Are There Ethnic Disparities in Risk of Preterm Birth among Infants Born with Congenital Heart Defects?

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BACKGROUND: Birth defects and preterm birth (PTB) are leading causes of infant morbidity and mortality in the United States. Infants with birth defects are more likely to be born preterm (<37 weeks), yet the roles of maternal ethnicity and fetal growth in this relationship are unclear. This study aimed to assess the risk of PTB among non-Hispanic (NH) Black, NH-White, and Hispanic infants with congenital heart defects (CHD), adjusting for fetal growth. **METHODS:** Florida Birth Defects Registry data were used to conduct a retrospective cohort study on 14,319 live-born infants with CHDs born January 1, 1998 to December 31, 2002. ORs and 95% CIs were computed for each growth category (small-for-gestational age [SGA], appropriate-for-gestational-age [AGA], and large-for-gestational-age [LGA]) by ethnicity and adjusted for maternal and infant covariates using logistic regression. **RESULTS:** After adjusting for potential confounders, SGA and AGA NH-Black infants with CHDs had increased risk of PTB compared to NH-White infants with CHDs (OR 1.79; 95% CI: 1.40, 2.30 and OR 1.89; 95% CI: 1.68, 2.13, respectively). Hispanic SGA, AGA, and infants with CHDs had no increased risk of PTB compared to NH-White infants. **CONCLUSIONS:** The increased risk of PTB among SGA and AGA NH-Black infants with CHDs is not explained by the overall disparities in risk of PTB between NH-Blacks and NH-Whites. Additional studies are needed to determine the specific subtypes of CHD for which these relationships are present and if these findings are seen among infants with other birth defects. *Birth Defects Research (Part A) 79:754–764, 2007.* © 2007 Wiley-Liss, Inc.

Key words: fetal growth; preterm birth; birth weight; birth defects; congenital heart defects; racial disparity; Black infants

INTRODUCTION

Despite recent advances in medical care and numerous public health initiatives, preterm birth (PTB) remains a major public health problem in the United States, with a high prevalence (12% of all births in 2004) (Martin et al., 2006) and an associated increased risk of infant morbidity and mortality (Kiely et al., 2000; Kramer et al., 2000; Save the Children, 2001). Infants born preterm are more often small for gestational age (SGA) or growth restricted (Goldenberg et al., 1985; Ott, 1993). The complications associated with PTB may be compounded for children with birth defects.

Exact causes for PTB remain unknown, but maternal ethnicity has been implicated as a marker of risk: Black infants are 1.5 times more likely to be born preterm than White infants. The cause of this disparity, although

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hypothesized (Alexander et al., 1991; Bibby, 2004; Holzman et al., 2001; Wadhwa et al., 1993, 1996, 2001), is unknown. The etiology of the increased risk of PTB among Black infants is also unknown. It has been suggested that the increased risk of spontaneous PTB is due to infection (Holzman et al., 1999, 2001), inflammation (Wadhwa et al., 2001), chronic psychosocial stress (Dunkel-Schetter et al., 2000, 2001; Hobel and Culhane, 2003; Lobel, 1994; Lobel et al., 1992, 2000; Rini et al., 1999; Sandman et al., 1997, 1999; Wadhwa et al., 1993, 1996), ''weathering'' (a hypothesis suggesting that African-American women experience early health deterioration as a result of the cumulative effect of repeated experience with social, economic, or political exclusion) (Geronimus, 2001), and social environment (Lu and Halfon, 2003). Moreover, while infants with birth defects have a greater likelihood of being preterm than infants without birth defects (Khoury et al., 1988; Shaw et al., 2001; Tanner et al., 2005), it is unclear whether maternal ethnicity modifies this relationship, or if the maternal ethnicity-birth defect PTB propensity is itself influenced by fetal growth.

The purpose of this study was to assess the risk of non-Hispanic (NH) Black and Hispanic infants with birth defects for PTB when compared to NH-White infants, adjusted for fetal growth strata (SGA, appropriate for gestational age [AGA], large for gestational age [LGA]). We hypothesized that NH-Black and Hispanic infants with birth defects have similar risk of PTB compared to NH-White infants with birth defects after adjusting for their fetal growth.

METHODS

Study Design

Using data from the Florida Birth Defects Registry (FBDR), a passive population-based surveillance system, we conducted a retrospective cohort study. Since 1998 the FBDR has monitored birth defects in Florida by merging data from birth vital statistics, hospital discharge databases for both inpatients and ambulatory patients, and from the Florida Department of Health Children's Medical Services. Infants are eligible for inclusion in the registry if they are live-born to a Florida resident and have an included birth defect diagnosed during the first year of life as determined through the ICD-9-CM diagnosis coding system.

Study Population

Since birth defects are a constellation of heterogeneous defects affecting all organ systems with differing etiologies and severity, we tested our hypotheses on infants with congenital heart defects (CHD), the most common of all birth defects, with an annual prevalence of 10 to 12 affected infants per 1,000 live births (Hoffman and Kaplan, 2002). We selected all live-born, singleton infants having at least one of 12 selected CHDs diagnosed in the first year of life, and born between January 1, 1998 and December 31, 2002 to Florida resident NH-Black, NH-White, or Hispanic women, 15 to 49 years of age. We confined cases of CHDs to aortic valve stenosis (746.3), atrial septal defect (745.5), coarctation of the aorta (747.10), common truncus (745.0), Ebstein's anomaly (746.2), endocardial cushion defect (745.60, 745.61, or 745.69), hypoplastic left heart syndrome (746.7), pulmonary valve atresia and stenosis (746.01 or 746.02), tetralogy of Fallot (745.2), transposition of the great arteries (745.10–745.12 or 745.19), tricuspid valve atresia and stenosis (746.1), and ventricular septal defect (745.4).

