Pediatr Cardiol (2009) 30:800–809
DOI 10.1007/s00246-009-9420-7

ORIGINAL ARTICLE

Are Black and Hispanic Infants with Specific Congenital Heart Defects at Increased Risk of Preterm Birth?

Wendy N. Nembhard · Jason L. Salemi · Melissa L. Loscalzo · Tao Wang · Kimberlea W. Hauser

Received: 29 July 2008 / Accepted: 11 March 2009 / Published online: 2 May 2009

Abstract Congenital heart defects (CHDs) are a leading cause of infant morbidity and mortality. Infants with CHDs have increased risk of preterm birth (PTB) compared to infants without birth defects. Although non-Hispanic (NH) Blacks are more likely to be born preterm and Hispanics have rates similar to those of PTB to NH-Whites, it is unknown if this pattern is present for infants with specific types of CHDs. Our intent was to determine if defect-specific risk of PTB varies by maternal race/ethnicity among infants with CHDs. We conducted a retrospective cohort study with 14,888 singleton infants from the Florida Birth Defects Registry, born in 1998–2003 to resident NH-White, NH-Black, and Hispanic women aged 15–49, diagnosed with 11 CHDs. Covariates were taken from Florida live birth certificates. PTB was defined as 20–36 weeks of gestation. Odds ratios (OR) and *P*-values were calculated from defect-specific multivariable logistic regression models; statistical significance was set at $P < 0.002$. The greatest risk of PTB was for NH-Black infants with conotruncal CHDs. NH-Blacks with common truncus, transposition of the great vessels, and tetralogy of Fallot had increased risk of PTB compared to NH-Whites (OR = 4.8, $P = 0.015$; OR = 3.1, $P = 0.004$; and OR = 2.0, $P = 0.005$, respectively). Hispanics with conotruncal CHDs had almost a twofold risk of PTB compared to NH-Whites ($P > 0.002$). NH-Blacks with tricuspid valve atresia/stenosis had 4.1 times ($P = 0.034$) and Hispanics had 2.1 times ($P = 0.314$) the risk for PTB compared to NH-Whites. NH-Blacks with hypoplastic left heart syndrome had 2.0 times ($P = 0.047$) the risk for PTB as NH-Whites. Both NH-Black and Hispanic infants with CHDs may be at increased risk of PTB, depending on the type of CHD, but the etiology is unknown. Future research is needed to further examine this complex relationship.

Keywords Fetal growth · Preterm birth · Birth defects · Congenital heart defects · Racial disparity · Black infants

Congenital heart defects (CHDs) are the most common of all birth defects, with an annual prevalence of 6–12 affected infants per 1,000 live births [11, 17, 32, 35]. Birth defects are the primary cause of infant mortality in the developed world, and CHDs are the leading cause of death among all infants with birth defects. Although 5–10% of CHDs can be attributed to chromosomal abnormalities and single-gene defects, the etiology of most nonsyndromic CHDs remains unknown, but likely involves a complex interplay between genetic and environmental factors. It is unclear whether infants with CHDs are at an increased risk of being born preterm (<37 completed weeks of gestation), since epidemiologic evidence has been inconsistent. Kramer et al. reported that the frequency of preterm birth (PTB) was not higher among infants with CHDs compared to unaffected infants [34], but more recent studies have

W. N. Nembhard (✉) · J. L. Salemi · T. Wang
Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, 13201 Bruce B. Downs Boulevard, MDC 56, Tampa, FL 33612-3805, USA
e-mail: wnembha@health.usf.edu

J. L. Salemi · K. W. Hauser
Birth Defects Surveillance Program, Department of Pediatrics, College of Medicine, University of South Florida, Tampa, FL, USA

M. L. Loscalzo
Department of Pediatrics, Division of Genetics, College of Medicine, University of South Florida, Tampa, FL, USA

reported an increased risk of PTB [43], with some studies reporting as high as a twofold increase in risk [46]. Those infants with CHDs born preterm or very preterm are at increased risk of morbidity and mortality compared to infants with CHD born at term [18, 33, 40].

Racial/ethnic disparities in PTB rates are well established, with non-Hispanic (NH) Blacks consistently having an increased risk of PTB compared to NH-Whites, while Hispanics have PTB rates comparable to NH-Whites [3, 7, 8, 45]. However, few studies have examined racial/ethnic differences in rates of PTB among infants with CHDs [37] and no studies have examined racial/ethnic differences in defect-specific risk of PTB among infants with CHDs. Therefore, the primary purpose of this study was to determine defect-specific risk of PTB for NH-Black and Hispanic infants with selected CHDs.

Materials and Methods

Study Design

We conducted a retrospective cohort study using data from the Florida Birth Defects Registry (FBDR), a passive population-based surveillance system. Since 1998 the FBDR has monitored birth defects in Florida by merging data from birth vital records, hospital discharge databases for both inpatients and ambulatory patients, and programs administered by the Florida Department of Health's (FDOH) Children's Medical Services, such as the Early Steps and Regional Perinatal Intensive Care Centers programs. 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 (ICD-9-CM), diagnosis coding system.

Study Population

We selected 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 NH-Black, NH-White, or Hispanic women, 15–49 years of age. During the study period, 1,216,142 live-born infants were born to Florida residents. Of these, 18,503 had at least one of the selected CHDs. We excluded infants who were not from a singleton birth ($n = 727$), had a maternal race/ethnicity not designated NH-Black, NH-White, or Hispanic ($n = 415$), or had a maternal age of <15 or >49 years ($n = 56$), for an unduplicated total of 1,180 (6.4%) excluded infants (the numbers do not add up to 1,180 because 18 infants had more than one exclusion).

