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Racial Differences in Neonatal Hypoglycemia among Very Early Preterm Births

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Abstract

Objective—To determine whether the prevalence of neonatal hypoglycemia differs by race/ethnicity.

Study Design—A retrospective cohort study using prospectively collected data from 515 neonates born very preterm (<32 weeks) to normoglycemic women and admitted to the neonatal intensive care unit (NICU) at a major tertiary hospital in Boston, MA between 2008 and 2012.

Results—A total of 61%, 12%, 7%, 7%, and 13% were White, Black, Hispanic, Asian, and Other, respectively. Among the 66% spontaneous preterm births, 63% of the black neonates experienced hypoglycemia (blood glucose level<40 mg/dL), while only 22–30% of the other racial/ethnic neonates did so (Black *v.* White RR 2.15; 95% CI: 1.54–3.00). After adjusting for maternal education, maternal age, multiple gestations, delivery type, gestational age, birth weight and neonates' sex, this association remained significant (adjusted Black *v.* White RR: 1.61, 95%

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CI: 1.13–2.29). An increased risk of infant hypoglycemia was not seen in infants of other racial/ethnic groups, nor in any racial/ethnic group with a medically-indicated preterm birth.

Conclusions—Black neonates delivered for spontaneous (but not medical) indications at <32 weeks had a higher risk of hypoglycemia, which could provide critical information about mechanisms of preterm birth and adverse postnatal outcomes in this high-risk group.

Key terms

race; disparity; preterm birth; hypoglycemia; neonatal

Introduction

Hypoglycemia is common in preterm infants in the neonatal intensive care setting.[1] It often requires costly diagnostic evaluation, impedes progress towards discharge home,[2] and may have important long-term consequences, including lower childhood school performance.[3] It has multiple causes including gestational or pre-existing maternal diabetes, inadequate fetal accretion of adipose, muscle or glycogen energy stores, increased energy expenditure from various causes including sepsis, and rare genetic disorders of metabolism or insulin secretion.[4]

While marked racial disparity is seen in the rate of preterm delivery,[5] it is not known whether similar racial/ethnic differences exist in the prevalence of hypoglycemia among spontaneously-delivered preterm infants. If present, this may give insight into potentially linked mechanisms of spontaneous preterm birth[6] and hypoglycemia.[4] Using a racially/ethnically diverse population of mother-child pairs, we conducted a retrospective cohort study to evaluate the association between race/ethnicity and hypoglycemia in neonates born very preterm.

Methods

Utilizing an electronic database of all infants admitted to the Neonatal Intensive Care Unit (NICU) at Beth Israel Deaconess Medical Center (BIDMC), we identified those infants with gestational age <32 weeks admitted between February 2008 and August 2012. Maternal and neonatal records were then reviewed for demographic and clinical data, including maternal-reported race/ethnicity, pregnancy complications, mode of delivery, birth weight, and neonatal blood glucose values. Infants were excluded if their mothers had pre-existing diabetes mellitus or gestational diabetes mellitus, or if they had no glucose values documented while in the NICU. The BIDMC Institutional Review Board approved this study. Given no patient contact, the BIDMC Institutional Review Board waived the requirement of informed consent.

Reason for preterm birth

Preterm birth was categorized as either spontaneous or medically-indicated.[7] Spontaneous preterm birth was defined as delivery at <32 weeks gestation due to preterm labor, preterm premature rupture of membranes (PPROM), cervical insufficiency, and/or placental abruption. Medically-indicated preterm birth was defined as delivery <32 weeks due to a

complication of pregnancy of sufficient severity to warrant delivery for either a maternal or fetal indication, such as preeclampsia or eclampsia, intrauterine growth restriction, non-reassuring fetal testing, oligohydramnios, abnormal Doppler indices, vasa previa, placental disorders, and/or maternal medical disease. All delivery data including indication for preterm delivery were reviewed and categorized by an experienced obstetrician (M.M.).

Race/ethnicity

Infant race/ethnicity was based on maternal self-report at the time of first prenatal visit. Race/ethnicity was reported as “Asian”, “Black”, “Hispanic”, “White” or “Other”. Women were considered to be “Hispanic” if self-reported, regardless of their selected race.