During the study period, there were 1,004,938 live-born infants to Florida residents. Of these, 80,215 were born with an included birth defect and 14,319 were identified as having at least one of the 12 selected CHDs. Infants were excluded for the following: not a singleton birth (n = 593), maternal race/ethnicity was not designated as NH-Black, NH-White, or Hispanic (n = 310), and maternal age was less than 15 or greater than 49 years (n = 49) with an unduplicated total of 939 (6.6%) (numbers do not add up to 939 because 13 infants had more than one exclusion) infants excluded.

Study Variables

CHDs were classified using select ICD-9-CM diagnosis codes in the 745.00–747.99 range. Infants were considered to have an ''isolated'' heart defect if they had at least one of 12 selected CHDs but no other extracardiac defect diagnosed within the first year of life. However, infants considered to have an isolated CHD may have had more than one of the selected heart defects, although this percentage was fairly small (17.4%). An infant was classified as having ''multiple'' defects if he/she had at least one of the 12 CHDs *and* another extracardiac defect (diagnosed using select ICD-9-CM codes in the 740.0–759.9 range). Infants with known chromosomal abnormalities and/or syndromes were included in this category.

Data on gestational age, infant birth weight, maternal ethnicity, and potential confounders such as maternal age, maternal education, parity, maternal tobacco use, and infant sex were obtained from the Florida Office of Vital Statistics. We categorized gestational age as: very preterm, 20 to 31 weeks; moderately preterm, 32 to 36 weeks; and term, greater than 36 weeks, by using the mother's LMP. When the LMP was missing (6.6%) we substituted the clinical estimate of gestation. Infant birth weight was categorized as: very low birth weight, less than 1,500 g; moderately low birth weight, 1,500 to 2,499 g; and normal birth weight, greater than or equal to 2,500 g. Fetal growth was determined using race-specific growth curves (Alexander et al., 1999). One hundred and seven infants with implausible birth weight and gestational age combinations were excluded. Categories of fetal growth were defined as: SGA, birth weights less than 10th percentile; AGA, between the 10th and 90th percentiles; LGA, birth weights greater than 90th percentile.

Maternal race/ethnicity was based on maternal self-report and was initially grouped by ethnicity (Hispanic or NH). The NH group was then subdivided into White, Black, and other. All mothers classified as ''other'' were excluded from the analysis (2.2%). Prenatal maternal tobacco use was classified as ''yes'' or ''no'', and maternal education, based on years of education, was categorized as less than high school (0 to 11 years), high school (12 years), and greater than high school (13 years or more). Maternal age was categorized as 15 to 19, 20 to 29, 30 to 39, and 40 to 49 years. We also used data on livebirths in Florida during the study period from the Florida Community Health Assessment Resource Tool Set (Florida Department of Health Office of Planning Evaluation & Data Analysis, 2007) to obtain race/ethnic-specific PTB rates in the general Florida population. We

used this data to determine if the PTB rates observed in our study were in excess of the PTB rates present in the general population.

An additional 3.1% of the study population were excluded due to missing data on key study variables: 2.8% had missing or out of range fetal growth; 2.0% were missing gestational age; 0.3% were missing maternal education; 0.03% were missing data on parity; 0.02% were missing data on birth weight; and 0.01% were missing data on maternal smoking. The final sample consisted of 12,964 infants with CHD, of which 10,870 (83.9%) were categorized with an isolated CHD and 2,094 (16.2%) as having a CHD and an extracardiac defect (numbers do not add up to 3).

Statistical Methods

SAS software version 9.1.3 was used for all data analyses. Univariate analyses were used to calculate descriptive statistics, ORs, and 95% CIs to evaluate the distribution of study variables and crude associations. In multivariate logistic regression analyses, ORs and 95% CIs were used to determine the independent effects of ethnicity on risk of PTB while adjusting for potential confounders. We generated separate multivariate logistic regression models for each category of fetal growth for: (1) all infants with CHD; (2) infants with isolated CHD; and (3) infants with multiple (CHD + extracardiac) birth defects. ORs and 95% CIs were also calculated from the Florida Community Health Assessment Resource Tool Set data to determine risk of PTB during the study period for each race/ethnic group in the general Florida population. All statistical tests performed were two-sided and declared at the 5% significance level.

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

RESULTS

Sociodemographic Characteristics

Overall, 20.3% of infants with CHDs were low or very low birth weight, 15.5% were SGA, and 24.2% were born preterm. Among NH-Whites, 22.2% of infants were born preterm, whereas 32.0% of NH-Black and 20.6% Hispanic infants with CHDs were born preterm. NH-Blacks had an increased risk of PTB compared to NH-Whites in each PTB category. For very preterm, the risk was 2.47 (95% CI: 2.12, 2.88), for moderately preterm, the risk was 1.35 (95% CI: 1.21, 1.51), and for all PTB, the risk was 1.64 (95% CI: 1.49, 1.81). We found no increased risk of PTB among infants with CHDs born to Hispanic women.

