Impact of Maternal HbA1c Levels ≤6% and Race in Nondiabetic Pregnancies on Birthweight and Early Neonatal Hypoglycemia

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Objective To evaluate whether pregnancy glycated hemoglobin (HbA1c) levels of ≤6% and maternal race impacts neonatal hypoglycemia and birthweight, and whether diabetes and beta blocker use during pregnancy additively impacts neonatal outcomes.

Study design Retrospective chart review of 4769 infants born at ≥34 weeks; 21 482 glucose measurements were assessed. Predefined groups were infants born to mothers without documented pregnancy conditions (group N), prenatal exposure of beta blockers (group B), diabetes (group D), or both (group DB).

Results In group N, both in Caucasian (Caucasian, n = 1756; $\beta = 2.6$, $P < .001$) and African American (n = 1872; $\beta = 2.2$, $P = .002$) race, there was a direct relationship between pregnancy HbA1c levels and birthweight. HbA1c (aOR 1.8; 95% CI [1.3-2.5]) levels, maternal race, prematurity, cesarean delivery, and birth weight predicted hypoglycemia. Each 0.1% increase in HbA1c levels between 4.8 and 6 increased the odds of neonatal hypoglycemia by 6.4% in African American (β 0.62, SE 0.22, $P = .01$) and by 12.0% in Caucasian (β 1.13, SE 0.23 $P < .001$) population. The odds of neonatal hypoglycemia were 1.7 (group B), 2.1 (group D), and 3.1 (group DB) times higher compared with group N.

Conclusions Pregnancy HbA1c levels between 4.8% and 6.0% considered acceptable during pregnancy impacts neonatal hypoglycemia and birthweight especially in Caucasian race. A third trimester HbA1c >5.2 is a potential risk factor for neonatal hypoglycemia, especially in preterm infants. Although we report new findings on the relationship between maternal HbA1c levels and neonatal outcomes, a prospective study is required to validate our findings and determine "optimal" HbA1C levels during pregnancy. *(J Pediatr 2020;227:121-7)*.

Hypoglycemia is a frequent neonatal complication, often requiring parenteral intravenous therapy, can prolong hospital stay, and may impair neurologic development.[1,2] Prematurity, fetal growth restriction, large for gestational age (LGA), maternal diabetes, and beta blockers use are risk factors of neonatal hypoglycemia.[3-8] However, many neonates who develop hypoglycemia do not have these risk factors. Furthermore, whether race impacts neonatal blood glucose homeostasis remains unknown. Maternal blood glucose levels can stimulate fetal hyperinsulinemia, affecting both growth and blood glucose homeostasis in the newborn. Neonatal blood glucose levels and hypoglycemia immediately after birth is inversely related to maternal glucose levels close to delivery[9,10] and can persist for 1-2 days after delivery.[11] Glycated hemoglobin (HbA1c) is a widely used laboratory test to determine the index of mean glycaemia, and is reflective of glucose control over 2-3 months.[12,13] The current clinical practice recommendation of American Diabetes Association (ADA) classifies HbA1c levels of ≥6.5% as diabetic and 5.7%-6.4% as prediabetic in nonpregnant adults.[14] Although ADA recommends that during pregnancy, HbA1c levels of ≤6% in the second and third trimesters can be considered optimal,[15] this has not been rigorously evaluated in relationship to neonatal outcomes such as birth weight (BW) and hypoglycemia.

Recent studies from mothers with gestational diabetes have suggested that HbA1c levels close to delivery correlated with neonatal hyperinsulinemia and predicted hypoglycemia.[5,16,17] Higher HbA1c level has also been associated with an increased risk for LGA.[18] In the Hyperglycemia and Pregnancy Outcomes (HAPO) trial, the authors found a continuous correlation between elevated maternal blood glucose obtained during oral glucose tolerance test and neonatal hypoglycemia and BW >90% percentile.[19,20] However, the relationship between long-term pregnancy glycemic control, assessed by HbA1c in our study, and the influence of maternal race on neonatal outcomes remains undefined. In a smaller study of ≈90 Caucasian (Caucasian) mothers, an increase in HbA1c

AAP	American Academy of Pediatrics
ADA	American Diabetes Association
AGA	Appropriate for gestational age
BW	Birth weight
BWz	Birth weight z score
HAPO	Hyperglycemia and Pregnancy Outcomes
HbA1c	Glycated hemoglobin
LGA	Large for gestational age
OGT	Oral glucose tolerance test
POC	Point of care glucose
SGA	Small for gestational age

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from first to second trimester correlated with neonatal BW percentile.[21] Furthermore, although differences in HbA1c levels has been reported among Caucasian and African American races in the nonpregnant population,[22-25] there are a paucity of data regarding the racial influences on HbA1c levels during pregnancy and its impact on neonatal hypoglycemia and BW. Furthermore, beta blockers are frequently used to manage hypertension during pregnancy and can impair neonatal glycemic homeostasis.[26] Whether beta blocker use, either alone or in patients with diabetes during pregnancy, alters their glycemic control or further increases the risk of neonatal hypoglycemia is also not very well studied.

The aims of this study were to investigate the relationships between pregnancy HbA1c levels ≤6% (in mothers with no documented disease) and neonatal hypoglycemia and BW, to evaluate the effect of African American or Caucasian race on HbA1c levels during pregnancy and neonatal hypoglycemia and BW, and to determine whether in the diabetic state, beta blocker use during pregnancy alters the HbA1c profile and increases the risk of neonatal hypoglycemia additively or independently.

