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BRIEF COMMUNICATION

Fetal Growth Among Infants With Congenital Heart Defects by Maternal Race/Ethnicity

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PURPOSE: Congenital heart defects (CHDs) are the most prevalent birth defects. Infants with CHDs more often are small-for-gestational age (SGA) than infants without CHD; however, little is known about racial/ethnic variations in prevalence of SGA or large-for-gestational age (LGA) for infants born with CHDs. This study determined the risk of SGA and LGA for non-Hispanic (NH)-black and Hispanic infants with CHDs.

METHODS: Data from the Florida Birth Defects Registry were used in a retrospective cohort study of 10,027 live-born infants to resident NH-White, NH-Black, and Hispanic women ages 15–49 years from January 1, 1998, to December 31, 2003, and diagnosed with 11 CHDs. Defect-specific odds ratios and 95% confidence intervals were computed for risk of SGA and LGA by race/ethnicity and adjusted for covariates using multinomial logistic regression.

RESULTS: After adjusting for covariates, we found there were no statistically significant racial/ethnic differences in risk of SGA. However, NH-Blacks with ventricular septal defect had increased risk of LGA and NH-Blacks with tetralogy of Fallot had decreased risk of LGA compared to NH-Whites.

CONCLUSIONS: Very few racial/ethnic differences in fetal growth are present among infants with CHD. Further elucidation of the factors involved in fetal growth and the impact of CHD itself on fetal development is needed.

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KEY WORDS: Birth Defects, Black, Congenital Heart Defects, Fetal Growth, Hispanic, Infants, Intrauterine Growth Restriction, Large-for-Gestational Age, Small-for-Gestational Age.

INTRODUCTION

Congenital heart defects (CHD), malformation of the heart and major blood vessels between the third and eighth week gestation, are the most prevalent birth defects, with an estimated annual prevalence of 6–12 affected infants per 1000 live births (1, 2) and remain the leading cause of infant mortality from birth defects (3). But despite advances in the diagnosis and treatment of CHDs and our understanding embryonic and fetal development, the etiology of CHD remains unclear, with only 5–10% of CHDs attributed to chromosomal abnormalities and single-gene defects (4).

Infants with CHDs are at increased risk of infant morbidity and mortality, often requiring invasive surgical and medical interventions to repair or manage the malformation. Compared with infants without birth defects, infants with CHD have a 1.8 to 3.6 times increased risk of being small-for-gestational age (SGA; <90th percentile for birthweight-gestational age curve) than infants without CHDs (5, 6). Infants with CHD who also are SGA may have increased risk of morbidity during childhood because size at birth is one of the factors that determines medical and surgical outcomes (7, 8).

Although differences in fetal growth between infants with CHDs and infants without CHDs has been established, it is unclear whether there are racial/ethnic differences in fetal growth among infants with CHD. It is well established that black infants without birth defects are more likely to be born SGA (9), whereas Hispanic infants without birth defects have SGA rates similar to non-Hispanic (NH) white infants (10). Furthermore, black infants have an increased risk of other adverse infant outcomes, such as preterm birth and low birth weight, compared with NH-white infants (11, 12). Previous research also has shown that black infants with CHDs have increased risk of preterm birth compared with NH-white infants (13). Hence, the pattern of racial/ethnic differences in fetal growth may persist among infants with CHDs. Thus, the purpose of this study was to determine whether there were racial/ethnic differences in the distribution of fetal growth and the risk of SGA and large-for-gestational age (LGA) among infants with CHD.

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Selected Abbreviations and Acronyms

CHD = congenital heart defects
SGA = small-for-gestational age
NH = non-Hispanic
LGA = large-for-gestational age
FBDR = Florida Birth Defects Registry
OR = odds ratio
CI = confidence interval
AGA = appropriate-for-gestational age
IRB = Institutional Review Board

METHODS

Case Ascertainment

We used data from the Florida Birth Defects Registry (FBDR), to conduct a retrospective cohort study of live births. The FBDR has monitored birth defects in Florida since 1998 by merging data from birth vital records, hospital discharge databases for both inpatients and ambulatory patients, and from programs administered by the Florida Department of Health's Children's Medical Services. Infants are included in the FBDR if they are live-born to a Florida resident and have an included birth defect as coded by the *International Classification of Diseases, Ninth edition, Clinical Modification* diagnosis coding system.