Study Variables

CHDs were classified using select ICD-9-CM diagnosis codes in the 745.00–747.99 range and were categorized into five categories: (1) conotruncal, (2) right ventricular outflow tract obstruction, (3) left ventricular outflow tract obstruction, (4) septal, and (5) atrioventricular septal defect based on cardiac phenotype [12]. 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 ventricular outflow tract 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 ventricular outflow tract obstructive CHDs included hypoplastic left heart syndrome (746.7), aortic valve stenosis (746.3), and coarctation of the aorta (747.10). Septal CHDs included ventricular septal defect (745.4) and atrial septal defect (745.5). Atrioventricular septal defects were the final category (745.60, 745.61, or 745.69).

We then subclassified cases into three categories based on the number and type of birth defects: (1) isolated heart defect, (2) multiple heart defects, and (3) extracardiac defects. If an infant had one of the selected CHDs and no extracardiac defects diagnosed within the first year of life, he or she had an "isolated heart defect." If an infant had more than one of the selected CHD types diagnosed within the first year of life but no extracardiac defects, he or she was classified as having "multiple heart defects." Infants with known chromosomal abnormalities and/or syndromes were not included in either the "isolated" or the "multiple" heart defect categories. Infants were classified as having "extracardiac defects" if they had at least one of the 12 CHDs *and* another extracardiac defect (identified using select ICD-9-CM codes in the 740.00–754.99 range).

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 live birth certificate. We categorized gestational age as preterm (20–36 weeks) and term (37+ completed weeks) using the mother's last menstrual period (LMP). The clinical estimate of gestation (CEG) was substituted when the LMP was missing (6.9%). Infant birth weight was categorized as very low (<1,500 g), moderately low (1,500–2,499 g), and normal birth weight (2,500+ g). Fetal growth was determined using race-specific growth curves [6]. Infants with implausible birth weight and gestational age combinations were excluded (4.9%) [5]. Categories of fetal growth were defined as small for gestational age (SGA; birth weights less than 10th percentile), appropriate for gestational age (AGA; birth weights between 10th and 90th percentiles), and large for

gestational age (LGA; birth weights greater than 90th percentile).

Maternal race/ethnicity was determined 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. We excluded all women classified as "other" from the analysis (2.2%). Although the term *Hispanic* is a nonspecific term that includes immigrants from Spain, Puerto Rico, Cuba, Mexico, South America, and other Spanish-speaking countries due to our sample size and limited information on country of origin, we have included all Hispanic/Spanish/Latin ethnicities in the category *Hispanic*, which is consistent with the practice of the U.S. Census Bureau and Florida Department of Health. Maternal age was categorized as 15–19, 20–29, 30–39, and 40–49 years. Prenatal maternal tobacco use was classified as "yes" or "no" and maternal education was categorized, based on years of education, as less than high school (0–11 years), high school (12 years), and more than high school (13+ years).

We also used data on all live births in Florida during the study period from the Florida Community Health Assessment Resource Tool Set (CHARTS) to obtain race/ethnic–specific PTB rates in the general Florida population [24]. These data were used to determine if the PTB rates observed in our study were in excess of the PTB rates present in the general population.

We excluded an additional 3.1% ($n = 535$) of the study population due to missing data on key study variables: 467 had missing or out of range fetal growth indexes (gestational age, birth weight), 69 were missing maternal education, 3 were missing data on parity, and 3 were missing data on prenatal maternal smoking (numbers do not add up to 535 since some infants had more than one exclusion). Finally, we excluded all infants who were LGA ($n = 1{,}900$) due to small numbers within defect categories.

Statistical Methods

We calculated descriptive statistics, chi-square tests, odds ratios (ORs), and 95% confidence intervals (CIs) to evaluate the distribution and bivariate associations for maternal race/ethnicity, study covariates, and the outcome, PTB. ORs and 95% CIs were calculated from the Florida CHARTS data to determine risk of PTB during the study period for each race/ethnic group in the general Florida population [24]. We used logistic regression models to calculate ORs and 95% CIs for the association between race/ethnicity and risk of specific types of CHD (using NH-Whites as the referent group) and the association between race/ethnicity and overall risk of having an isolated, multiple, syndromic, or trisomy and a CHD. Logistic regression was also used to determine the association between race/ethnicity and risk of PTB comparing NH-Blacks and Hispanics with NH-Whites.

Separate models were computed for risk of PTB among infants with any CHD and for each type of CHD adjusting for potential covariates. We included two effect modification (interaction) terms in the model to examine the effects of intrauterine growth and maternal race/ethnicity on PTB. Likelihood ratio tests evaluated model fit comparing the full model to a model with just the interaction terms removed. The effect modification terms were not statistically significant in the multivariable models so we report only final main effect models.

Our initial statistical significance level was set at $P < 0.05$ for main effects. However, since hypotheses were tested simultaneously, at least two results from our final models would be statistically significant by chance alone at the $P < 0.05$ level. Thus, we used the Bonferroni correction to adjust for multiple hypothesis testing, which reduces the statistical significance level of each individual test from $P < 0.05$ to a more stringent level in order to keep the familywise error rate (FWER) at 0.05 [30]. Specifically, the Bonferroni method [42] tests each of the n hypotheses at significance level α/n to control FWER at α. All P-values were two sided in our analyses. SAS software version 9.1.3 and STATA [44] were used for all analyses.

The Office of Research Integrity and Compliance, Institutional Review Board, at the University of South Florida approved the study. The FDOH approved the use of data from Florida birth records and FBDR data.