Methods

Study Design

This retrospective study was conducted in the neonatal unit at Hurley medical center. The study population consisted of all the infants born ≥34 weeks from January 2015 to April 2018. Infants were excluded if they were out born, length of stay was less than 24 hours, and had congenital malformations or chromosomal abnormalities. We retrospectively collected data from the electronic medical record from the day of admission until discharge. Each patient's Epic electronic medical record was reviewed for the following variables: neonatal data such as gestational age, BW, sex, point of care (POC) glucose level and collection time, type of feeding (breastfeeding or formula), timing of first feed, and transfer to the neonatal intensive care unit for intravenous dextrose infusion; maternal information regarding self-declared race, mode of delivery (vaginal or cesarean delivery), use of general anesthetic at the time of delivery, along with prenatal information such as hypertension, pre-eclampsia, eclampsia, medications including beta blocker use during current pregnancy, diabetes mellitus and maternal HbA1c level and gestational age at which HbA1c was measured was collected. Gestational diabetes was diagnosed if there were 1 abnormal oral glucose tolerance test value with blood glucose (mg/dL) more than 92 at fasting, 180 at 1 hour or 153 at 2 hour, or HbA1c >6.5. Fenton Growth Chart (version 2013)[27] z scores for BW were calculated of each infant in addition to their absolute weight measurements. The Human Research and Ethics Committees of our institution approved this study.

Blood Glucose Monitoring

All infants born at ≥34 weeks who had POC glucose level documented were included in the study and final analysis (**Figure 1**; available at www.jpeds.com). POC levels were measured according to the standardized protocol for postnatal glucose monitoring at our institution. In our institution, POC glucose is measured by the Nova StatStrip Glucose Hospital Meter System (Nova Biomedical, Waltham, Massachusetts) that measures whole blood glucose utilizing glucose oxidase technology and electrochemical biosensors with a reading range of 10-600 mg/dL. This system is calibrated every 24 hours.[28] First screening of blood glucose is done at bedside as, POC, as per the American Academy of Pediatrics (AAP) guidelines.[29] Neonatal feeding is initiated as soon as possible after delivery. POC is checked at least 30 minutes after feeding. POC is also checked if the first feeding is delayed due to any reason, the timing of which is variable mainly based on the bed side nursing discretion. POC is repeated at least once if it is <40 mg/dL. POC is repeated more than once if the infants had low blood glucose and was deemed symptomatic. Routine blood glucose monitoring is done for at least 24 hours in late preterm and small for gestational age (SGA), and for the first 12 hours in LGA infants and infants of mothers with diabetes. POC values less than 40 mg/dL were frequently confirmed by laboratory blood glucose measurement. Although POC testing is not as accurate as laboratory measurement at low levels, it is the standard of care in most neonatal intensive care units because the turn-around time of laboratory results for blood glucose precludes immediate therapy. Infants were categorized based on the POC levels within 24 hours of their life. Infants with at least 1 POC <40 mg/dL were defined as cases (hypoglycemia) and infants with no POC <40 mg/dL as controls (normoglycemia). All available POC readings, including first level, minimum level, and the maximum level were collected.

Study Population Categorization

The study population was categorized into 4 groups based on the documentation, in the mother's chart of, either no disease (both prepregnancy and pregnancy complications) (group N), maternal diabetes (group D), beta-blocker exposure (group B), or both maternal diabetes and beta-blocker exposure (group DB) during the current pregnancy. All available maternal HbA1c levels checked during the current pregnancy was collected from mother's chart. In case of multiple readings, the highest value was taken to analyze the overall distribution of HbA1c level and its association with neonatal BW and blood glucose. In addition, in group N, levels ≤6% were considered as "normal", based on the current ADA recommendation.[15]

Statistical Analyses

Baseline characteristics were compared, first between hypoglycemia and normoglycemia and then between the groups based on the maternal pre-existing conditions. Univariate analysis of continuous variables was done via the t test and ANOVA or Kruskal-Wallis test based on the distribution of the data, and categorical variables were evaluated via χ^2 tests.

Data are presented as either mean (SD) or median (IQR) for continuous variables and number (percentage) for categorical variables. Distribution of HbA1c was analyzed by kernel density plots. We initially examined the relationships between "normal" maternal HbA1c levels (≤6%) and neonatal outcomes in group N. We then compared neonatal blood glucose across all 4 groups (N, D, B, and DB). To analyze the predictive value of HbA1c for BW and blood glucose we performed multiple regression analysis and to analyze the association of hypoglycemia (dependent variable), we performed multiple logistic regression analysis. Based on our regression models, we performed postestimation analysis to depict the linear prediction of BW and blood glucose and to depict the predicted probability of hypoglycemia. A P value of <.05 was considered statistically significant. All statistical analysis was performed using StataCorp 2015 (Stata Statistical Software, Release 14; StataCorp LP, College Station, Texas).

Results

Study Population and Demographics

Medical records were reviewed for a total of 8341 infants (Figure 1). Overall, the mean (SD) gestational age at delivery was 37.3 (2.7) weeks and BW was 3025 (693) g; 63% of neonates were delivered vaginally, 54% were Caucasian, and 50% were male; 10.4% were SGA and 4.9 % were LGA. POC levels were available for 4769 infants with a total number of 21 482 measurements, and HbA1c values were available for 4391 mothers with a total number of 6312 measurements during the current pregnancy. Three thousand three (68.4%) mothers had 1 and 1388 (31.6%) mothers had more than 1 HbA1c level checked during current pregnancy. POC was not monitored in 3572 infants. The average gestational age in weeks (39.1 ± 0.9 vs 38.1 ± 1.6; P < .001) and average BW in g (3312 ± 352 vs 3086 ± 595; P < .001) was higher in infants who did not have POC measured. There was no difference in BW (3089 ± 597 vs 3081 ± 593; P = .66) among infants whose mothers did or did not have HbA1c levels. Overall, hypoglycemia (POC <40 mg/dL) was noted in 1152 (24.2%) infants, whereas 3617 infants were normoglycemic. In the study, 33% of infants who were hypoglycemic in the cohort were transferred to neonatal intensive care unit for more intensive blood glucose monitoring and/or IV glucose, 24.5% in the term 49.4% in late preterm population. Baseline characteristics of infants with hypoglycemia and normoglycemia are depicted in Table I (available at www.jpeds.com) and for the 4 predefined groups in Table II (available at www.jpeds.com).