The distribution of demographic, obstetric, and reproductive variables for infants with CHDs by maternal ethnicity is presented in Table 1. Mean maternal age was 28.4 (SD = 6.4) for NH-Whites, 26.2 (SD = 6.8) for NH-Blacks, and 27.9 (SD = 6.4) for Hispanics. After adjusting for maternal and infant characteristics, NH-Black mothers were more likely to be younger, have less than a high school education, and were less likely to smoke during pregnancy than NH-White women. NH-Black infants were more likely to be born very preterm or moderately preterm, LGA, and were more likely to have an isolated CHD than NH-White infants. In addition, when compared to NH-Whites, Hispanic mothers were more likely to have less than high school education and were less likely to smoke during pregnancy and Hispanic infants were less likely to have multiple birth defects. Table 2 presents the distribution of demographic, obstetric, and reproductive variables for SGA, AGA, and LGA infants with CHD. After adjusting for potential confounders, SGA infants were more likely to have a CHD with an extracardiac defect (OR 2.77; 95% CI: 2.47, 3.11) and were more likely to be born to women who smoked during pregnancy (OR 1.86; 95% CI: 1.60, 2.16), and who were nulliparous (OR 1.34; 95% CI: 1.20, 1.49).

Unadjusted and adjusted ORs and 95% CIs for the risk of PTB among all infants with CHDs by fetal growth category are presented in Table 3. After adjusting for potential confounders, SGA and AGA infants born to NH-Black women were at higher risk of PTB than infants born to NH-White women (OR 1.79; 95% CI: 1.39, 2.29 and OR 1.91; 95% CI: 1.70, 2.15, respectively). Prenatal maternal smoking was associated with increased risk of PTB only among infants who were AGA (OR 1.73; 95% CI: 1.47, 2.03).

"Isolated" CHDs

The risk of PTB among infants with isolated CHDs by fetal growth category was also evaluated (Table 4). SGA NH-Black infants with isolated CHDs were 2.15 times more likely to be born preterm than NH-White infants with isolated CHDs (95% CI: 1.59, 2.91). Similarly, AGA NH-Black infants with isolated CHDs were 1.96 times more likely to be born preterm than NH-White infants with isolated CHDs (95% CI: 1.73, 2.23). Although they were less likely to be SGA, infants born to Hispanic women had no increased risk of PTB as compared to NH-White infants with isolated CHD, regardless of fetal growth category. Maternal prenatal smoking was associated with increased risk of PTB for all categories of fetal growth.

"Multiple" (Congenital Heart + Extracardiac) Defects

The risk of PTB among infants with congenital heart and extracardiac defects was assessed and unadjusted and adjusted ORs and 95% CIs are presented in Table 5. Unlike infants with isolated CHD, NH-Black SGA infants were not at increased risk of PTB (OR 1.26; 95% CI: 0.79, 1.99) compared to NH-White SGA infants. However, increased risk of PTB was present for NH-Black AGA infants compared to NH-White AGA infants (OR 1.68; 95% CI: 1.25, 2.27).

DISCUSSION

We examined the relationship between fetal growth, maternal race/ethnicity, and risk of PTB among infants with 12 selected CHDs. An increased risk of PTB among NH-Black infants with CHDs as compared to NH-Whites was observed. Interestingly, the increased risk was heterogeneous; increased almost twofold for NH-Black SGA and AGA infants with *isolated* CHDs compared to their NH-White counterparts. This increased risk was not fully explained by the overall increased rate of PTB present among NH-Black infants. Increased risk of PTB among

Table 1
Distribution of maternal and infant characteristics of infants born with congenital heart defects by maternal race and ethnicity, Florida Birth Defects Registry, 1998–2002 (n = 12,964)

	Non-Hispanic white (n = 6404)		Non-Hispanic black (n = 3177)		Hispanic (n = 3383)		
	n	%†	n	%†	n	%†	P (χ^2 test)*
Maternal age							<0.0001
15–19 years	608	9.5	555	17.5	352	10.4	
20–29 years	2953	46.1	1667	52.5	1644	48.6	
30–39 years	2584	40.3	835	26.3	1249	36.9	
40–49 years	259	4.0	120	3.8	138	4.1	
Maternal education							<0.0001
<High school	1008	15.7	919	28.9	859	25.4	
High school	2069	32.3	1336	42.1	1115	33.0	
>High school	3327	52.0	922	29.0	1409	41.6	
Prenatal smoking							<0.0001
Yes	1032	16.1	165	5.2	75	2.2	
No	5372	83.9	3012	94.8	3308	97.8	
Parity							<0.0001
Nulliparous	2786	43.5	1109	34.9	1392	41.1	
Multiparous	3618	56.5	2068	65.1	1991	58.9	
Infant sex							0.29
Female	3043	47.5	1550	48.8	1657	49.0	
Male	3361	52.5	1627	51.2	1726	51.0	
Gestational age							<0.0001
20–31 weeks	374	5.8	401	12.6	178	5.3	
32–36 weeks	1052	16.4	616	19.4	518	15.3	
37+ weeks	4978	77.7	2160	68.0	2687	79.4	
Birth weight							<0.0001
VLBW (<1500g) ‡	335	5.2	390	12.3	169	5.0	
LBW (1500–2499g) §	849	13.3	519	16.3	370	10.9	
Normal (2500+g)	5220	81.5	2268	71.4	2844	84.1	
Intrauterine growth							<0.0001
SGA¶	1040	16.2	480	15.1	490	14.5	
AGA#	4707	73.5	2274	71.6	2483	73.4	
LGA**	657	10.3	423	13.3	410	12.1	
Type of heart defect							<0.0001
Isolated	5277	82.4	2703	85.1	2890	85.4	
Multiple	1127	17.6	474	14.9	493	14.6	

