37, 2.21]
Quintero stage	-0.19	[-0.68, 0.31]	0.10	[-0.64, 0.85]	0.75	[0.33, 1.69]	1.32	[0.85, 2.04]
IUGR ^a status	-0.11	[-0.63, 0.41]	-0.12	[-0.62, 0.37]	0.78	[0.22, 2.74]	0.75	[0.26, 2.15]
Cardiomyopathy ^b	0.28	[-0.22, 0.79]	0.07	[-0.3, 0.43]	3.96	[0.42, 37.49]	2.13	[0.51, 8.94]
<i>Neonatal Risk Factors</i>								
SGA status ^c	-0.42	[-0.81, -0.02]	-0.32	[-0.75, 0.11]	0.77	[0.22, 2.64]	0.66	[0.26, 1.66]
Birth weight (kg)	-0.09	[-0.30, 0.12]	-0.09	[-0.32, 0.14]	0.73	[0.29, 1.85]	0.64	[0.37, 1.11]
Gestational age at birth	-0.43	[-0.85, 0.00]	-0.98	[-4.72, 2.75]	0.84	[0.67, 1.05]	0.89	[0.8, 1]
<i>Current Risk Factors</i>								
Weight	0.15	[-0.05, 0.35]	0.10	[-0.1, 0.31]	1.13	[0.75, 1.68]	0.90	[0.68, 1.18]
Weight % ^d	0.19	[-0.01, 0.40]	0.08	[-0.13, 0.29]	1.01	[0.99, 1.03]	0.99	[0.98, 1]
Weight Z-score	0.17	[-0.02, 0.36]	0.09	[-0.13, 0.3]	1.24	[0.72, 2.12]	0.76	[0.51, 1.14]
BMI	0.09	[-0.16, 0.34]	0.14	[-0.08, 0.35]	1.39	[0.76, 2.53]	1.03	[0.75, 1.41]
BMI Z-score	0.11	[-0.14, 0.36]	0.15	[-0.06, 0.35]	1.62	[0.7, 3.74]	1.05	[0.67, 1.64]
Congenital heart disease	0.38	[-0.03, 0.78]	0.09	[-0.63, 0.81]	4.14	[0.62, 27.71]	2.24	[0.43, 11.67]

^aIntrauterine growth restriction;

^bAmong N=40 children who could be categorized for cardiomyopathy status;

^cSmall for gestational age;

^dBased on LMS Parameters for Boys and Girls: Weight for Age.

National health and nutrition survey (NHANES), CDC/National Center for Health Statistics.