Neonate hypoglycemia

Preterm infants <32 weeks had glucose levels measured upon admission to the NICU and at least every 12 hours for 48 hours, and then following changes in fluid management until they reached full feeds, after which testing frequency decreased to once per day for 7 to 14 days. Blood glucose levels were measured using the Precision Xceed Pro Point of Care System (Abbott Diagnostics, Lake Forest, IL). Although point of care testing is not as accurate as laboratory testing at low levels, it is the standard of care in our NICU, as the turn-around-time of laboratory assessment of glucose does not allow timely response and adjustment of IV fluids. If hypoglycemia was noted, glucose was measured more frequently. Hypoglycemia was defined as point-of-care blood glucose <40 mg/dl. At the time of this study, a glucose value of 40 mg/dL was that used by our NICU to identify hypoglycemia that required intervention. For each infant, we dichotomized neonate hypoglycemia as “ever having hypoglycemia during the NICU stay” or “never having hypoglycemia during the NICU stay”.

Covariates

Neonate data were derived from a prospectively entered structured database for newborns admitted to the NICU. Maternal data were collected from electronic medical records and included age at delivery, gravidity and parity, self-reported education level, and type of delivery (vaginal, cesarean, operative vaginal). If the delivery was by cesarean section, the indications for this were recorded. In a randomly selected subset of 43 women additional data were collected on height, weight, and BMI at the first prenatal visit. This information was used for a sensitivity analysis.

Statistical analysis

We calculated means and standard deviations for continuous variables, and frequencies and proportions for categorical variables stratified by hypoglycemia and type of preterm birth. ANOVA and chi-square tests were used to assess statistical differences using two-tailed tests. To assess the association between race/ethnicity and neonate hypoglycemia, we used multivariable generalized estimating equations (GEE), which accounted for the correlated data structure due to the presence of twins and triplets in our study population.[8, 9] We calculated odds ratios and 95% confidence intervals. Potential confounders were considered *a priori* due to their known association with race/ethnicity and neonate hypoglycemia; these

included: maternal age (continuous), multiples gestation (2 or more fetuses versus singleton (reference), maternal education (≤high school, some college, college or greater (reference), or information not available), and neonate sex (female *v.* male (reference)). As a sensitivity analysis, we additionally adjusted for: delivery type (cesarean *v.* vaginal delivery (reference) and sex-specific birth weight for gestational age (small for gestational age, large for gestational age, or average for gestational age (reference). All models were stratified by the indication for delivery (spontaneous *v.* medically-indicated). Data were analyzed with SAS 9.3 (SAS Institute Inc., Cary, NC). As this is private hospital data, code can be made available, but data is restricted for use.

Results

Of 21,696 neonates delivered between February 2008 through August 2012, we evaluated 515 neonates admitted to the NICU who were born <32 weeks gestation to normoglycemic women (Figure 1). Of these, 339 (66%) neonates were born to women who delivered spontaneously, and 176 (34%) neonates were born to mothers with medically-indicated deliveries (Figure 1, Table 1). The racial distribution among the neonates delivered <32 weeks gestation largely reflected that of the original population of all deliveries at BIDMC during the study period (p=0.45, Figure 1).

Table 1 describes the characteristics of the study population stratified by spontaneous *v.* medically-indicated delivery and neonate hypoglycemia status in the NICU. Among neonates born spontaneously <32 weeks, neonates with hypoglycemia during NICU admission had lower gestational age, lower birth weight, and a lower prevalence of multiple gestation pregnancy than neonates without hypoglycemia. In the spontaneously-delivered group, 63% of black neonates experienced hypoglycemia, as compared to 22–30% of the other racial/ethnic groups (Table 1, Figure 2). In a subgroup analysis of n=41 women with BMI data, we did not find a significant association between BMI and infant hypoglycemia (p=0.19).

Among neonates with medically-indicated delivery <32 weeks, neonates with hypoglycemia had lower birth weight than infants without hypoglycemia, and trended towards lower gestational age and lower birth weight for gestational age. No significant difference was seen with respect to hypoglycemia among the different racial/ethnic groups, with 58–63% of infants in each racial/ethnic category experiencing hypoglycemia among medically-indicated deliveries (Table 1, Figure 3).