The Effect of Race on Maternal HbA1c Levels in Pregnancies Uncomplicated by Disease (Group N) and with HbA1c ≤6%

The average HbA1c level was higher (5.2 ± 0.4 vs 5.0 ± 0.3; P < .001) with an overall distribution shifted to the right in African American mothers (Figure 2, A). In mothers with multiple readings, an increase in HbA1c was noted in 16.7% of mothers in second trimester vs 43.8% in third trimester (P < .001). The increase in HbA1c levels in the third trimester was significantly higher in Caucasian population compared with the African American population (5.9% [2.6-8.9] vs 4.3% [2.2-8.0]; P = .02). In addition, the comparison of HbA1c among the 4 groups (Figure 2, B) revealed that the median level was 5.1 in group N, 5.2 in group B (on β blockers), 5.8 in group D (diabetes during pregnancy), and 6.3 in group DB (diabetes plus β blockers) (P < .001) (Table II).

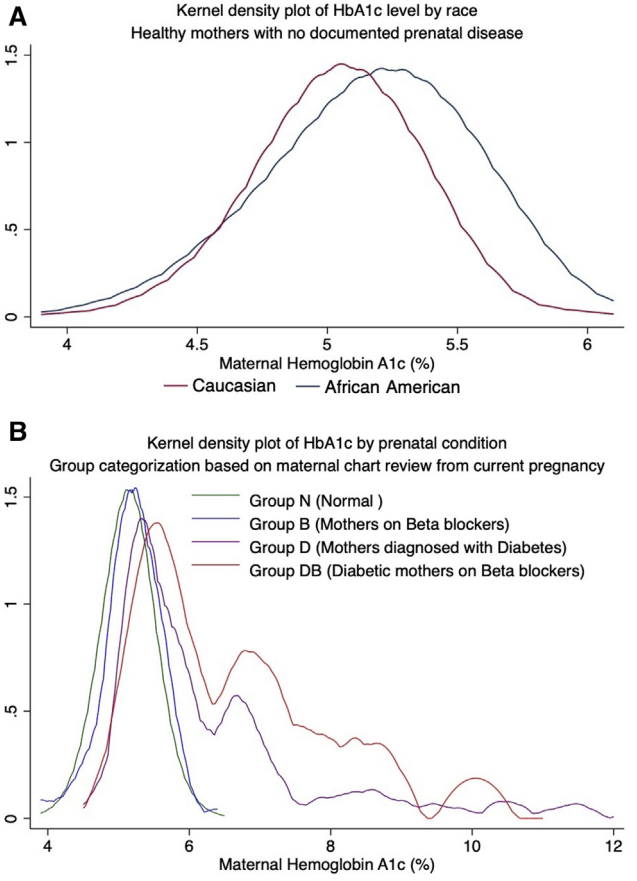

Figure 2. Distribution of maternal HbA1c level by Kernel density plot. **A,** Kernel density distribution plot by race in healthy mothers with no documented prenatal disease and HbA1c ≤ 6%. Data representative of 3628 mothers (Caucasian: 1756; African American: 1872). **B,** Kernel density distribution plot of HbA1c by prenatal condition. Data representative of 4391 mothers: group N (n 3792), group B (n 189); group D (n 354); group DB (n 56).

Association of Neonatal BW with Maternal HbA1c Level ≤6% in Group N

Neonatal BW z scores (BWz) were analyzed in relation with maternal HbA1c values in each trimester (Table III; available at www.jpeds.com). Simple linear regression of

HbA1c in the third trimester showed that BWz in both African American (β = 0.21, P = .002) and Caucasian (β = 0.59, P < .001) population increased with HbA1c levels. Subsequent multiple regression analysis, correcting for gestational age at birth, gestational age at which HbA1c was measured, neonatal sex, mothers' race, and 2-way interaction of HbA1c and race, indicated significant prediction of BW (R^2 = .37; P < .001) with increasing HbA1c levels. It was noted that levels in Caucasian mothers better predicted the BW (β = 2.6, P < .001) as opposed to African American mothers (β = 2.2, P = .002). In mothers with multiple reading (n 805), gestational increase in HbA1c was positively associated with BW only in Caucasian mothers (β = 0.17, P < .001). Subsequently, postestimation analysis of predictive margins of BWz scores were plotted for each race (Figure 3, A and B). Our model suggests that, in mothers with HbA1c levels ≤6%, there is a nonlinear relation between BW and HbA1c values, more so in Caucasian population, from 4.8%-6%, indicating that BW is more sensitive to changes in HbA1c in Caucasian population.