Classification of Congenital Heart Defects

All live-born, singleton infants diagnosed with a CHD in the first year of life, born between January 1, 1998, and December 31, 2003, to Florida resident women ages 15 to 49 years were eligible for inclusion. CHDs were classified with the use of select *International Classification of Diseases, Ninth edition, Clinical Modification* diagnosis codes in the 745.00–747.99 range and affected infants were placed into four categories. Conotruncal CHDs included common truncus arteriosus (745.0), transposition of the great arteries (745.10–745.12 or 745.19), and tetralogy of Fallot (745.2). Right obstructive CHDs included tricuspid valve atresia and stenosis (746.1), pulmonary valve atresia and stenosis (746.01 or 746.02), and Ebstein's anomaly (746.2). Left obstructive CHDs included hypoplastic left heart syndrome (746.7), aortic valve atresia and stenosis (746.3), and coarctation of the aorta (747.10). Septal CHDs included ventricular septal defect (745.4), and atrioventricular septal defect (745.60, 745.61, or 745.69).

Study Variables

Data on gestational age, infant birth weight, maternal race/ethnicity, and potential confounders such as maternal age, maternal education, parity, maternal prenatal tobacco use, and infant sex were taken from the Florida Office of Vital Statistics birth certificate. Maternal race/ethnicity was based on maternal self-report and was first grouped by ethnicity (Hispanic or NH) and the NH group was subdivided into white, black, and other. Maternal age was categorized as 15–19, 20–29, 30–39, and 40–49 years and maternal education was group, based on years of education, as < 12, 12, and 13+ years. Fetal growth was determined using race-specific growth curves (14). Categories of fetal growth were defined as SGA (birth weights less than 10th percentile), appropriate-for-gestational age (AGA; birth weights between the 10th and 90th percentiles), and LGA (birth weights greater than 90th percentile).

We excluded 966 (9.6%) infants because they were not from a singleton birth (3.9%), had a maternal race/ethnicity designated as "Other" (2.2%), or had a maternal age less than 15 or greater than 49 years (0.3%). Infants missing data on fetal growth indices (2.5%) gestational age (1.8%), maternal education (0.4%), parity (0.03%), birth weight (0.03%), or prenatal maternal smoking (0.02%) also were excluded (numbers do not add up to 966 because some infants had more than one exclusion).

Data Analysis

Univariate analyses were used to calculate descriptive statistics, odds ratios (OR), and 95% confidence intervals (CI) to evaluate the distribution of study variables and crude associations. In multivariate multinomial logistic regression analyses, ORs and 95% CIs were used to determine the independent effects of ethnicity on risk of SGA and LGA (compared with AGA) while adjusting for maternal age, maternal education, maternal prenatal smoking, parity, and infant sex. We calculated separate multivariate multinomial regression models for each type of CHD. All statistical tests performed were two-sided and declared at the 5% significance level. The Office of Research Integrity and Compliance, Institutional Review Board (IRB) at the University of South Florida approved the study. The Florida Department of Health IRB approved the use of data from Florida birth records and FBDR data.