*All p-values are two sided.
†Percentages may add up to greater than 100% due to rounding.
‡VLBW: very low birth weight.
§LBW: moderately low birth weight.
¶SGA: small-for-gestational-age.
#AGA: appropriate-for-gestational age.
**LGA: large-for-gestational age.

infants with CHD (OR 1.64) was similar to the increased risk of PTB (20–36 weeks) among all infants born to resident NH-White, NH-Black, and Hispanic Florida women during the study period (OR 1.73; 95% CI: 1.70, 1.75) (Florida Department of Health Office of Planning Evaluation & Data Analysis, 2007). From 1998–2002, the rate of PTB (20–36 weeks gestation) in Florida was 13.0%, but the rate differed by maternal race/ethnicity; 11.4% for NH-Whites, 18.1% for NH-Blacks, and 11.7% for Hispanics. However, the twofold increased risk of PTB among NH-Black SGA and AGA infants with CHDs compared to NH-White infants with CHDs is greater than the 1.73 increased risk observed for NH-Black infants compared to NH-White infants in the general population. The association between fetal growth and risk of PTB among NH-Black infants is complicated by the presence of extracardiac defects. Among infants with an extracardiac defect, risk of PTB was only elevated among AGA NH-Black infants, but it did not differ from the rate of PTB observed in the general population. These patterns were not observed among Hispanic infants.

To our knowledge, few studies have investigated the relationship between fetal growth, maternal race/ethnicity, and risk of PTB. However, our findings are consistent with aspects of this relationship reported in other published research. Infants with CHDs are more likely to be born low birth weight (Levy et al., 1978; Mehrizi and Drash, 1961; Naeye, 1967; Richards et al., 1955; Rosenthal et al., 1991) and intrauterine growth restricted (IUGR) (Reynolds, 1972; Spiers, 1982). Previous research has only examined the prevalence of CHDs among low birth weight/preterm infants, and several studies reported increased prevalence of CHDs among these infants (Warkany et al., 1961) and IUGR infants (Levin et al., 1975; Levy et al., 1978; Reynolds, 1972). Prior evidence regarding increased risk of PTB among infants with CHDs is

Table 2
Adjusted and unadjusted odds ratios and 95% confidence intervals for maternal and infant characteristics of infants born with congenital heart defects by fetal growth, Florida Birth Defects Registry, 1998–2002 (n = 12,964)

	Small-for-Gestational-Age (n = 2010)				Appropriate-for-Gestational-Age (n = 9464)	Large-for-Gestational-Age (n = 1490)			
	Unadjusted		Adjusted		Referent group	Unadjusted		Adjusted	
	OR[†]	95%CI[‡]	OR	95%CI	OR	OR	95%CI	OR	95%CI
Race-Ethnicity									
Non-Hispanic white	1.00		1.00		1.00	1.00		1.00	
Non-Hispanic black	0.96	0.85, 1.08	1.06	0.93, 1.20	1.00	1.33	1.17, 1.52	1.36	1.18, 1.57
Hispanic	0.89	0.79, 1.00	1.01	0.89, 1.14	1.00	1.18	1.04, 1.35	1.11	0.97, 1.28
Maternal Age					1.00				
15–19 years	1.35	1.17, 1.57	1.15	0.98, 1.36	1.00	0.60	0.49, 0.75	0.70	0.55, 0.88
20–29 years	1.00		1.00		1.00	1.00		1.00	
30–39 years	1.01	0.90, 1.12	1.05	0.94, 1.19	1.00	1.15	1.02, 1.29	1.15	1.02,1.30
40–49 years	1.31	1.04, 1.66	1.11	0.87, 1.42	1.00	0.92	0.68, 1.24	0.98	0.72, 1.33
Maternal Education									
<High school	1.10	0.97, 1.25	1.03	0.89, 1.18	1.00	0.79	0.68, 0.93	0.88	0.74, 1.04
High school	1.00		1.00		1.00	1.00			
>High school	0.82	0.73, 0.91	0.85	0.76, 0.96	1.00	0.95	0.84, 1.07	0.91	0.80, 1.04
Prenatal Smoking									
Yes	1.86	1.62, 2.13	1.86	1.60, 2.16	1.00	0.56	0.44, 0.71	0.59	0.46, 0.76
No	1.00		1.00		1.00	1.00		1.00	
Parity									
Nulliparous	1.24	1.13, 1.37	1.34	1.20, 1.49	1.00	0.65	0.58, 0.73	0.70	0.62, 0.80
Multiparous	1.00		1.00		1.00	1.00		1.00	
Infant Sex									
Female	1.00		1.00		1.00	1.00		1.00	
Male	0.72	0.65, 0.79	0.68	0.62, 0.76	1.00	1.52	1.36, 1.70	1.57	1.40, 1.76
Gestational Age									
20–31 weeks	0.77	0.63, 0.94	0.70	0.57, 0.86	1.00	0.51	0.40, 0.66	0.52	0.40, 0.67
32–36 weeks	1.38	1.23, 1.56	1.27	1.12, 1.44	1.00	0.67	0.57, 0.79	0.67	0.57, 0.79
37+ weeks	1.00		1.00		1.00	1.00		1.00	
Type of Heart Defect									
Isolated	1.00		1.00		1.00	1.00		1.00	
Multiple	2.75	2.46, 3.07	2.77	2.47, 3.11	1.00	0.68	0.57, 0.81	0.67	0.56, 0.81