Results

Among the 1,216,142 live-born infants in Florida during the study period, the rate of PTB was 13.0%, but it was 11.4% for NH-Whites, 18.1% for NH-Blacks, and 11.7% for Hispanics. The relative risk of PTB for NH-Black infants was 1.7. Our final study population included 14,888 infants with CHD, of which 68.8% had isolated CHD, 14.9% had multiple heart defects, and 16.3% had extracardiac defects. Twenty-two percent were born low birth weight, 17.4% were SGA, and 24.5% were born preterm. The rate of PTB varied by maternal race/ethnicity; 22.3% of NH-Whites were preterm, and 33.1% of NH-Blacks and 21.0% of Hispanics were born preterm. We observed no increased risk of PTB overall for Hispanics compared to NH-Whites.

Sociodemographic and obstetric characteristics of the study population by maternal race/ethnicity are reported in Table 1. As shown in Table 2, there was no difference in risk of PTB for NH-Black compared to NH-White infants except for pulmonary valve atresia/stenosis (OR = 1.5, $P < 0.002$) and atrial septal defects (OR = 1.2,

Table 1 Maternal and infant characteristics of infants born with congenital heart defects by maternal race/ethnicity, Florida Birth Defects Registry, 1998–2003 ($N = 14,888$)

	Non-Hispanic White ($n = 7,223$)		Non-Hispanic Black ($n = 3,519$)		Hispanic ($n = 4,146$)		P (χ^2 test)[b]
	n	%[a]	n	%[a]	n	%[a]	
Maternal age							
15–19 yr	684	9.5	624	17.7	434	10.5	
20–29 yr	3,317	45.9	1,867	53.1	2,023	48.8	
30–39 yr	2,921	40.4	894	25.4	1,530	36.9	
40–49 yr	301	4.2	134	3.8	159	3.8	<0.001
Maternal education							
<High school	1,151	15.9	1,010	28.7	1,022	24.7	
High school	2,315	32.1	1,495	42.5	1,382	33.3	
>High school	3,757	52.0	1,014	28.8	1,742	42.0	<0.001
Prenatal smoking							
Yes	1,178	16.3	182	5.2	82	2.0	
No	6,045	83.7	3,337	94.8	4,064	98.0	<0.001
Parity							
Nulliparous	3,182	44.0	1,279	36.3	1,783	43.0	
Multiparous	4,041	56.0	2,240	63.7	2,363	57.0	<0.001
Infant sex							
Female	3,526	48.8	1,761	50.0	2,109	50.9	
Male	3,697	51.2	1,758	50.0	2,037	50.9	0.096
Gestational age							
20–31 wk	402	5.6	456	13.0	225	5.4	
32–36 wk	1,208	16.7	708	20.1	647	15.6	
37+ wk	5,613	77.7	2,355	66.9	3,274	79.0	<0.001
Birth weight							
VLBW (<1,500 g)	398	5.5	456	13.0	220	5.3	
MLBW (1,500–2,499 g)	1,013	14.0	658	18.7	499	12.0	
Normal (2,500+ g)	5,812	80.5	2,405	68.3	3,427	82.7	<0.001
Intrauterine growth							
SGA	1,288	17.8	627	17.8	668	16.1	
AGA	5,935	82.2	2,892	82.2	3,478	83.9	0.046
Method of delivery							
Vaginal	4,495	71.1	2,104	69.5	2,411	69.3	
Cesarean section	1,830	28.9	924	30.5	1,067	30.7	0.117

VLBW very low birth weight, *MLBW* moderately low birth weight, *SGA* small for gestational age, *AGA* appropriate for gestational age

[a] Percentages may add up to more than 100% due to rounding

[b] All *P*-values are two-sided

$P < 0.002$). A similar pattern was seen for Hispanics. Hispanic infants were less likely to be born with any CHD compared to NH-Whites except for ventricular septal defect, for which they were at increased risk (OR = 1.8, $P < 0.002$). NH-Black and Hispanic infants with CHDs had decreased risk of being born with multiple CHD, extracardiac defects, syndromes, or trisomies compared to NH-Whites. We also observed few racial/ethnic differences in the distribution of isolated CHDs, multiple CHDs, and extracardiac defects among infants with CHD (data not shown).

Conotruncal Congenital Heart Defects

Table 3 displays the unadjusted and adjusted ORs, *P*-values, and 95% CIs from each logistic regression model for risk of PTB by maternal race/ethnicity. After adjusting for maternal education, maternal age, parity, prenatal maternal smoking, infant sex, and number of birth defects, overall, NH-Black infants with CHDs had almost a twofold increased risk of PTB compared to NH-Whites (OR = 1.8, $P < 0.002$). The greatest risk of PTB for NH-Blacks was observed for infants with conotruncal CHD; NH-Blacks

Table 2 Number, percentage, odds ratios, 95% confidence intervals, and *P*-values for the association between congenital heart defects and maternal race/ethnicity, Florida Birth Defects Registry, 1998–2003 ($N = 14{,}888$)