Among spontaneously-delivered infants, only black neonates had an increased risk of hypoglycemia compared to white neonates (unadjusted OR 2.15; 95% CI: 1.54–3.00, Table 2). After adjusting for maternal education, maternal age at delivery, multiple gestations, delivery type, gestational age, birth weight, and neonates' sex, associations were reduced but remained significant (adjusted OR: 1.61; 95% CI: 1.13–2.29). Additional adjustment for birth weight for gestational age yielded similar associations (data not shown). No racial/ethnic differences in hypoglycemia existed for medically-indicated deliveries, regardless of adjustment (Table 2).

Discussion

Black infants are much more likely to be delivered prematurely than infants of other racial/ethnic groups in the United States.[5] To our knowledge, racial/ethnic differences in neonate hypoglycemia—a related adverse outcome of preterm birth—has not been not been studied. We found that among infants delivered spontaneously at <32 weeks gestation, black infants had a prevalence of hypoglycemia over two-fold greater than whites and other groups, with a 60% increased odds of hypoglycemia after adjustment for potential confounding factors. Despite the potential for undetected residual confounding, our findings should increase vigilance for hypoglycemia among black preterm infants in the neonatal intensive care setting.

These racial/ethnic differences were not observed among infants delivered for medical indications, suggesting that hypoglycemia in black preterm neonates may be specifically associated with spontaneous preterm birth. Hypoglycemia occurs when there is a mismatch between low glucose availability and higher glucose utilization. Although we found no evidence that spontaneously-delivered black preterm neonates with hypoglycemia differed from other ethnic groups in gestational age or birth weight (data not shown), it remains possible that ethnic differences in glucose availability could be a factor, especially since maternal under-nutrition is strongly associated with the risk of preterm delivery in blacks.[10] Alternatively, it is possible that black neonates had greater energy expenditure resulting in higher glucose utilization, due to undetected differences in health status related to sepsis[11] or unknown factors more prevalent in black preterm neonates born spontaneously. Unfortunately we did not routinely record the presence of sepsis in our database. The metabolic crossover hypothesis suggests that normal labor is initiated when fetal energy demands exceed the capacity for maternal energy delivery, initiating a fetal stress response that triggers labor.[12] Postnatal hypoglycemia does not validate the metabolic crossover hypothesis, which concerns the interplay between maternal energy supplies and fetal metabolic needs. However, if higher glucose utilization or decreased glucose availability in black neonates originated during fetal life, it is possible that this group may experience more fetal hypoglycemia, which could be downstream of prematurely activated stress pathways that could contribute to the onset of spontaneous preterm labor.

Strengths of this study include: it is among the first to evaluate the association between race/ethnicity and neonatal hypoglycemia, it utilized maternal-reported race/ethnicity, neonates were identified from a large racially/ethnically diverse urban population, data were collected prospectively into a structured database, and the database was large enough to permit the study of very preterm infants, which allowed for stratification by spontaneous and medically-indicated deliveries. Weaknesses include the fact that data on maternal pre-pregnancy BMI was limited, and we did not investigate all possible confounding variables. Although we did not find a significant association between maternal BMI and infant hypoglycemia in the small subgroup analysis, our sample size was too small to further account for maternal BMI, particularly with additional stratification by type of preterm. Nevertheless, we found statistically significant associations for black race/ethnicity and neonate hypoglycemia among those delivered spontaneously. Future studies will be needed to confirm these findings. If replicated, the higher prevalence of hypoglycemia among black

very preterm neonates could provide key information about potential pathways leading to preterm birth, as well as useful clinical information regarding an important adverse outcome related to preterm birth.

Acknowledgments

Author contributions: JM and FB conceived of the work; TJT, MM, MG and JS acquired and analyzed the data; all authors interpreted the data; all authors drafted and revised the manuscript, all authors approved the final version to be published, and all authors agree to be accountable for all aspects of the work. None of the authors declares any conflicts in relevant financial interests, activities, relationships, or affiliations. We thank Dave Miedema from the Department of Neonatology at BIDMC for assistance with data extraction and management of the BIDMC NICU database.