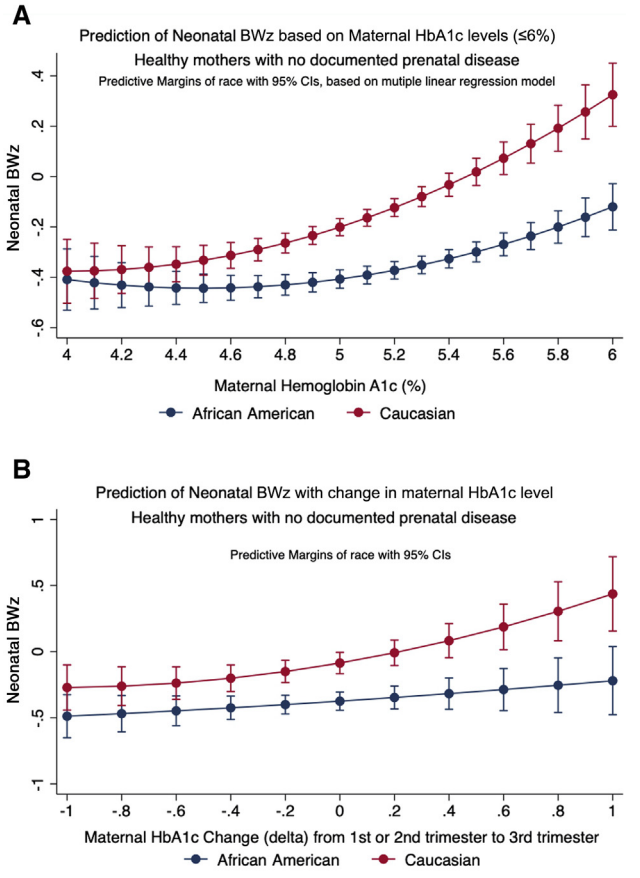

Figure 3. Prediction of BWz in neonates born to healthy mothers with no documented prenatal disease. **A,** Predictive margins with 95%CI of BWz plotted by race in healthy mothers with no documented prenatal disease and HbA1c ≤6%. Data representative of 3628 mothers (Caucasian: 1756; African American: 1872). **B,** Predictive margins with 95% CI of BWz score plotted for delta change in HbA1c levels from first or second trimester to third trimester by race. Data representative of 805 healthy mothers with no documented prenatal disease mothers (Caucasian: 440; African American: 365).

Association of Neonatal Blood Glucose with Maternal HbA1c Level ≤6% in Group N

First Blood Glucose Levels Before Feeding. The mean time of blood glucose check was the same in both races at 1.6 ± 0.4 hours (P = .32). The mean blood glucose was higher in African American (57.5 ± 18) than Caucasian (54.1 ± 17.9) infants (P = .009). On multiple regression analysis (R^2 = .04; P < .001), correcting for mode of delivery, prematurity, BW, maternal HbA1c, and race, HbA1c levels in Caucasian mothers were relatively better in predicting the blood glucose (β = −0.27, P = .02) as opposed to African American mothers (β = −0.20, P = .08). The other significant predictor in this model was prematurity (β = −0.16, P < .001).

Maternal HbA1c Levels and Lowest Blood Glucose Levels in the First 24 Hours. Univariate analysis showed an inverse relationship between lowest blood glucose and increasing HbA1c levels in third trimester (Table III). Multiple regression was done correcting for maternal race, mode of delivery, maternal use of general anesthesia, time of blood glucose check, time of first feeding, type of feeding (breastmilk vs formula), prematurity, and appropriate for gestational age (AGA). Results indicated 5 significant predictors (R^2 = .15; P < .001) for lowest blood glucose levels in first 24 hours. HbA1c levels in Caucasian mothers were relatively better in predicting the blood glucose (β = −0.46, P < .001) as opposed to African American mothers (β = −0.32, P < .001). The other significant predicators were cesarean delivery (β = −0.06, P = .015), prematurity (β = −0.24, P < .001), AGA (β = 0.23, P < .001), and formula feeding (β = 0.09, P < .001). Based on our model, postestimation analysis of predictive margins of the mean blood glucose for each race was plotted (Figure 4, A).

Maternal HbA1c and Neonatal Glycemic Status. The overall third trimester HbA1c was higher in mothers whose infants had hypoglycemia (5.3 ± 0.4 vs 5.1 ± 0.4; P < .001). Infants born to Caucasian mothers manifested this at a lower level compared with those born to African American mothers (5.2 ± 0.4 vs 5.4 ± 0.4; P = .04). Multiple logistic regression performed, correcting for confounding variables (Table IV), indicated that HbA1c, Caucasian race, prematurity, and cesarean delivery increased the odds, whereas AGA decreased the odds of hypoglycemia. Our model predicted that in infants born to Caucasian mothers, increases in HbA1c levels from 4.8 to 6, increases the risk of hypoglycemia from 25% to 48% in late preterm (gestational age <37 weeks, n = 215), and 12% to 22% in term (gestational age ≥37 weeks, n = 1541). In African