Congenital heart defect	Non-Hispanic White ($n = 7{,}223$)		Non-Hispanic Black ($n = 3{,}519$)			Hispanic ($n = 4{,}146$)		
	n (%[a])	OR [95% CI]	*n* (%[a])	OR [95% CI]	*P*-value[b]	*n* (%[a])	OR [95% CI]	*P*-value[b]
Conotruncal								
Truncus arteriosus	58 (52.7)	1.00	30 (27.3)	1.06 [0.68, 1.65]	0.789	22 (20.0)	0.66 [0.40, 1.08]	0.097
Transposition of great vessels	253 (58.2)	1.00	90 (20.7)	0.72 [0.57, 0.92]	0.009	92 (21.1)	0.63 [0.49, 0.80]	0.000
Tetralogy of Fallot	313 (55.3)	1.00	131 (23.1)	0.85 [0.69, 1.05]	0.136	122 (21.6)	0.67 [0.54, 0.83]	0.000
Right VOTO								
Tricuspid valve atresia	66 (47.5)	1.00	42 (30.2)	1.31 [0.89, 1.93]	0.174	31 (22.3)	0.82 [0.53, 1.25]	0.355
Pulmonary valve atresia/stenosis	517 (46.7)	1.00	361 (32.6)	1.48 [1.29, 1.71]	0.000	229 (20.7)	0.76 [0.65, 0.89]	0.001
Ebstein's anomaly	38 (65.5)	1.00	5 (8.6)	0.27 [0.11, 0.68]	0.006	15 (25.9)	0.69 [0.38, 1.25]	0.218
Left VOTO								
Hypoplastic left heart	138 (51.9)	1.00	75 (28.2)	1.12 [0.84, 1.49]	0.441	53 (19.9)	0.66 [0.48, 0.91]	0.012
Aortic valve stenosis/atresia	109 (69.0)	1.00	22 (13.9)	0.41 [0.26, 0.65]	0.000	27 (17.1)	0.43 [0.28, 0.65]	0.000
Coarctation of the aorta	320 (59.4)	1.00	110 (20.4)	0.70 [0.56, 0.87]	0.001	109 (20.2)	0.58 [0.47, 0.73]	0.000
Septal								
Ventricular septal defect	2734 (54.9)	1.00	983 (19.7)	0.64 [0.58, 0.69]	0.000	1267 (25.4)	1.76 [1.61, 1.91]	0.000
Atrial septal defect	4573 (45.4)	1.00	2394 (23.7)	1.23 [1.13, 1.34]	0.000	3117 (30.9)	0.72 [0.67, 0.78]	0.000
Atrioventricular septal defect								
Atrioventricular septal defect	272 (60.3)	1.00	99 (22.0)	0.74 [0.59, 0.93]	0.011	80 (17.7)	0.50 [0.39, 0.65]	0.000
Type of defect								
Isolated heart defect	4768 (66.0)	1.00	2535 (72.0)	1.00		2942 (71.0)	1.00	
Multiple heart defects	1159 (16.1)	1.00	445 (12.7)	0.72 [0.64, 0.81]	0.000	607 (14.6)	0.85 [0.76, 0.95]	0.003
Extracardiac defects	1296 (17.9)	1.00	539 (15.3)	0.78 [0.70, 0.87]	0.000	597 (14.4)	0.75 [0.67, 0.83]	0.000
Syndromes								
Yes	535 (7.4)	1.00	214 (6.1)	0.81 [0.69, 0.95]	0.011	261 (6.3)	0.84 [0.72, 0.98]	0.026
No	6688 (92.6)	1.00	3305 (93.9)	1.00		3885 (93.7)	1.00	
Trisomies								
Yes	456 (6.3)	1.00	182 (5.2)	0.81 [0.68, 0.97]	0.019	234 (5.6)	0.89 [0.75, 1.04]	0.151
No	6767 (93.7)	1.00	3337 (94.8)	1.00		3912 (94.4)	1.00	

VOTO ventricular outflow tract obstructive defect

[a] Percentages may add up to more than 100% due to rounding

[b] All *P*-values are two-sided

Table 3 Unadjusted and adjusted[a] odds ratios and 95% confidence intervals from separate logistic regression models for risk of preterm birth among infants born with CHD by maternal race/ethnicity, Florida Birth Defects Registry, 1998–2003 ($N = 14{,}888$)

Congenital heart defect	n[c]	Non-Hispanic White ($n = 7{,}223$)	Non-Hispanic Black ($n = 3{,}519$)				Hispanic ($n = 4{,}146$)				
		OR [95% CI]	Unadjusted		Adjusted			Unadjusted		Adjusted		
			OR	[95% CI]	OR	[95% CI]	P-value[b]	OR	[95% CI]	OR	[95% CI]	P-value[b]
Conotruncal defects												
Common truncus	110	Referent	2.8	[1.0, 7.6]	4.8	[1.4, 16.7]	0.015	1.1	[0.3, 3.8]	1.3	[0.3, 5.6]	0.737
Transposition of great vessels	435	Referent	2.7	[1.5, 4.8]	3.1	[1.6, 5.9]	0.001	1.5	[0.8, 2.8]	1.8	[0.8, 3.7]	0.134
Tetraology of Fallot	566	Referent	1.8	[1.2, 2.9]	2.0	[1.2, 3.4]	0.005	0.8	[0.4, 1.3]	0.7	[0.4, 1.2]	0.207
Right VOTO												
Tricuspid valve atresia/stenosis	139	Referent	2.0	[0.8, 5.1]	4.5	[1.2, 16.2]	0.022	2.2	[0.3, 3.1]	2.3	[0.5, 9.9]	0.254
Pulmonary valve atresia/stenosis	1,108	Referent	1.8	[1.4, 2.3]	1.6	[1.2, 2.2]	0.001	0.7	[0.5, 1.1]	0.8	[0.5, 1.1]	0.165
Ebstein's anomaly	58	Referent	0.7	[0.1, 7.0]	0.4	[0.03, 5.5]	0.517	0.6	[0.1, 2.3]	0.7	[0.1, 5.1]	0.688
Left VOTO												
Hypoplastic left heart	267	Referent	2.2	[1.1, 4.3]	2.0	[1.0, 4.2]	0.047	1.4	[0.6, 3.1]	1.2	[0.5, 2.8]	0.712
Aortic valve atresia/stenosis	158	Referent	0.9	[0.3, 3.0]	1.0	[0.3, 3.4]	0.938	3.0	[1.2, 7.1]	2.9	[1.0, 8.1]	0.043
Coarctation of aorta	539	Referent	1.2	[0.7, 2.2]	1.1	[0.6, 2.0]	0.861	1.3	[0.8, 2.3]	1.3	[0.7, 2.4]	0.349
Septal defects												
Ventricular septal defect	4,985	Referent	1.9	[1.6, 2.2]	2.0	[1.6, 2.3]	<0.002	1.1	[0.9, 1.3]	1.1	[1.0, 1.4]	0.157
Atrial septal defect	10,087	Referent	1.6	[1.4, 1.8]	1.7	[1.5, 1.9]	<0.002	0.9	[0.8, 1.0]	0.9	[0.8, 1.0]	0.216
Atrioventricular septal defect												
Atrioventricular septal defect	451	Referent	1.8	[1.1, 3.2]	1.9	[1.1, 3.5]	0.023	1.2	[0.6, 2.2]	1.3	[0.7, 2.5]	0.434
All hearts	14,888	Referent	1.7	[1.6, 1.9]	1.8	[1.6, 2.0]	<0.002	0.9	[0.9, 1.0]	1.0	[0.9, 1.1]	0.835