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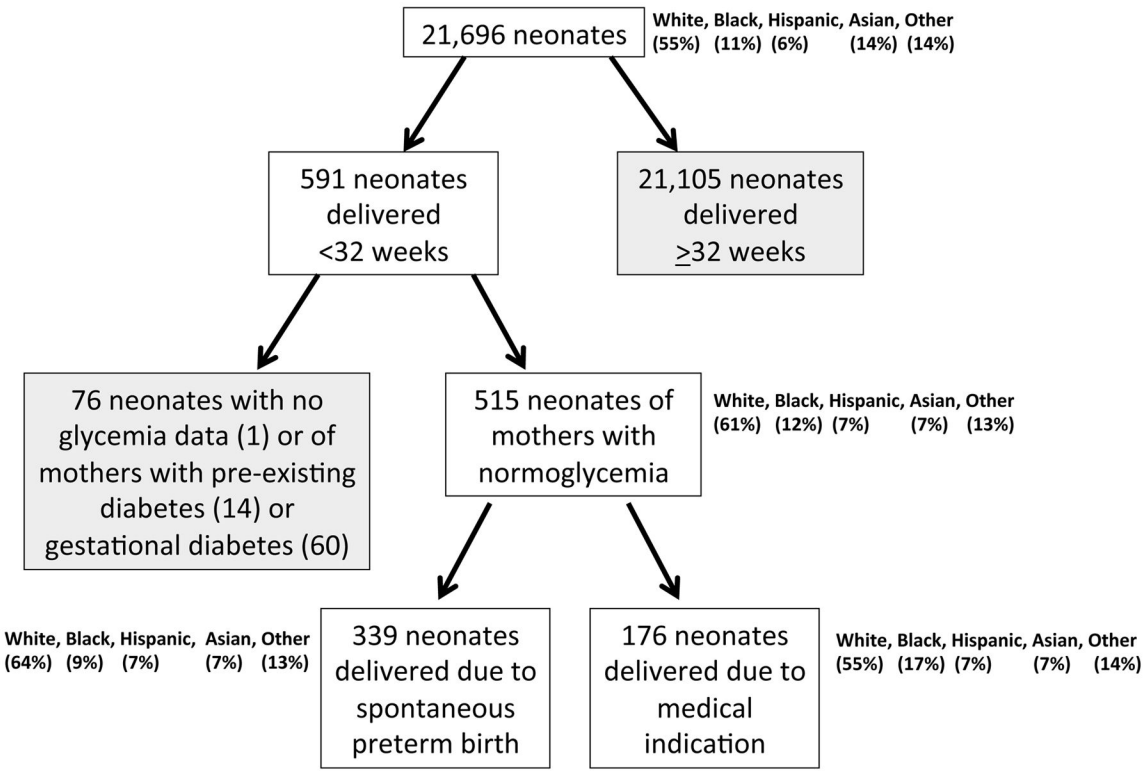