[†]OR: odds ratio.
[‡]CI: confidence interval.

inconsistent. Kramer et al. (1990) reported that the frequency of PTB was not higher among CHD infants, whereas more recent studies report an increased risk of PTB among infants with CHDs (Shaw et al., 2001; Tanner et al., 2005). Tanner et al. (2005) noted a twofold increased risk of PTB among infants with cardiovascular malformations (OR 2.4; 95% CI: 2.2, 2.7) and that 16% of all infants with cardiovascular malformations were preterm. In our study, 24.2% of infants with a CHD were born preterm.

Our findings have implications for the persistent disparity in rates of PTB between NH-Blacks and NH-Whites. Despite decades of research, the racial/ethnic disparity in spontaneous PTB rates between White and Black unaffected infants is unexplained. Traditional risk factors, such as obstetric history, prenatal care, maternal comorbid conditions (e.g., maternal diabetes, maternal hypertension, and pre-eclampsia), socioeconomic status (e.g., poverty, maternal age, marital status), and maternal behaviors during pregnancy (prenatal maternal smoking, substance abuse, nutrition, etc.) combined fail to identify over 50% of the women who will have preterm delivery and do not fully explain this persistent disparity (Austin and Leader, 2000; Copper et al., 1996; Norwitz et al., 1999). More recently studied risk factors such as maternal infection, inflammation, prenatal maternal psychosocial stress, and ''weathering'' have provided new insights into this complex phenomenon, but have not provided conclusive findings or clear directions for intervention. We demonstrate that the racial/ethnic disparity in PTB also exists among infants with CHDs and is greater for infants with isolated CHDs. The etiology of this disparity among infants with CHDs is not readily apparent and is intriguing. Maternal psychosocial stress, infection, and chronic diabetes are also associated with increased risk of CHDs (Adams et al., 1989; Botto et al., 2001; Carmichael and Shaw, 2000; Chavez et al., 1988; Correa-Villasenor et al., 1991; Ferencz et al., 1997; Hernandez et al., 1969; Jenkins et al., 2007; Tikkanen and Heinonen, 1991; Zhang and Cai, 1993) as well as PTB (Dunkel-Schetter et al., 2001; Geronimus, 2001; Hobel and Culhane, 2003; Holzman et al., 1999, 2001; Wadhwa et al., 2001). We did not assess the potential effect of these risk factors in our analyses because the FBDR does not collect this information.

Our findings which indicate a difference in risk of PTB between infants with an isolated CHD and infants with CHDs in conjunction with extracardiac defects is difficult to explain. We found that among infants with CHDs and extracardiac defects, the increased risk of PTB was only present for NH-Black infants that were AGA. However, the association was weaker than that found for infants with isolated CHDs. These findings are counterintuitive;

Table 3
Unadjusted and Adjusted odds ratios and 95% confidence intervals from logistic regression analysis for risk of preterm birth among infants born with congenital heart defects by fetal growth, Florida Birth Defects Registry, 1998–2002 (n =12,964)

	Small-for-Gestational-Age (n = 2010)				Appropriate-for-Gestational-Age (n = 9464)				Large-for-Gestational-Age (n = 1490)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR[†]	95%CI[‡]	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Race-Ethnicity												
Non-Hispanic white	Referent		Referent		Referent		Referent		Referent		Referent	
Non-Hispanic black	1.59	1.26, 2.01	1.79	1.39, 2.29	1.80	1.61, 2.01	1.91	1.70, 2.15	1.02	0.75, 1.39	1.04	0.75, 1.45
Hispanic	1.06	0.83, 1.35	1.11	0.86, 1.44	0.95	0.85, 1.07	1.03	0.91, 1.17	0.45	0.31, 0.66	0.47	0.31, 0.69
Maternal Age												
15–19 years	0.95	0.71, 1.27	0.91	0.66, 1.26	1.24	1.07, 1.44	1.04	0.88, 1.22	1.69	1.05, 2.71	1.41	0.84, 2.37
20–29 years	Referent		Referent		Referent		Referent		Referent		Referent	
30–39 years	0.98	0.79, 1.22	1.01	0.83, 1.31	1.00	0.90, 1.11	1.13	1.02, 1.27	0.68	0.50, 0.93	0.73	0.53, 1.00
40–49 years	1.27	0.81, 1.99	1.46	0.92, 2.33	1.46	1.16, 1.84	1.46	1.15, 1.86	2.01	1.08, 3.72	1.88	0.98, 3.62
Maternal Education												
<High school	0.75	0.58, 0.97	0.73	0.56, 0.96	1.14	1.00, 1.29	1.08	0.95, 1.24	1.71	1.19, 2.45	1.53	1.04, 2.25
High school	Referent		Referent		Referent		Referent		Referent		Referent	
>High school	0.89	0.71, 1.11	0.94	0.74, 1.19	0.79	0.71, 0.88	0.87	0.78, 0.98	0.89	0.65, 1.22	1.00	0.72, 1.40
Prenatal Smoking												
Yes	1.08	0.83, 1.40	1.33	0.99, 1.76	1.63	1.40, 1.89	1.73	1.47, 2.03	3.25	2.02, 5.22	2.53	1.52, 4.21
No	Referent		Referent		Referent		Referent		Referent		Referent	
Parity												
Nulliparous	1.15	0.95, 1.40	1.28	1.03, 1.59	1.00	0.90, 1.09	1.11	1.00, 1.23	1.11	0.83, 1.49	1.07	0.78, 1.47
Multiparous	Referent		Referent		Referent		Referent		Referent		Referent	
Infant Sex												
Female	Referent		Referent		Referent		Referent		Referent		Referent	
Male	0.96	0.79, 1.17	0.97	0.79, 1.18	1.13	1.03, 1.24	1.11	1.01, 1.22	0.95	0.72, 1.26	0.95	0.71, 1.27
Type of Heart Defect												
Isolated	Referent		Referent		Referent		Referent		Referent		Referent	
Multiple	0.91	0.74, 1.13	0.91	0.73, 1.13	1.51	1.33, 1.71	1.48	1.30, 1.69	1.92	1.29, 2.84	1.83	1.22, 2.77