VOTO ventricular outflow tract obstructive defect

[a] All models adjusted for maternal education, maternal age, prenatal smoking, parity, infant sex, and number of defects

[b] Statistical significance level for Bonferroni adjusted P-value is $P < 0.002$

[c] Numbers do not add up to 14,888 since an infant may have more than one CHD

had a two- to fourfold increased risk of PTB compared to NH-Whites. NH-Black infants with common truncus had 4.8 times increased risk of PTB ($P = 0.015$), those with transposition of the great vessels 3.1 times the risk of PTB ($P = 0.001$), and those with tetralogy of Fallot 2.0 times the risk of PTB ($P = 0.005$) in comparison to NH-White infants. Although not statistically significant and of a lesser magnitude, a similar pattern of increased risk was seen among Hispanics.

Right Ventricular Outflow Tract Obstructive CHDs

Risk of PTB was also increased among NH-Black infants with right obstructive heart defects. NH-Black infants with pulmonary valve atresia/stenosis had 1.6 times ($P = 0.001$) the risk of PTB compared to NH-White affected infants.

Left Outflow Tract Obstructive CHDs

The only increased risk of PTB observed for NH-Blacks with left obstructive CHD was for infants with hypoplastic left heart syndrome (OR = 2.0, $P = 0.047$). We also found that Hispanics had nearly three times higher risk of aortic valve atresia/stenosis than NH-Whites (OR = 2.9, $P = 0.043$).

Septation Congenital Heart Defects

We observed increased risk of PTB only among NH-Black infants with septal defects. NH-Black infants with ventricular and atrial septal defects had increased risk of PTB compared to NH-White infants.

Discussion

We found that NH-Black infants with CHDs had increased defect-specific risk of PTB compared to NH-Whites. Specifically, we observed increased risk of PTB for NH-Black infants with conotruncal, right outflow tract obstructive, and septation CHDs. The greatest risks observed were for NH-Black infants with conotruncal CHDs. One potential explanation for these findings is that the increased risks we observed reflect the underlying increased risk of PTB present between NH-Blacks and NH-Whites in the general Florida population. While this may explain some of our results, it does not fully explain the increased risk we observe for some types of CHD. It is true that our overall risk of PTB for NH-Black infants with CHDs compared to affected NH-White infants was the same as the risk of PTB observed for the general population of NH-Black infants born to resident Florida women during the study period (OR = 1.7). While the risk for NH-Black infants with septation CHDs and pulmonary valve atresia/stenosis had risks of PTB similar to the risk in the general population, the increased risk observed for NH-Black infants with conotruncal CHDs, tricuspid valve atresia/stenosis, and hypoplastic left heart syndrome was more than a twofold increased risk (in some cases as high as a fourfold increase) of PTB compared to NH-Whites, which is larger in magnitude than the 1.7 increased risk for NH-Black infants observed in the general population. Although the increased risk observed for NH-Black infants with common truncus was not statistically significant at the conservative significance level of $P < 0.002$, the magnitude of the increased risk is consistent with the overall pattern of risk observed for NH-Blacks with conotruncal defects.

It is unclear why NH-Black infants with these defects are at much higher risk of PTB than NH-White infants or NH-Black infants in the general population. A potential explanation is that the prevalence of conotruncal CHDs and tricuspid valve atresia/stenosis was higher among NH-Black infants than among NH-White infants. In contrast, we found that NH-Black infants were less likely or had similar rates of conotruncal CHD and a similar rate of tricuspid valve atresia/stenosis compared to NH-Whites. We also did not observe statistically significant differences in rates of isolated CHDs, multiple CHDs, or multiple defects or in rates of syndromes or trisomies between NH-Blacks and NH-Whites with conotruncal CHDs or tricuspid valve atresia/stenosis.

Another important finding in our study was the consistent increased risk of PTB for Hispanic infants with conotruncal CHDs, tricuspid valve atresia/stenosis, and pulmonary valve atresia/stenosis. Unlike NH-Black infants, there was no increased risk of PTB for Hispanics compared to NH-Whites in the general Florida population, and it is well established that Hispanic infants have similar or slightly lower rates of PTB compared to NH-Whites in the United States [36]. Thus, the increased risks we observed are surprising. One potential explanation is that the proportion of Black Hispanics among cases is high enough to account for the increase risk of PTB; however, of the 5,021 Hispanics in our study, only 2.3% were of Black race. Although none of the increased risks we observed were statistically significant at $P < 0.002$, the consistency and magnitude of the associations provide support for the main findings of our study and further investigation is needed.