RESULTS

During the study period, 1,216,142 infants were live births to Florida residents, of these 10,027 had at least one of the selected CHD. After exclusions, our final study population included 9061 infants with CHD; 4851 (53.5%) were born to NH-white, 2004 (22.1%) to NH-black, and 2206 (24.4%) to Hispanic women. As seen in Table 1, we found no statistically significant racial/ethnic differences in the distribution of intrauterine growth for any type of CHD. Table 2 displays adjusted ORs and 95% CI for risk of SGA and LGA for infants with CHD by race/ethnicity. Although there were several ORs greater than or less than the null value (1.0), very few were statistically significant, indicating

TABLE 1. The distribution of intrauterine fetal growth among infants with congenital heart defects by maternal race/ethnicity, Florida Birth Defects Registry, 1998–2003

				NH-white			NH-black			Hispanic		
Defect	NH-white	NH-black	Hispanic	SGA	AGA	LGA	SGA	AGA	LGA	SGA	AGA	LGA
	n (%[a])	n (%[a])	n (%[a])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])	n (%[a,b])
Conotruncal												
Common truncus	60 (53.6)	30 (26.8)	22 (19.6)	15 (25.0)	43 (71.7)	2 (3.3)	10 (33.3)	20 (66.7)	0 (00.0)	3 (13.6)	19 (86.4)	0 (00.0)
Transposition of the great vessels	271 (57.4)	98 (20.8)	103 (21.8)	59 (21.8)	194 (71.6)	18 (6.6)	16 (16.3)	74 (75.5)	8 (8.2)	20 (19.4)	72 (69.9)	11 (10.7)
Tetralogy of Fallot	336 (55.8)	136 (22.6)	130 (21.6)	86 (25.6)	227 (67.6)	23 (6.9)	34 (25.0)	97 (71.3)	5 (3.7)	37 (28.5)	85 (65.4)	8 (6.2)
Right obstructive												
Tricuspid valve atresia/stenosis	70 (47.3)	47 (31.8)	31 (21.0)	20 (28.6)	46 (65.7)	4 (5.7)	7 (14.9)	35 (74.5)	5 (10.6)	5 (16.1)	26 (83.9)	0 (00.0)
Pulmonary valve atresia/stenosis	553 (45.9)	399 (33.1)	252 (20.9)	112 (20.3)	405 (73.2)	36 (6.5)	77 (19.3)	284 (71.2)	38 (9.5)	40 (15.9)	189 (75.0)	23 (9.1)
Ebstein's anomaly	40 (65.6)	6 (9.8)	15 (24.6)	6 (15.0)	32 (80.0)	2 (5.0)	0 (00.0)	5 (83.3)	1 (16.7)	3 (20.0)	12 (80.0)	0 (00.0)
Left obstructive												
Hypoplastic left heart syndrome	144 (50.9)	81 (28.6)	58 (20.5)	30 (20.8)	108 (75.0)	6 (4.2)	18 (22.2)	57 (70.4)	6 (7.4)	16 (27.6)	37 (63.8)	5 (8.6)
Aortic valve atresia/stenosis	123 (69.9)	24 (13.6)	29 (16.5)	23 (18.7)	86 (69.9)	14 (11.4)	9 (37.5)	13 (54.2)	2 (8.3)	5 (17.2)	22 (75.9)	2 (6.9)
Coarctation of the aorta	352 (59.5)	123 (20.8)	117 (19.8)	66 (18.8)	254 (72.2)	32 (9.1)	31 (25.2)	79 (64.2)	13 (10.6)	24 (20.5)	85 (72.7)	8 (6.8)
Septal												
Ventricular septal defect	3000 (54.3)	1109 (20.1)	1419 (25.7)	526 (17.5)	2208 (73.6)	266 (8.9)	192 (17.3)	791 (71.3)	126 (11.4)	248 (17.5)	1019 (71.8)	152 (10.7)
Atrioventricular septal defect	281 (60.2)	104 (22.3)	82 (17.6)	79 (28.1)	193 (68.7)	9 (3.2)	27 (26.0)	72 (69.2)	5 (4.8)	23 (28.1)	57 (69.5)	2 (2.4)
Total	8039 (47.9)	4032 (24.0)	4717 (28.1)	1288 (16.0)	5935 (73.8)	816 (10.2)	627 (15.6)	2892 (71.7)	513 (12.7)	668 (14.2)	3478 (73.7)	571 (12.1)

NH = non-Hispanic; SGA = small-for-gestational age; AGA = appropriate-for-gestational age; LGA = large-for-gestational age.
[a]Percentages may add up to greater than 100% as the result of rounding.
[b]Percentage of infants within each racial/ethnic group.

very few racial/ethnic differences in risk of SGA or LGA. However, after adjusting for potential confounders, NH-black infants with tetralogy of Fallot had decreased risk of LGA (OR, 0.30; 95% CI, 0.1– 0.9) compared with NH-white AGA infants. NH-blacks infants with ventricular septal defect had a modest increased risk of LGA compared with NH-white AGA infants with ventricular septal defect (OR, 1.3; 95% CI, 1.0–1.6).