*All odds ratios are adjusted for the other variables in the model.
[†]OR: odds ratio.
[‡]CI: confidence interval.

Table 4
Adjusted and unadjusted odds Ratios and 95% confidence intervals from logistic regression analysis for risk of preterm birth among infants born with isolated congenital heart defects by fetal growth, Florida Birth Defects Registry, 1998–2002 (n = 10,870)

	Small-for-Gestational-Age (n = 1389)				Appropriate-for-Gestational-Age (n = 8139)				Large-for-Gestational-Age (n = 1342)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR[†]	95%CI[‡]	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Race-Ethnicity												
Non-Hispanic white	Referent		Referent		Referent		Referent		Referent		Referent	
Non-Hispanic black	1.78	1.34, 2.36	2.15	1.59, 2.91	1.85	1.64, 2.09	1.96	1.73, 2.23	1.09	0.78, 1.52	1.06	0.74, 1.51
Hispanic	1.14	0.86, 1.52	1.27	0.94, 1.72	0.95	0.83, 1.08	1.03	0.90, 1.18	0.45	0.30, 0.68	0.45	0.29, 0.69
Maternal Age												
15–19 years	0.99	0.71, 1.39	0.91	0.62, 1.33	1.22	1.04, 1.44	1.02	0.85, 1.23	1.84	1.12, 3.01	1.47	0.84, 2.55
20–29 years	Referent		Referent		Referent		Referent		Referent		Referent	
30–39 years	1.07	0.82, 1.39	1.18	0.90, 1.56	1.02	0.91, 1.14	1.18	1.04, 1.33	0.63	0.45, 0.87	0.68	0.48, 0.97
40–49 years	1.05	0.51, 2.16	1.16	0.56, 2.42	1.46	1.11, 1.93	1.59	1.19, 2.11	1.74	0.82, 3.69	1.93	0.89, 4.20
Maternal Education												
<High school	0.73	0.54, 0.99	0.71	0.51, 0.98	1.10	0.96, 1.26	1.03	0.89, 1.20	1.84	1.24, 2.71	1.55	1.02, 2.37
High school	Referent		Referent		Referent		Referent		Referent		Referent	
>High school	0.92	0.70, 1.20	0.96	0.72, 1.28	0.78	0.69, 0.87	0.85	0.75, 0.96	0.91	0.65, 1.28	1.04	0.73, 1.49
Prenatal Smoking												
Yes	1.11	0.81, 1.51	1.50	1.06, 2.12	1.68	1.43, 1.98	1.81	1.52, 2.16	3.03	1.80, 5.08	2.37	1.36, 4.13
No	Referent		Referent		Referent		Referent		Referent		Referent	
Parity												
Nulliparous	1.38	1.09, 1.74	1.60	1.24, 2.07	0.98	0.88, 1.09	1.10	0.98, 1.24	1.26	0.93, 1.72	1.13	0.80, 1.59
Multiparous	Referent		Referent		Referent		Referent		Referent		Referent	
Infant Sex												
Female	Referent		Referent		Referent		Referent		Referent		Referent	
Male	0.89	0.70, 1.12	0.88	0.69, 1.12	1.11	1.00, 1.23	1.10	0.99, 1.22	0.94	0.69, 1.26	0.95	0.70, 1.30

*All odds ratios are adjusted for the other variables in the model.
[†]OR: odds ratio.
[‡]CI: confidence interval.