Differences in the prevalence of conotruncal CHDs, tricuspid valve atresia/stenosis, and aortic valve atresia/stenosis between Hispanic and NH-White infants also do not explain our observations for Hispanics. Hispanic infants were less likely or had similar rates of conotruncal CHDs and a similar rate of tricuspid valve atresia/stenosis and aortic valve atresia/stenosis compared to NH-Whites. There were no statistically significant differences in rates

of isolated CHDs, multiple CHDs, or multiple defects in rates of syndromes or trisomies between Hispanics and NH-Whites with conotruncal CHDs or tricuspid valve atresia/stenosis.

Another concern might be that our results reflect only differences in rates of iatrogenic PTB among racial/ethnic groups rather than true differences in rates of spontaneous PTB. However, no statistically significant racial/ethnic differences in rates of inductions, cesarean sections, or rates of iatrogenic PTB for each type of CHD were observed.

The absence of prior published research on risk of PTB for NH-Black or Hispanic infants with specific types of CHDs precludes direct comparison of our results. Kramer et al. reported no differences in the frequency of PTB for CHD infants [34], whereas Shaw et al. and Tanner et al. reported increased risk of PTB among infants with CHDs [43, 46]. Even less is known about racial/ethnic differences in PTB among infants with CHDs. We recently reported increased risk of PTB among NH-Black SGA and AGA infants with CHDs [37]. Due to the paucity of research in this area, it is unclear whether the etiology of PTB among infants with CHDs is similar to unaffected infants. Furthermore, in contrast to the plethora of studies on the Black-White disparity in PTB among unaffected infants, there is little knowledge about racial/ethnic differences in risk of PTB among infants with birth defects; hence it is unclear whether the risk factors associated with increased risk of PTB for unaffected Black infants are the same for increased risk of PTB for Black infants with CHDs. This relationship is further complicated because some of the risk factors associated with PTB in unaffected infants are associated with increased risk of CHDs [2, 11, 14, 16, 17, 21, 26, 31, 47, 54] as well as PTB [20, 25, 27–29, 48]. Therefore it may be difficult to disentangle the complex issue of excess risk of PTB for infants with CHDs born to Black women.

Major strengths of our study include our large, population-based, ethnically diverse sample and inclusion of the most prevalent types of CHDs with a major impact on infant morbidity and mortality. We also adjusted for the potential effects of important covariates and examined the role of effect modification between intrauterine fetal growth and race/ethnicity.

Despite these strengths, some potential limitations should be addressed. First, we used the FBDR, a passive surveillance system, to ascertain cases of CHD. Compared to active surveillance systems, which ascertain cases from medical record abstraction, passive systems usually underestimate the number of infants with birth defects, particularly CHDs. Thus it is probable that our data underestimate the true number of CHD cases in Florida. Another possible criticism of our data is that, in general, birth defects registries which limit case ascertainment to the first year of life usually exclude infants who die shortly after birth without an autopsy, whose CHD is not diagnosed until after hospital discharge, or who are diagnosed later in childhood or adulthood. Another related issue is the possibility that infants born to NH-Black women may be more likely to have their CHD diagnosed since NH-Black infants are more likely to be born preterm and those infants may have more diagnostic procedures and examinations at the neonatal intensive care unit, etc. (more opportunity to have CHD diagnosed) than NH-Whites. But, there is no evidence to support that there are racial/ethnic differences in age at diagnosis, i.e., differential ascertainment of CHD by maternal race/ethnicity [22, 23]. Another important potential limitation is our method for determining gestational age (PTB). Misclassification of PTB can occur, depending on the source of the estimation of gestational age [53] and pattern of missing data in the study population [4, 9, 50–52]. In our study, only 6.9% of the study population had missing data on LMP and there were no differences in the missing pattern by maternal race/ethnicity. To assess the bias injected into our study by substitution of CEG for LMP, we compared gestational age data obtained by using the CEG and the LMP for infants who had both measures available and found that using the CEG as the gestational age determinant for all analyses would not have affected our results. Another possible criticism of our study is lack of information on potentially important clinical factors such as subclassification, case confirmation, and severity of CHD.

Nevertheless, despite these potential limitations, we found racial/ethnic differences in risk of PTB for infants with specific types of CHD and our findings have several implications for future clinical research. While it is clear from this analysis that the presence of CHD, particularly of a complex nature, in the fetus confers a significant risk for PTB, the reasons for this are unknown. Ultimately, of most interest is whether the increased risk of PTB we observed for NH-Black and Hispanic infants with specific CHD translates into increased risk of morbidity and mortality during infancy and childhood. Infants born with CHD require intensive surgical and medical interventions to repair malformations of the heart. In the infant with CHD, the added complication of PTB has serious consequences. Preterm infants have immature respiratory structures and other vital organ systems, which pose cardiorespiratory challenges for the preterm infant. Complications associated with concomitant morbidities of PTB such as hyaline membrane disease, necrotizing enterocolitis, and intraventricular hemorrhage add further complexity to management of infants with CHD born preterm. Some debate persists as to whether early surgical intervention or medical therapy is the best course of management for these infants [1, 10, 13,

15, 19, 38, 40, 41]. Notwithstanding, compared to infants with CHD born at term or preterm infants without CHD, infants with CHD born preterm have higher morbidity and mortality rates [18, 39, 49]. At present racial/ethnic differences in risks of morbidity and mortality for these infants is unknown. If racial/ethnic differences are present, minority infants will require more invasive procedures, which may necessitate longer hospital stays, generating increased demand on the healthcare system and greater medical costs. With the disparity in PTB rates increasing between Whites and Blacks in the United States, our findings may have serious consequences for the health-care system if increasing trends in PTB are also present for infants with CHD. Further research is needed to evaluate trends in PTB among infants with CHD, as well as to determine if racial/ethnic differences are present in these trends. Furthermore, this study underscores the importance of heightened surveillance of pregnancies known or suspected to be affected with CHD by high-risk perinatologists and perinatal/pediatric cardiologists. This would be particularly important in those ethnic groups at greatest risk. Further investigation will be instrumental in working toward identifying causative factors leading to preterm birth in neonates with CHD. Our increased understanding of these risk factors potentially may offer means by which to reduce this significant contributor to infant morbidity and mortality.