DISCUSSION

Our intent was to determine the risk of SGA and LGA among NH-black and Hispanic infants with 11 types of CHD compared with similarly affected NH-white infants. On the basis of the racial/ethnic pattern of risk of SGA and LGA for unaffected infants (14), we hypothesized that NH-blacks have increased risk of SGA and decreased risk of LGA for each type of CHD compared with similarly affected NH-white infants. However, we did not observe a statistically significant increased risk of SGA for NH-black infants with any type of CHD. We observed a decreased risk of LGA only for NH-black infants with tetralogy of Fallot.

Contrary to our hypothesis, we observed increased risk of LGA for NH-black infants with several types of CHD, but increased risk was statistically significant only for infants with ventricular septal defect. For Hispanics, we hypothesized no differences in SGA or LGA rates compared with NH-whites but observed increased risk of SGA for infants with hypoplastic left heart syndrome and decreased risk of SGA for infants with common truncus and tricuspid valve atresia/stenosis compared to NH-whites; however, these findings were not statistically significant.

There are several potential explanations for our findings. Our results may suggest no racial/ethnic differences in exposure to environmental agents or genetic insult, which caused a CHD during fetal development, thus affecting the growth of all fetuses similarly. Alternatively, it could be surmised that the effect of having a CHD supersedes the fetus' inherent tendency to have SGA or LGA. This is strengthened by our results for infants with left obstructive, right obstructive, and septal CHDs with presumably a variety of genetic and nongenetic causes.

It is also highly probable that we lacked sufficient power in several CHD categories to observe statistically significant racial/ethnic differences in fetal growth, if present. For example, NH-black infants with aortic valve atresia/stenosis had more than a twofold increased risk of SGA, but there were fewer than 10 infants in this category; thus, we had insufficient power to detect a statistically significant difference, if present. Our study suggests few racial/ethnic differences in fetal growth for infants with specific types of CHD;

TABLE 2. Adjusted[a] odds ratios and 95% confidence intervals from multinomial logistic regression models for risk of small for gestational age (SGA) and large for gestational age (LGA) for infants with congenital heart defects by maternal race/ethnicity