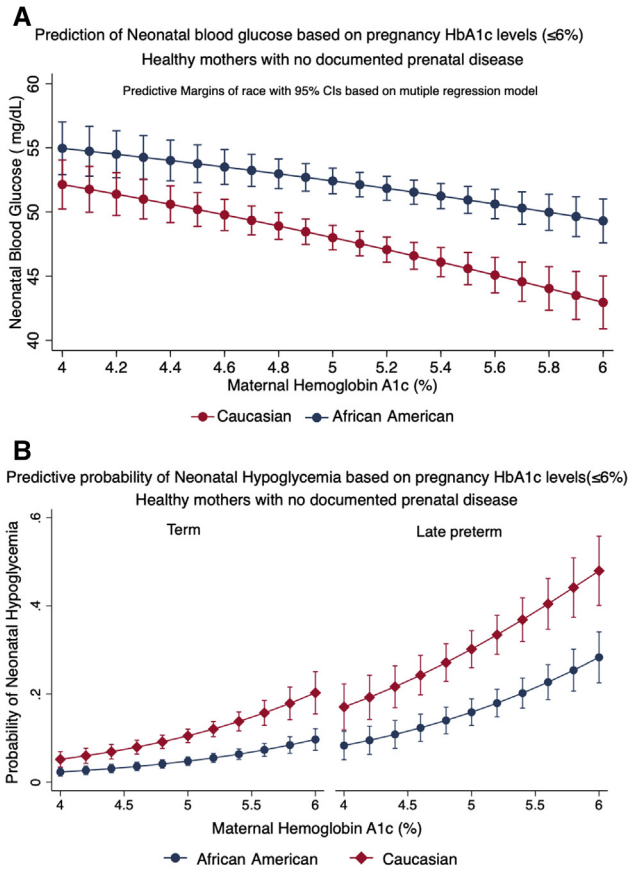

Figure 4. Prediction of blood glucose profile in first 24 hours in neonates born to healthy mothers with no documented prenatal disease and HbA1c ≤6%. **A,** Predictive margins with 95% CI of lowest neonatal blood glucose (mg/dL) plotted for maternal HbA1c levels by race. Data representative of 3628 healthy mothers with no documented prenatal disease and HbA1c ≤6% (Caucasian: 1756; African American: 1872). **B,** Predictive margins with 95% CI of probability of neonatal hypoglycemia plotted for maternal HbA1c levels by race in term vs late preterm infants. Data representative of 3628 healthy mothers with no documented prenatal disease and HbA1c ≤6%: (Caucasian: 1756; African American: 1872).

American population, this risk increased from 15% to 26% in late preterm (n = 223), and 5% to 10% in term (n = 1649) infants (**Figure 4**, B).

Neonatal Blood Glucose Profile in Additional Groups

Finally, we contrasted the blood glucose profile in all the 4 groups. Group DB had the lowest first blood glucose level at 48 mg/dL (36-58) and minimum blood glucose level at 42 mg/dL (32-49) (**Table II**). Multiple regression results indicated (R^2 = .17; P < .001) that the significant predicators of lowest blood glucose in the model were maternal diabetes (β = −6.6, P < .001), beta blocker use in mothers with diabetes (β = −9.8, P < .001), cesarean section (β = −0.10, P < .001), prematurity (β = −0.24, P < .001), AGA (β = 0.20, P < .001), and formula feeding (β = 0.10, P < .001). The results of multiple logistic regression showed that in comparison with mothers in group N, the odds of neonatal hypoglycemia were 1.75 times higher with maternal beta blocker, 2.08 times higher with maternal diabetes, and 3.15 times higher with both maternal diabetes and beta blocker (**Table V**; available at www.jpeds.com). The overall percentage of hypoglycemia was plotted for term and late preterm across the 4 groups (**Figure 5**; available at www.jpeds.com).

Table IV. Multivariate logistic regression equation predicting hypoglycemia in first 24 hours in infants of mothers with no prenatal disease and HbA1c level of ≤6

Variables	B	SE	OR	95% CI	*P* value
Maternal HbA1c level					
African American	0.64	0.22	1.89	1.22-2.94	***.005***
Caucasian	1.10	0.23	3.01	1.90-4.76	***<.001***
Prematurity*	1.30	0.13	3.67	2.83-4.76	***<.001***
Race (Caucasian)†	−1.57	1.70	0.21	0.01-5.79	.355
Mode of delivery (Cesarean delivery)‡	0.64	0.14	1.89	1.45-2.48	***<.001***
General anesthesia	0.38	0.25	1.46	0.90-2.38	.129
Sex (male)§	0.06	0.12	1.06	0.83-1.36	.620
AGA	−1.50	0.15	0.22	0.17-0.30	***<.001***
Type of feeding (formula feeding)¶	0.17	0.15	1.19	0.88-1.60	.256
Time of first feeding	−0.18	0.11	0.84	0.68-1.03	.101
Time of blood glucose check	0.00	0.00	1.00	1.00-1.00	.993
Constant	−4.69	1.25	0.01	0.00-0.11	.000

Variables include in the regression: HbA1c level, maternal race, mode of delivery, use of general anesthesia at delivery, neonatal sex, type of feeding (breast milk vs formula), time of feeding, and timing of blood glucose check.
Referent group: *Prematurity (gestational age >37 weeks as referent); †Maternal race (African American as referent); ‡Mode of delivery (vaginal as referent); §Sex (female as referent); ¶Type of feeding (breast feeding) as referent.
Significant *P* values are depicted in bold/italics.

Discussion

We examined the relationship between maternal HbA1c levels, self-declared race, and neonatal outcomes in pregnancies with HbA1c ≤6%, generally considered safe during pregnancy.[15] We found that African American mothers had higher pregnancy HbA1c levels when compared with Caucasian mothers. Pregnancy HbA1c levels correlated with BW in both races, with a nonlinear increase in BWz scores with increasing HbA1c levels, particularly in Caucasian infants. Strikingly, we noted an inverse relationship between increasing third trimester HbA1c levels and early neonatal blood glucose values in both Caucasian and African American term and preterm infants, although the relationship was stronger in Caucasian infants. Finally, we also noted an additive effect of maternal diabetes and beta blocker use on neonatal hypoglycemia. Although our results were obtained from 1 center, with spot HAb1c levels and POC values, they suggest that HbA1c ≤6% during pregnancy can potentially influence neonatal outcomes.

Racial and ethnic variations in HbA1c levels have been reported in the non-pregnant population.[22,24,25,30] Consistent with these reports, we show that racial differences in

HbA1c levels also exist in nondiabetic pregnancies. The overall HbA1c levels in Caucasian mothers were significantly lower compared with African American others. This is likely to be a complex phenomenon influenced by genetics, diet, and nutritional status. Furthermore, although we also noted that HbA1c levels were lower in second trimester compared with first and third trimesters,[21,31] the increase between second and third trimester was higher in Caucasian mothers. However, we found a significantly greater increase from second to third trimester in Caucasian mothers compared with African American mothers. These data suggest that in pregnancies uncomplicated by disease with maternal HbA1c ≤6%, considered optimal by ADA during pregnancy, there are clear racial differences. As this was a retrospective study and there was variation in practices across different obstetric groups, we did not have HbA1c measurements on all mothers during the study period. This limitation tempers generalizability of our findings and is best addressed through prospective multicenter studies.