Figure 1.
Derivation of spontaneous preterm birth study population

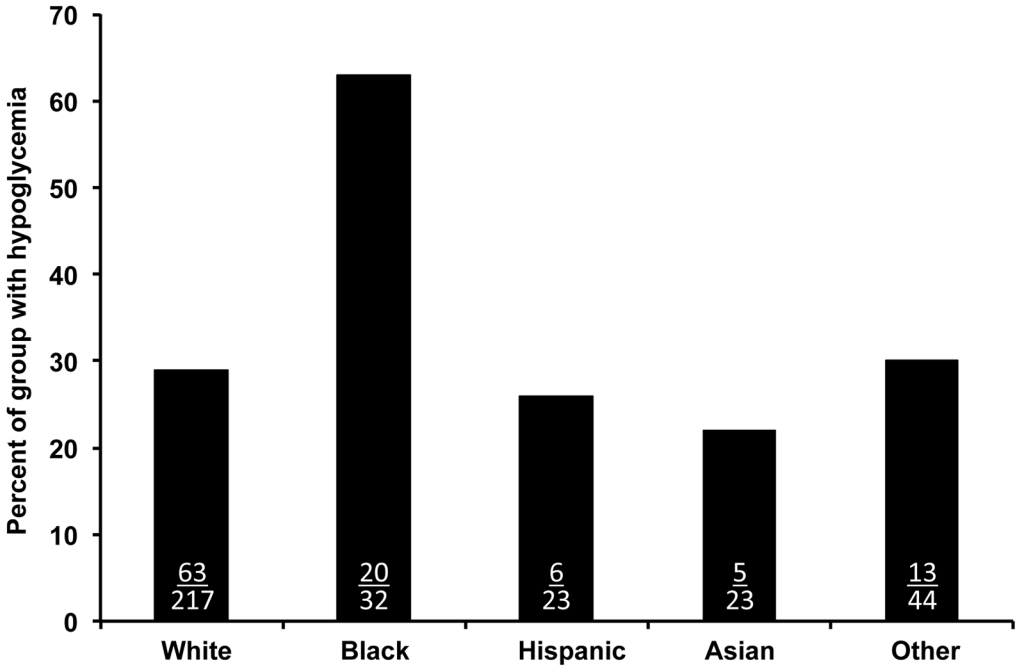

Figure 2.

Percentage of neonates born spontaneously <32 weeks gestation with hypoglycemia by race/ethnicity. For each group, the number of hypoglycemic neonates divided by the total number of neonates (from Table 1) is shown within each bar. *P = 0.003, differences among racial/ethnic groups, by ANOVA.

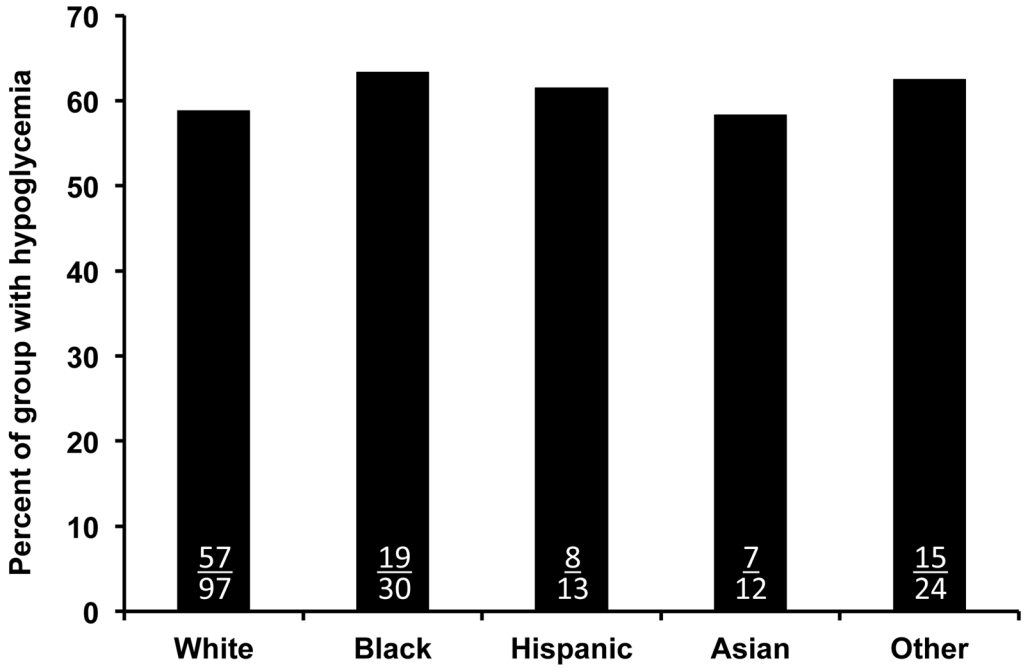

Figure 3.