	SGA					LGA				
	NH-whites[b]	NH-blacks	Hispanics	NH-blacks	Hispanics	NH-whites[b]	NH-blacks	Hispanics	NH-blacks	Hispanics
Congenital heart defect	n (%)	n (%)	n (%)	OR (95% CI)	OR (95% CI)	n (%)	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Conotruncal										
Common truncus	15 (53.6)	10 (35.7)	3 (10.7)	1.0 (0.3, 3.2)	0.4 (0.1, 1.9)	2 (100.0)	0 (00.0)	0 (00.0)	–[c]	–[c]
Transposition of the great vessels	59 (62.1)	16 (16.8)	20 (21.1)	0.8 (0.4, 1.5)	1.0 (0.5, 2.0)	18 (48.7)	8 (21.6)	11 (29.7)	1.1 (0.4, 2.8)	1.6 (0.7, 4.1)
Tetralogy of Fallot	227 (55.5)	97 (23.7)	85 (21.8)	1.0 (0.6, 1.7)	1.2 (0.7, 1.9)	23 (63.9)	5 (13.9)	8 (22.2)	**0.3 (0.1, 0.9)**	0.6 (0.2, 1.4)
Right Obstructive										
Tricuspid valve atresia/ stenosis	20 (62.5)	7 (21.9)	5 (15.6)	0.5 (0.1, 1.5)	0.4 (0.1, 1.5)	4 (44.4)	5 (55.6)	0 (00.0)	2.9 (0.5, 16.0)	–[c]
Pulmonary valve atresia/ stenosis	112 (48.9)	77 (33.6)	40 (17.5)	1.2 (0.8, 1.7)	0.8 (0.5, 1.3)	36 (37.1)	38 (39.2)	23 (23.7)	1.4 (0.8, 2.3)	1.3 (0.7, 2.2)
Ebstein's anomaly	6 (66.7)	0 (00.0)	3 (33.3)	–[c]	–[c]	2 (66.7)	1 (33.3)	0 (00.0)	–[c]	–[c]
Left obstructive										
Hypoplastic left heart syndrome	30 (46.9)	18 (28.1)	16 (25.0)	1.1 (0.6, 2.3)	1.7 (0.8, 3.8)	6 (35.3)	6 (35.3)	5 (29.4)	1.9 (0.6, 6.4)	2.0 (0.5, 7.2)
Aortic valve atresia/ stenosis	23 (62.2)	9 (24.3)	5 (13.5)	2.3 (0.7, 7.5)	0.7 (0.2, 2.5)	14 (77.8)	2 (11.1)	2 (11.1)	1.0 (0.2, 5.6)	0.4 (0.1, 2.0)
Coarctation of the aorta	66 (54.6)	31 (25.6)	13 (24.5)	1.4 (0.8, 2.5)	1.2 (0.7, 2.2)	32 (60.4)	13 (24.5)	8 (15.1)	1.5 (0.7, 3.0)	0.7 (0.3, 1.6)
Septal										
Ventricular septal defect	526 (54.5)	192 (19.9)	248 (25.7)	1.0 (0.9, 1.3)	1.1 (0.9, 1.3)	266 (48.9)	126 (23.2)	152 (27.9)	**1.3 (1.0, 1.6)**	1.2 (0.9, 1.5)
Atrioventricular septal defect	79 (61.2)	27 (20.9)	231 (17.8)	1.0 (0.6, 1.8)	1.1 (0.6, 1.9)	9 (56.3)	5 (31.2)	2 (12.5)	2.0 (0.6, 6.7)	1.0 (0.2, 5.4)
Total										

Bold items indicate that it is statistically significant.
NH = non-Hispanic; OR = odds ratio; CI = confidence interval.
[a]All odds ratios are adjusted for maternal age, maternal education, parity, prenatal maternal smoking and infant sex.
[b]Referent group is NH-whites.
[c]Dashed lines (–) indicate that the OR could not be computed due to zero cells or extremely small numbers.

however, direct comparison of our results to those from previously published reports is not possible because very few studies have published racial/ethnic differences in rates of SGA or LGA for infants with CHD.

Notwithstanding, our data must be interpreted in the context of several study limitations. Although our study population is from a large population-based registry, we had approximately twice as many NH-white infants as Hispanic and NH-black infants with CHD. Another potential limitation is our use of data from a passive registry constructed from merged administrative datasets. Compared with active surveillance systems, passive systems can overestimate or underestimate cases of CHDs depending on the type of CHD. A further limitation is that we used the SGA category to identify infants who are growth restricted, but this category may include infants who are constitutionally small and not growth restricted. Other study limitations include lack of detailed information on type of SGA, lack of information on subclassifications of CHD.

Despite these limitations, our study suggests some racial/ethnic differences in fetal growth among infants with CHD and further confirms that SGA is common among infants regardless of ethnic background. If NH-black infants with CHD have increased risk of SGA, they may experience even greater excess morbidity and mortality because small size at birth is associated with poor medical and surgical outcomes for infants with CHD. Poor surgical outcomes often require longer hospital stays greatly increasing medical costs. Future study is essential to determine the factors leading to decreased growth during CHD-affected pregnancies and potential interventions which decrease the incidence of SGA among infants with CHD.

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