In contrast to previous studies investigating the association between pregnancy glycemic control and neonatal outcomes that focused on oral glucose tolerance tests and serum glucose measurements, we targeted HbA1c levels, as it is a better indicator of long-term glycemic control. The HAPO study looked at the relationship between both fasting and 2-hour serum glucose obtained as part of the oral glucose tolerance test (OGT) and cord-blood serum C-peptide levels and neonatal outcomes such as BW.[20,32] Our data are consistent with HAPO study, as our results also demonstrate an association between maternal glycemic control and BW. However, by not using a dichotomous cut-off such as BW >90% percentile, we were better able to demonstrate a continuous relationship between BW and long-term pregnancy glycemic control (HbA1c). Measurement of C-peptide levels in our neonatal cohort could have provided further insight into the relationships between maternal HbA1c levels and neonatal hypoglycemia. We also discovered that the relationship between any HbA1c or third trimester HbA1c levels and birthweight to be more sensitive in Caucasian race. Interestingly, a recent study in south Asian and British mothers also identified race/ethnicity-dependent variation in the relationship between BW and fasting pregnancy glucose level.[33] Our data also showed that BW associates with increases in HbA1c levels between the first or second to third trimester in Caucasian mothers. This is similar to a recent study in healthy Caucasian mothers, where the risk for LGA increased with either no change or increase in HbA1c from first to second trimester.[21] Overall our results show that BW better correlates with maternal HbA1c levels in Caucasian population.

In comparing relationships between maternal HbA1c levels and neonatal blood glucose in the first 24 hours, we found an inverse relationship, with better correlation in Caucasian population. We also noted that neonates born to Caucasian mothers had hypoglycemia at lower HbA1c levels than African American mothers, and this occurred more frequently in late preterm infants. The predicted probability of POC <40 mg/dL in the first 24 hours increases by more than 50% in African American population, and by 180% in Caucasian population with increases in HbA1c from 4.2% to 6%. The HAPO study examined the relationship between both fasting and 2-hour serum glucose obtained as part of the OGT and cord-blood serum C-peptide levels and neonatal blood glucose. Our data are consistent with HAPO study, in that both demonstrate an association with maternal glycemic control and blood glucose. However, the association between hypoglycemia and maternal glucose levels obtained during an OGT at 24-32 weeks of gestation was weak as opposed to cord C-peptide levels in the HAPO study.[34] We were able to demonstrate that maternal HbA1c level, a measure of long-term maternal glycemia better predicted overall blood glucose and risk of hypoglycemia, and this association was stronger in Caucasian vs African American race, a novel finding. We speculate that racial differences in the correlation may be due to different thresholds of either placental glucose transfer or fetal insulin levels in response to glucose levels. Our study suggests that transitional neonatal blood glucose homeostasis and physiological hypoglycemia is impacted by maternal third trimester HbA1c levels, uncovering a potential contributing factor to this common newborn phenomenon, and upon further validation, serve as a tool to identify "at risk neonates" for closer monitoring. Whether a third trimester maternal HbA1c level can potentially augment current AAP guidelines for hypoglycemia surveillance in late preterm infants needs to be investigated.[29]

A limitation of our data is that POC testing rather than laboratory blood glucose measurements was used for analysis. Another limitation of our study is that POC measurements were not available for all the neonates, but this is consistent with AAP guidelines for not routinely checking blood sugars. Some infants had their POC measured before feeds if for maternal conditions (cesarean delivery, magnesium) or other reasons nursing staff felt that delay in institution of feeds may result in hypoglycemia. Infants who had POC measurements before feeds were born on average a week earlier. Although this limitation decreases ready generalizability of our findings, >92% of infants with blood glucose measurements had maternal HbA1c levels so our large number (>4000 infants) support our findings.

Finally, comparison of the 4 predefined groups we found that concomitant use of beta blocker in patients with diabetes leads to higher median HbA1C levels. Almost one-half of neonates in this group (DB) had hypoglycemia compared with about one-third of the infants exposed to maternal diabetes (D) or beta blocker (B) alone. Overall predicted probability of hypoglycemia in Caucasian term infants increased from 28% in group D to 55% in group DB and in Caucasian late preterm from 70% in group D to 90% in group DB. The change in African American population was not significantly different. Although the proportion of small for gestational age infants were higher in group DB compared with group D, our results were still significant after correcting for it in logistic regression model. We speculate that this higher risk of hypoglycemia may be due to relatively greater sensitivity to higher HbA1c levels in Caucasian population. Our data

highlight the importance of close monitoring of blood glucose in infants of mothers with diabetes on β-blocker especially in Caucasian population.

Although this was a single center study and we did not have HbA1c data on all mothers, as routine HbA1c is not currently required, our data suggest that maternal HbA1c levels may impact important early neonatal outcomes. We clearly demonstrate that HbA1c levels >5.2% in nondiabetic pregnancies (HbA1c <6%) is associated with nonlinear increases in birthweight z scores, and importantly >20% risk of early hypoglycemia in a race-dependent manner. Our data lend credence to the existence of a prediabetic state with varying thresholds in Caucasian and African American pregnancies, which nonetheless can impact neonatal outcomes adversely.[19,20] Future studies to prospectively define the relationships between race, pregnancy HbA1c, and glycemic control, are required to define, categorize, and mechanistically evaluate "optimal" glycemic control in mothers with neonatal outcomes in mind. If our results are replicated in other studies, it might warrant a re-think of "safe" HbA1c levels in pregnancy, and closer monitoring for neonatal hypoglycemia in mothers with elevated HbA1c levels. ■