Table 5
Adjusted and unadjusted odds Ratios and 95% confidence intervals from logistic regression analysis for risk of preterm birth among infants born with congenital heart defects and another major defect by intrauterine growth, Florida Birth Defects Registry, 1998–2002 (n = 2,094)

	Small-for-Gestational-Age (n = 621)				Appropriate-for-Gestational-Age (n = 1325)				Large-for-Gestational-Age (n = 148)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR[†]	95%CI[‡]	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Race-Ethnicity												
Non-Hispanic white	Referent		Referent		Referent		Referent		Referent		Referent	
Non-Hispanic black	1.23	0.80, 1.88	1.26	0.79, 1.99	1.65	1.24, 2.19	1.68	1.25, 2.27	0.80	0.31, 2.03	0.91	0.32, 2.55
Hispanic	0.85	0.53, 1.37	0.85	0.51, 1.39	1.02	0.76, 1.36	1.05	0.77, 1.42	0.52	0.20, 1.34	0.62	0.22, 1.78
Maternal Age												
15–19 years	0.83	0.46, 1.48	0.95	0.50, 1.80	1.35	0.92, 1.98	1.09	0.71, 1.68	0.73	0.14, 3.84	0.84	0.15, 4.68
20–29 years	Referent		Referent		Referent		Referent		Referent		Referent	
30–39 years	0.81	0.53, 1.22	0.77	0.50, 1.18	0.86	0.66, 1.12	0.96	0.73, 1.26	0.98	0.43, 2.21	1.03	0.43, 2.45
40–49 years	1.44	0.79, 2.62	1.43	0.77, 2.64	1.11	0.73, 1.70	1.19	0.77, 1.84	1.96	0.60, 6.41	1.73	0.47, 6.36
Maternal Education												
<High school	0.81	0.50, 1.31	0.79	0.48, 1.30	1.37	1.01, 1.86	1.32	0.95, 1.84	1.04	0.39, 2.76	1.13	0.39, 3.25
High school	Referent		Referent		Referent		Referent		Referent		Referent	
>High school	0.84	0.56, 1.26	0.89	0.58, 1.38	0.89	0.68, 1.17	1.00	0.75, 1.32	0.78	0.34, 1.78	0.75	0.29, 1.92
Prenatal Smoking												
Yes	1.01	0.62, 1.65	0.99	0.58, 1.68	1.32	0.91, 1.90	1.42	0.96, 2.11	4.77	1.27, 17.94	3.52	0.85, 14.52
No	Referent		Referent		Referent		Referent		Referent		Referent	
Parity												
Nulliparous	0.74	0.51, 1.07	0.74	0.49, 1.12	1.11	0.88, 1.41	1.15	0.88, 1.48	0.48	0.19, 1.20	0.60	0.23, 1.59
Multiparous	Referent		Referent		Referent		Referent		Referent		Referent	
Infant Sex												
Female	Referent		Referent		Referent		Referent		Referent		Referent	
Male	1.18	0.82, 1.68	1.19	0.83, 1.70	1.14	0.90, 1.44	1.13	0.89, 1.44	1.04	0.48, 2.22	1.12	0.49, 2.57

*All odds ratios are adjusted for the other variables in the model.
[†]OR: odds ratio.
[‡]CI: confidence interval.

we expected to find that risk of PTB would have increased for all groups because these infants experienced a greater insult in utero. We also postulated that the increased risk of morbidity and mortality frequently found among CHD infants with extracardiac defects may be due to increased risk of PTB (Greenwood et al., 1975). This cannot be inferred from our findings. We were concerned that the risk of PTB may be different for CHD infants with and without chromosomal abnormalities; however, the ORs did not significantly change when CHD infants with trisomies and other known chromosomal abnormalities were excluded from the analysis. It has been reported that the incidence of extracardiac anomalies is higher in SGA than in AGA infants with CHDs (Levy et al., 1978; Reynolds, 1972). It is plausible that in the smallest and sickest infants, the external factors driving the PTB ethnic disparity are overcome by obstetric factors.

Prior research investigating the relationship between SGA and presence of extracardiac defects among infants with CHDs focused on the prevalence of extracardiac defects among SGA infants. Levy et al. (1978) reported that SGA infants with CHDs were significantly more likely to have extracardiac defects than AGA infants. Reynolds (1972) found that in those infants without IUGR, the incidence of extracardiac anomalies was 8% compared to 32% among those infants with IUGR ($p < .01$). Levy et al. (1978) found that major extracardiac anomalies occurred in 9.8% of SGA infants versus 6.1% in the normal weight group ($p < .05$). The incidence of SGA among infants with extracardiac anomalies was 8% in contrast to 5% in infants without extracardiac defects ($p < .01$). We are unaware of previous research investigating the risk of PTB among infants with CHDs.

Our results are based on a large, multiethnic, population-based registry, making the results largely generalizable to NH-Black, NH-White, and Hispanic infants born in the U.S. In addition, we selected CHDs that not only have the highest prevalence, but also a high impact on infant morbidity and mortality. Although we demonstrate that increased risk of PTB among NH-Blacks is not limited to nonmalformed infants, there are limitations of our study that should be addressed.

First, a potential limitation is use of passive surveillance system data. Compared to active surveillance systems, passive systems often underestimate the number of infants with birth defects, particularly CHDs. However, this should have little effect (primarily underestimation) on the strength of the associations. In general, birth defects registries that limit case ascertainment to the first year of life exclude some infants with CHD; those whose CHDs are not detected until after hospital discharge or are not diagnosed until later in childhood or adult life (e.g., atrial septal defect or coarctation of the aorta). In addition, without an autopsy, infants who died shortly after birth may not have had their CHD detected. As a result, our surveillance system and consequently our study, does not include these cases. If ethnic differences are present in the numbers of missed cases of CHD, our estimate of the risk of NH-Black PTB depends on the distribution of PTB among those missed cases. However, there is no evidence to suggest differential ascertainment of CHD (as measured by age at diagnosis) by maternal race/ethnicity (Fixler et al., 1993).