In summary, we found that NH-Black infants with CHD have increased risk of PTB compared to NH-White infants and that the risk varies by type of CHD. At present, the consequences of these findings on morbidity and mortality are unclear. Future studies should investigate the etiologic factors underlying and the consequences of this complex association observed among infants with CHD.

Acknowledgments This project was funded in part by the Florida Department of Health, Florida Birth Defects Registry (contract no. CO0B5), and the authors would like to acknowledge the contributions of Dr. Lemuel Moye, who provided valuable feedback on several drafts of the manuscript. The authors do not have a commercial or other association that might pose a conflict of interest and this submission has the full knowledge and approval of the listed coauthors. The work for this article was done at the University of South Florida, College of Public Health, Tampa.

References

1. Abrishamchian R, Kanhai D, Zwets E, Nie L, Cardarelli M (2006) Low birth weight or diagnosis, which is a higher risk?—a meta-analysis of observational studies. Eur J Cardiothorac Surg 30:700–705
2. Adams MM, Mulinare J, Dooley K (1989) Risk factors for conotruncal cardiac defects in Atlanta. J Am Coll Cardiol 14:432–442
3. Ahern J, Pickett KE, Selvin S, Abrams B (2003) Preterm birth among African American and white women: a multilevel analysis of socioeconomic characteristics and cigarette smoking. J Epidemiol Commun Health 57:606–611
4. Alexander GR, Tompkins ME, Petersen DJ, Hulsey TC, Mor J (1995) Discordance between LMP-based and clinically estimated gestational age: implications for research, programs, and policy. Public Health Rep 110:395–402
5. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M (1996) A United States national reference for fetal growth. Obstet Gynecol 87:163–168
6. Alexander GR, Kogan MD, Himes JH (1999) 1994–1996 U.S. Singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. Matern Child Health J 3:225–231
7. Anonymous (1999) Preterm singleton births—United States, 1989–1996. MMWR Morb Mortal Wkly Rep 48:185–189
8. Ashton D (2006) Prematurity-infant mortality: the scourge remains. Ethn Dis 16:S3-58–S-62
9. Behrman RE, Butler AS (2007) Preterm birth: causes, consequences, and prevention. Available at: http://www.nap.edu/catalog/11622.html
10. Beyens T, Biarent D, Bouton JM, Demanet H, Viart P, Dessy H, Deville A, Lamote J, Deuvaert FE (1998) Cardiac surgery with extracorporeal circulation in 23 infants weighing 2500 g or less: short and intermediate term outcome. Eur J Cardiothorac Surg 14:165–172
11. Botto LD, Lynberg MC, Erickson JD (2001) Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. Epidemiology 12:485–490
12. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, National Birth Defects Prevention Study (2007) Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol 79:714–727
13. Bove T, Francois K, De Groote K, Suys B, De Wolf D, Verhaaren H, Matthys D, Moerman A, Poelaert J, Vanhaesebroeck P, Van Nooten G (2004) Outcome analysis of major cardiac operations in low weight neonates. Ann Thorac Surg 78:181–187
14. Carmichael SL, Shaw GM (2000) Maternal life event stress and congenital anomalies. Epidemiology (Cambr) 11:30–35
15. Chang AC, Hanley FL, Lock JE, Castaneda AR, Wessel DL (1994) Management and outcome of low birth weight neonates with congenital heart disease. J Pediatr 124:461–466
16. Chavez GF, Cordero JF, Becerra JE (1988) Leading major congenital malformations among minority groups in the United States, 1981–1986. MMWR CDC Surveill Summ 37:17–24
17. Correa-Villasenor A, McCarter R, Downing J, Ferencz C (1991) White-black differences in cardiovascular malformations in infancy and socioeconomic factors. The Baltimore–Washington Infant Study Group. Am J Epidemiol 134:393–402
18. Dees E, Lin H, Cotton RB, Graham TP, Dodd DA (2000) Outcome of preterm infants with congenital heart disease. J Pediatr 137:653–659
19. Dimmick S, Walker K, Badawi N, Halliday R, Cooper SG, Nicholson IA, Sherwood M, Chard RB, Hawker R, Lau KC, Jones O, Grant PW, Sholler GF, Winlaw DS (2007) Outcomes following surgery for congenital heart disease in low-birthweight infants. J Paediatr Child Health 43:370–375
20. Dunkel-Schetter C, Gurung RAR, Lobel M, Wadhwa PD (2000) Stress processes in pregnancy and birth: psychological, biological and sociocultural influences. In: Baum A, Revenson T, Singer J (eds) Handbook of health psychology. Lawrence Erlbaum, Hillsdale, NJ, pp 495–518
21. Ferencz C, Correa-Villasenor A, Loffredo C (1997) Genetic and environmental risk factors of major cardiovascular malformations: the Baltimore–Washington Infant Study: 1981–1989. Futura, Armonk, NY, pp 12–28
22. Fixler DE, Pastor P, Chamberlin M, Sigman E, Eifler CW (1990) Trends in congenital heart disease in Dallas County births. 1971–1984. Circulation 81:137–142