Percentage of neonates born for medical indications <32 weeks gestation with hypoglycemia by race/ethnicity. For each group, the number of hypoglycemic neonates divided by the total number of neonates (from Table 1) is shown within each bar. *P = 0.99, differences among racial/ethnic groups, by ANOVA

Table 1

Study population characteristics [n=515 infants]

	Spontaneous birth <32 weeks [n=339]			Medically-indicated birth <32 weeks [n=176]		
	Hypoglycemia [n=107]	**No hypoglycemia [n=232]**	**p-value**	**Hypoglycemia [n=106]**	**No hypoglycemia [n=70]**	**p-value**
Maternal characteristics						
Age [years] Mean (SD)	30.9 (6.0)	31.5 (6.3)	0.39	31.9 (5.8)	33.0 (6.7)	0.21
BMI [kg/m^2] Mean (SD)[a]	26.3 (4.0)	24.4 (4.3)	0.27	27.4 (5.2)	26.8 (3.2)	0.81
Education [N (%)][b]			0.10			0.74
<HS	17 (15.9)	42 (18.1)		21 (19.8)	17 (24.2)	
Some college	12 (11.2)	16 (6.9)		6 (5.7)	6 (8.6)	
>College	35 (32.7)	103 (44.4)		40 (37.7)	23 (32.9)	
Unknown	43 (40.2)	71 (30.6)		39 (36.8)	24 (34.3)	
Pregnancy & delivery characteristics						
Gestational age [weeks]						
Mean (SD)	27.5 (2.6)	28.6 (2.2)	0.0002	28.7 (1.9)	29.3 (2.0)	0.06
Type of delivery [N (%)]**						
C-section	73 (68.2)	154 (66.4)	0.74	104 (98.1)	70 (100.0)	0.52
Multiple gestation	37 (34.6)	113 (48.7)	0.01	34 (32.1)	23 (32.9)	0.91
Infant characteristics						
Race/Ethnicity [N (%)]**			0.005			0.99
White	63 (58.9)	154 (66.4)		57 (53.8)	40 (57.1)	
Black	20 (18.7)	12 (5.2)		19 (17.9)	11 (15.7)	
Hispanic	6 (5.6)	17 (7.3)		8 (7.5)	5 (7.1)	
Asian	5 (4.7)	18 (7.8)		7 (6.6)	5 (7.1)	
Other	13 (12.1)	31 (13.4)		15 (14.2)	9 (12.9)	
Male Sex [N (%)]**	59 (55.1)	132 (56.9)	0.76	51 (48.1)	36 (51.4)	0.67
Birth Weight [g]						
Mean (SD)	1154 (447.5)	1274 (350.8)	0.008	1031 (376.6)	1237 (349.3)	0.0004
Birth weight for gestational age [N (%)]**			0.16			0.07
SGA	8 (7.5)	8 (3.5)		43 (40.6)	17 (24.3)	
AGA	85 (79.4)	201 (86.6)		59 (55.7)	48 (68.6)	

	Spontaneous birth <32 weeks [n=339]			Medically-indicated birth <32 weeks [n=176]		
	Hypoglycemia [n=107]	**No hypoglycemia [n=232]**	**p-value**	**Hypoglycemia [n=106]**	**No hypoglycemia [n=70]**	**p-value**
LGA	14 (13.1)	23 (9.9)		4 (3.8)	5 (7.1)	

[a] Subset of population [n=41]

[b] Percents are column percents for each category [Education, Type of Delivery, Race/Ethnicity, Neonate sex, Birth weight for gestational age]

Abbreviations: SGA, AGA, and LGA, small, appropriate and large for gestational age, respectively

Table 2

Association between race/ethnicity and hypoglycemia

	Spontaneous birth <32 weeks		Medically-indicated birth <32 weeks	
	OR (95% CI)			
	Crude	Fully-adjusted[a]	Crude	Fully-adjusted[a]
Black	2.15 (1.54–3.00)	1.61 (1.13–2.29)	1.08 (0.78–1.49)	0.97 (0.72–1.36
Hispanic	0.90 (0.43–1.87)	0.86 (0.41–1.79)	1.05 (0.66–1.67)	0.96 (0.57–1.59)
Asian	0.75 (033–1.70)	0.70 (0.31–1.57)	0.99 (0.60–1.64)	1.06 (0.60–1.86)
Other	1.02 (0.62–1.67)	0.96 (0.59–1.55)	1.06 (0.72–1.57)	0.95 (0.66–1.37)
White	Ref.	Ref.	Ref.	Ref.

[a]Adujsted for maternal education, maternal age at delivery, multiple gestations, delivery type, gestational age, birth weight, and neonates' sex