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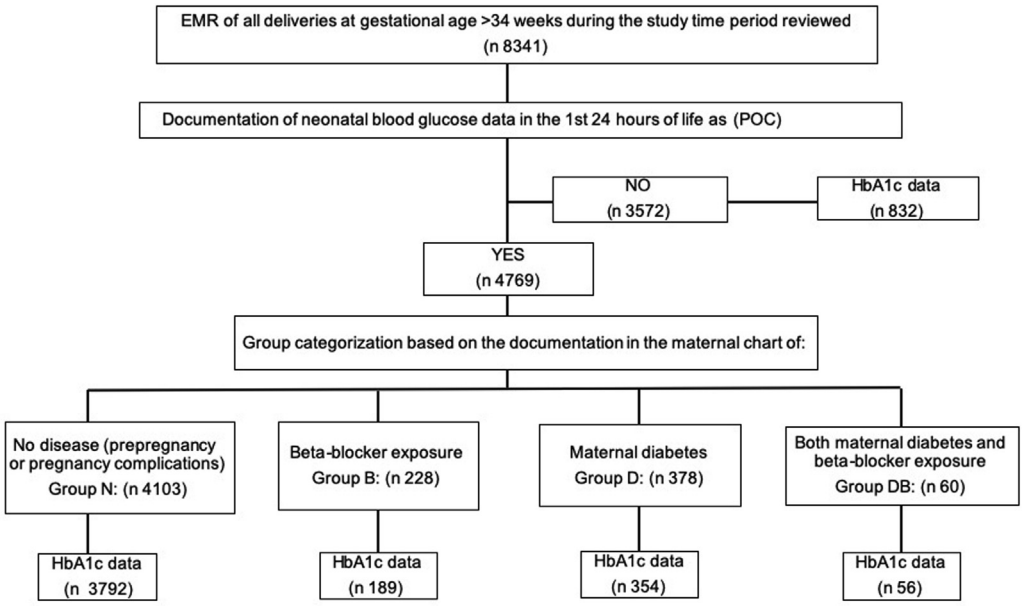

Figure 1. Flow diagram of study population. The flow chart depicts the mother and infant charts included in the final analysis based on data available on maternal HbA1c and neonatal POC levels. EMR, Electronic Medical Record.

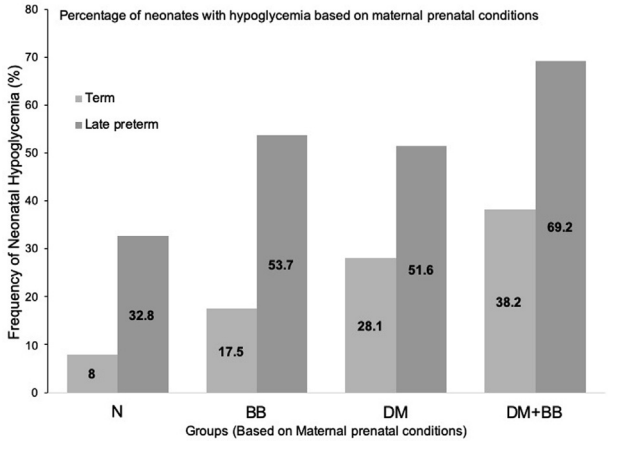

Figure 5. Incidence of neonatal hypoglycemia in first 24 hours in neonates by maternal prenatal condition: Incidence of neonatal hypoglycemia plotted for prenatal conditions in term vs late preterm infants. Data representative of group N (4103), group B (n 257); group D (387); group DB (n 60).

Table I. Baseline variables in infants based on POC in first 24 hours of life

Variables	POC >40 mg/dL (n 3617)	POC <40 mg/dL (n 1152)	*P* value
Gestational age, mean (SD), wk	38.7 (1.6)	37.6 (1.7)	**<.0001**
BW, mean (SD), g	3211 (483)	3007 (668)	**<.0001**
BWz, mean (SD)	−0.20 (0.8)	−0.18 (1.2)	.496
Male sex, n (%)	1901 (52.5)	576 (50.0)	.130
Caucasian, n (%)	1833 (50.7)	670 (58.1)	**<.0001**
Vaginal delivery, n (%)	2130 (58.9)	521 (45.2)	**<.0001**
General anesthesia, n (%)	251 (6.9)	134 (11.6)	**<.0001**
Breast milk, n (%)	1895 (52.4)	553 (48.0)	**.009**
HbA1c, n (%) with data	3297 (91.1)	1094 (94.9)	**.0001**
HbA1c level, median (IQR), (%)	5.2 (4.9-5.4)	5.3 (5.0-5.6)	**.0003**
Time of first feed, median (IQR), h	1.1 (0.7-1.9)	1.1 (0.8-1.7)	**.289**
First POC level, median (IQR), mg/dL	60 (51-71)	37 (30-46)	**<.0001**
First POC time, median (IQR), h	2.2 (1.7-2.9)	2.2 (1.7-2.8)	.05
Minimum POC level, median (IQR), mg/dL	54 (47-63)	33 (28-37)	**<.0001**
Minimum POC time, median (IQR), h	7.6 (2.8-15.1)	3.6 (2.0-10)	**<.0001**
Transferred to neonatal intensive care unit, n (%)	629 (17.4)	538 (46.7)	**<.0001**
Dextrose infusion, n (%)	73 (2.0)	381 (33.1)	**<.0001**
Length of stay, median (IQR), d	1.9 (1.4-2.2)	2.6 (2.0-4.4)	**<.0001**

Significant *P* values are depicted in bold.