23. Fixler DE, Pastor P, Sigman E, Eifler CW (1993) Ethnicity and socioeconomic status: impact on the diagnosis of congenital heart disease. J Am Coll Cardiol 21:1722–1726
24. Florida Department of Health Office of Planning Evaluation & Data Analysis (2007) Florida community health assessment resource tool set (charts). Available at: http://www.floridacharts.com
25. Geronimus AT (2001) Understanding and eliminated racial inequalities in women's health in the United States: the role of the weathering conceptual framework. JAMA 56:133–136
26. Hernandez FA, Miller RH, Schiebler GL (1969) Rarity of coarctation of the aorta in the American Negro. J Pediatr 74:623–625
27. Hobel CJ, Culhane J (2003) Role of psychosocial and nutritional stress on poor pregnancy outcome. J Nutr 133:1717S
28. Holzman C, Jetton J, Fisher R, Senagore P, Mohan M, Paneth N (1999) Association of maternal igm concentrations above the median at 15–19 weeks of gestation and early preterm delivery. Lancet 354:1095–1096
29. Holzman C, Bullen B, Fisher R, Paneth NS, Reuss L, Prematurity Study Group (2001) Pregnancy outcomes and community health: the pouch study of preterm delivery. Paediatr Perinat Epidemiol 15:136–158
30. Hsu JC (1996) Multiple comparisons: theory and methods. Chapman & Hall, London, pp 7–20
31. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL (2007) Noninherited risk factors and congenital cardiovascular defects: current knowledge. A scientific statement from the American heart association council on cardiovascular disease in the young: endorsed by the American Academy of Pediatrics. Circulation 115:2995–3014
32. Johnson KC, Rouleau J (1997) Temporal trends in Canadian birth defects birth prevalences, 1979–1993. Can J Public Health 88:169–176
33. Kecskes Z, Cartwright DW (2002) Poor outcome of very low birthweight babies with serious congenital heart disease. Arch Dis Child Fetal Neonatal Ed 87:F31–F33
34. Kramer HH, Trampisch HJ, Rammos S, Giese A (1990) Birth weight of children with congenital heart disease. Eur J Pediatr 149:752–757
35. Lin AE, Herring AH, Amstutz KS, Westgate MN, Lacro RV, Al-Jufan M, Ryan L, Holmes LB (1999) Cardiovascular malformations: changes in prevalence and birth status, 1972–1990. Am J Med Genet 84:102–110
36. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S (2006) Births: final data for 2004. Natl Vital Stat Rep 55:1–101
37. Nembhard WN, Salemi JL, Hauser KW, Kornosky JL (2007) Are there ethnic disparities in risk of preterm birth among infants born with congenital heart defects? Birth Defects Res A Clin Mol Teratol 79:754–764
38. Oppido G, Napoleone CP, Formigari R, Gabbieri D, Pacini D, Frascaroli G, Gargiulo G (2004) Outcome of cardiac surgery in low birth weight and premature infants. Eur J Cardiothorac Surg 26:44–53
39. Pawade A, Waterson K, Laussen P, Karl TR, Mee RB (1993) Cardiopulmonary bypass in neonates weighing less than 2.5 kg: analysis of the risk factors for early and late mortality. J Card Surg 8:1–8
40. Reddy VM, McElhinney DB, Sagrado T, Parry AJ, Teitel DF, Hanley FL (1999) Results of 102 cases of complete repair of congenital heart defects in patients weighing 700 to 2500 grams. J Thorac Cardiovasc Surg 117:324–331
41. Rossi AF, Seiden HS, Sadeghi AM, Nguyen KH, Quintana CS, Gross RP, Griepp RB (1998) The outcome of cardiac operations in infants weighing two kilograms or less. J Thorac Cardiovasc Surg 116:28–35
42. Shaffer J (1995) Multiple hypothesis testing. Annu Rev Psych 46:561–584
43. Shaw GM, Savitz DA, Nelson V, Thorp JM Jr (2001) Role of structural birth defects in preterm delivery. Paediatr Perinat Epidemiol 15:106–109
44. StataCorp (2003) Stata statistical software: release 8. StataCorp, College Station, TX
45. Stotland NE, Caughey AB, Lahiff M, Abrams B (2006) Weight gain and spontaneous preterm birth: the role of race or ethnicity and previous preterm birth. Obstet Gynecol 108:1448–1455
46. Tanner K, Sabrine N, Wren C (2005) Cardiovascular malformations among preterm infants. Pediatrics 116:e833–e838
47. Tikkanen J, Heinonen OP (1991) Maternal hyperthermia during pregnancy and cardiovascular malformations in the offspring. Eur J Epidemiol 7:628–635
48. Wadhwa PD, Culhane JF, Rauh V, Barve SS (2001) Stress and preterm birth: Neuroendocrine, immune/inflammatory, and vascular mechanisms. Mater Child Health J 5:119–125
49. Wernovsky G, Rubenstein SD, Spray TL (2001) Cardiac surgery in the low-birth weight neonate. New approaches. Clin Perinatol 28:249–264
50. Wilcox AJ, Dunson D, Baird DD (2000) The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ 321:1259–1262
51. Wingate MS, Alexander GR, Buekens P, Vahratian A (2007) Comparison of gestational age classifications: date of last menstrual period vs. clinical estimate. Ann Epidemiol 17:425–430
52. Yang H, Kramer MS, Platt RW, Blondel B, Breart G, Morin I, Wilkins R, Usher R (2002) How does early ultrasound scan estimation of gestational age lead to higher rates of preterm birth? Am J Obstet Gynecol 186:433–437
53. Yang J, Hartmann KE, Herring AH, Savitz DA (2005) Reducing misclassification in assignment of timing of events during pregnancy. Epidemiology (Cambr) 16:121–123
54. Zhang J, Cai WW (1993) Association of the common cold in the first trimester of pregnancy with birth defects. Pediatrics 92:559–563