A second limitation of passive surveillance system data is the inability to determine the age at diagnosis, and to subclassify or to determine the size and severity of CHD. For example, we were not able to subclassify ventricular septal defects (VSDs) (e.g., membranous vs. muscular), which are a large proportion of CHDs and are known to have a wide range in severity and size. Thirty-four percent of infants in our study had a VSD, and only 20.6% had a VSD and no other defect. It is plausible that the increased risk of PTB we observed for NH-Black infants with CHD is due to a higher prevalence of VSD or small and trivial VSD among NH-Blacks compared to NH-White or Hispanic infants. However, NH–Blacks had the lowest prevalence of VSD compared to NH–Whites and Hispanics (28.6 vs. 38.1 and 32.5%, respectively) and the lowest prevalence of ''isolated'' VSD (17.0%) compared to NH–Whites and Hispanics (23.6 and 18.1%, respectively). Although we are unable to determine the proportion of infants with small or trivial VSD, these data do not suggest that the observed association is explained by higher rates of VSD among NH-Blacks.

Thirdly, misclassification of fetal growth categories can occur. We used race-specific growth curves that allowed comparisons of infants that are classified as SGA based on growth patterns of their specific ethnic group, that is, those infants that are less than the 10th percentile of their population. We used the SGA category to identify those infants who are growth restricted, but this includes infants who are constitutionally small and not growth restricted because birth records did not allow us to differentiate those infants.

Fourth, there is potential for misclassification of PTB depending on the source of the estimation of gestational age (Yang et al., 2005). Early prenatal ultrasound is considered the most accurate method of gestational age determination (Committee on Understanding the Premature Birth and Assuring Healthy Outcomes, Board on Health Sciences Policy, 2007). Because early prenatal ultrasound information is not recorded on Florida birth records, we calculated PTB based on LMP recorded in the birth record. Maternal LMP is differentially missing when examined by socioeconomic status (Committee on Understanding the Premature Birth and Assuring Healthy Outcomes, Board on Health Sciences Policy, 2007) and maternal race/ethnicity, with the missing data more likely to occur for Black women (Savitz et al., 2002). The clinical estimate of gestation is often used for women missing LMP data. However, use of LMP to calculate gestational age in combination with clinical estimate of gestational age to determine differences in rates of PTB can result in over- or underestimation of PTB, depending on the pattern of missing data in the study population (Committee on Understanding the Premature Birth and Assuring Healthy Outcomes, Board on Health Sciences Policy, 2007). However, only 6.6% of our study population had missing data on LMP and there was no differential maternal race/ethnicity missing pattern. In those cases where LMP was missing we used the clinical estimate of gestation. To determine the amount of bias introduced by this procedure, we compared gestational age data obtained by the clinical estimate and that calculated from the LMP in 12,097 infants included in our analyses who had both measures available. The overall exact concordance between the two measures was 44%. For estimates within 1 week of each other it was 73%, and for ± 2 weeks, it was 86%. The exact concordance propor-

tion was similar for NH-Whites, NH-Blacks, and Hispanics. Using the LMP measures versus the clinical estimate did not significantly alter our rates of very preterm (13.2 vs. 12.9%) or preterm (10.3 vs. 9.5%). Thus, using the clinical estimate as the gestational age determinant for all analyses would not have affected our results. We were unable to confirm any gestational ages due to our inability to examine medical records.

Additionally, it is possible that our results reflect differences in rates of iatrogenic PTB among ethnicities rather than differences in rates of spontaneous PTB. However, we did not observe significant ethnic differences in rates of inductions or cesarean sections. NH-Blacks and Hispanics were only 13 and 17% more likely to be delivered via cesarean section than NH-Whites (OR 1.13; 95% CI: 1.03, 1.23 and OR 1.17; 95% CI: 1.08, 1.27, respectively).

Finally, in our analyses, we were unable to adjust for the effects of maternal and paternal body composition and maternal prenatal complications. It is possible that our results may have been attenuated in the presence of these variables. It is also important to note that although we adjusted for the independent effect of maternal education, which was used as a proxy for maternal social class, the potential effect of socioeconomic status may not have been fully removed and residual confounding may be present.

Our findings that NH-Black infants who are SGA and AGA with CHDs are at increased risk of PTB have implications for both infant and childhood morbidity and mortality. Infants born with CHDs require intensive surgical and medical interventions to correct or repair malformations of the heart. Complications associated with PTB may increase the risk of poor neonatal and infant outcomes for NH-Black infants with CHD. Infants with CHDs born preterm or very preterm are at increased risk of morbidity and mortality compared to infants with CHDs who are born at term (Dees et al., 2000; Kecskes and Cartwright, 2002; Reddy et al., 1999). As a result, NH-Black infants may experience excess morbidity and mortality and require more invasive procedures requiring longer hospital stays and greater medical costs.

CONCLUSIONS

Taken together, our results along with those from previous studies indicate that the disparity in risk of PTB between Blacks and Whites is not limited to infants unaffected by birth defects. Elucidating the etiology of PTB among infants with birth defects may help to understand the etiology of PTB in unaffected infants. Additional research is needed to determine whether the risk of PTB for NH-Black infants is limited to infants with CHDs or is present for infants with other types of defects.

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