Table II. Comparison of maternal and neonatal characteristics based on maternal prenatal condition

Variables	Group N (n 4103)	Group B (n 228)	Group D (n 379)	Group DB (n 60)	*P* value
Gestational age, wk*	38.7 (1.5)	37.6 (1.5)	37.7 (1.3)	37.2 (1.0)	**<.001**
BW, g*	3184 (515)	3032 (560)	3232 (531)	3131 (543)	**<.001**
BWz*	−0.22 (0.87)	−0.10 (0.9)	0.27 (1.0)	0.28 (1.2)	**<.001**
Male sex†	2061 (50.2)	107 (47.0)	192 (50.6)	22 (36.7)	.153
Caucasian†	2081 (50.7)	119 (52.3)	225 (59.2)	37 (61.7)	**.005**
Vaginal delivery†	2400 (58.5)	91 (39.9)	139 (36.8)	21 (35.6)	**<.001**
General anesthesia†	318 (7.7)	28 (12.3)	33 (8.7)	6 (10.1)	**.008**
Breast milk†	2049 (49.9)	95 (41.8)	208 (54.8)	21 (35.0)	**.016**
BW category†					
SGA	439 (10.7)	23 (9.9)	18 (4.9)	5 (8.5)	**<.001**
AGA	3486 (84.9)	195 (85.3)	303 (80.0)	45 (74.5)	
LGA	4.3 (4.3)	11 (4.7)	57 (15.1)	10 (17.1)	
POC <40 mg/dL†	914 (22.2)	78 (34.6)	132 (34.8)	28 (46.7)	**<.001**
Time of first feed, (h)‡	1.1 (0.7-1.9)	1.1 (0.8-1.9)	1.2 (0.8-2.0)	1.1 (0.7-1.4)	.299
First POC (mg/dL) level‡	56 (45-68)	50 (40-61)	54 (43-64)	48 (36-58)	**<.001**
First POC time (h)‡	2.2 (1.7-2.9)	2.0 (1.6-2.6)	2.1 (1.7-2.7)	1.9 (1.2-2.4)	**.002**
Minimum POC (mg/dL) level‡	51 (42-61)	48 (38-57)	46 (38-54)	42 (32-49)	**<.001**
Minimum POC time (h)‡	5.3 (2.3-10.9)	2.5 (1.7-4.2)	4.8 (2.2-9.6)	4.3 (1.7-9.9)	**<.001**
HbA1c data†	3792 (92.4)	189 (82.8)	354 (93.4)	56 (93.3)	
HbA1c level (%)‡	5.1 (4.9-5.4)	5.2 (5-5.5)	5.8 (5.3-6.8)	6.3 (5.6-7.4)	**<.001**

*Data represented as mean (SD).
†Data represented as n (%).
‡Data represented as median (IQR).
Significant *P* values are depicted in bold.

Table III. Relationship between maternal HbA1c level in the normal range and neonatal outcome

BWz

Trimesters	Race	B coefficient	SE	*P* value
First trimester	Overall	0.00	0.00	.97
	African American	0.12	0.08	.15
	Caucasian	0.13	0.1	.20
Second trimester	Overall	0.12	0.07	.06
	African American	0.13	0.08	.12
	Caucasian	0.23	0.12	.06
Third trimester	Overall	**0.32**	**0.05**	**<.001**
	African American	**0.21**	**0.07**	**.002**
	Caucasian	**0.59**	**0.09**	**<.001**

Lowest blood glucose in first 24 h of life

Trimesters	Race	B coefficient	SE	*P* value
First trimester	Overall	0.14	1.5	.924
	African American	1.0	1.9	.578
	Caucasian	−3.3	2.4	.171
Second trimester	Overall	−0.93	1.7	.565
	African American	−1.6	2.2	.456
	Caucasian	−0.9	2.9	.755
Third trimester	Overall	**−3.96**	**1.2**	**.001**
	African American	**−3.92**	**1.58**	**.014**
	Caucasian	**−5.13**	**1.8**	**.006**

Significant *P* values are depicted in bold.

Table V. Multivariate logistic regression equation predicting hypoglycemia in first 24 hours in infants of mothers with diabetes and or beta blocker

Variables	B	SE	OR	95% CI	*P* value
Beta blocker**	0.56	0.20	1.75	1.18-2.60	***.006***
Diabetes**	0.73	0.17	2.08	1.50-2.88	***<.001***
Diabetes and beta blocker**	1.15	0.35	3.15	1.59-6.25	***.001***
Prematurity*	1.17	0.10	3.23	2.68-3.90	***<.001***
Race (Caucasian)†	0.50	0.10	1.64	1.35-1.99	***<.001***
Mode of delivery (cesarean delivery)‡	0.53	0.10	1.70	1.40-2.05	***<.001***
General anesthesia	0.16	0.20	1.17	0.79-1.73	.423
Sex (male)§	0.11	0.09	1.11	0.93-1.33	.250
AGA	−1.01	0.12	0.37	0.29-0.46	***<.001***
Type of feeding (formula feeding)¶	−0.20	0.10	0.82	0.68-0.99	**.040**
Time of 1st feeding	−0.33	0.34	0.72	0.37-1.40	.334
Time of blood glucose check	0.00	0.00	1.00	1.00-1.00	.993
Constant	−1.24	0.29	0.29	0.16-0.51	.000

Variables include in the regression: HbA1c level, maternal race, mode of delivery, use of general anesthesia at delivery, neonatal sex, type of feeding (breast milk vs formula), time of feeding, and timing of blood glucose check.
Referent group: *Prematurity (gestational age >37 weeks as referent); †Maternal race (African American as referent); ‡Mode of delivery (vaginal as referent); §Sex (female as referent); ¶Type of feeding (breast feeding) as referent; **Mothers with no known prenatal disease as referent.
Significant *P* values are depicted in bold.