Racial disparities in cord blood vitamin D levels and its association with small-for-gestational-age infants

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OBJECTIVE: To examine the relationship of race and maternal characteristics and their association with cord blood vitamin D levels and small-for-gestational-age (SGA) status.

STUDY DESIGN: Cord blood vitamin D levels were measured in 438 infants (276 black and 162 white). Multivariable logistic regression models were used to evaluate associations between maternal characteristics, vitamin D status and SGA.

RESULTS: Black race, Medicaid status, mean body mass index at delivery and lack of prenatal vitamin use were associated with vitamin D deficiency. Black infants had 3.6 greater adjusted odds (95% confidence interval (CI): 2.4, 5.6) of vitamin D deficiency when compared with white infants. Black infants with vitamin D deficiency had 2.4 greater adjusted odds (95% CI: 1.0, 5.8) of SGA. Vitamin D deficiency was not significantly associated with SGA in white infants.

CONCLUSION: Identification of risk factors (black race, Medicaid status, obesity and lack of prenatal vitamin use) can lead to opportunities for targeted prenatal vitamin supplementation to reduce the risk of neonatal vitamin D deficiency and SGA status.

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INTRODUCTION

Vitamin D (25-hydroxyvitamin D (25(OH)D)) is commonly known for its role in calcium metabolism and bone health, but more recently has gained attention for the significant role it plays in pregnancy and perinatal outcomes. Vitamin D freely crosses the placenta during pregnancy. Thus, levels of neonates at birth depend entirely on that of the mother and, accordingly, several studies have consistently correlated cord blood 25(OH)D levels to those of their mothers.1–6 In addition, maternal vitamin D deficiency has been linked to decreased fetal growth and birth size in observational studies.7–9

Maternal vitamin D deficiency is prevalent, the extent of which can be influenced by many variables including skin pigmentation, sun exposure, season, age, vitamin supplementation and obesity. Several large observational studies and meta-analyses have described the association of maternal vitamin D deficiency with pregnancy complications such as pre-eclampsia, gestational diabetes and premature birth.10–13 Racial disparities in maternal and neonatal vitamin D deficiency have been described.1,14–15 Vitamin D deficiency is more common and more severe in black mothers.10,15–19 Racial disparities are also seen with pregnancy complications such as preterm birth, pre-eclampsia and gestational diabetes, as well as adverse neonatal outcomes including low birth weight and small-for-gestational-age (SGA) status.15,17,20,21 However, the majority of studies examined maternal vitamin D levels during the first and second trimesters of pregnancy,7,8,22,23 and correlated these levels to neonatal outcomes. Far fewer studies have examined the relationship between cord blood vitamin D levels, which may more accurately reflect fetal levels of vitamin D, and neonatal outcomes.14,24 Given the racial disparities seen in both vitamin D deficiency and perinatal outcomes, vitamin D has been proposed as part of the explanation for this disparity, particularly with regard to fetal growth and SGA.8

Increased awareness of the growing prevalence of maternal vitamin D deficiency has led to an urgent need for consideration of supplementation during pregnancy. Although studies have shown that supplementation increases maternal and cord blood vitamin D levels, changes in clinical outcomes have not yet been well proven. Thus, sufficient evidence is lacking at this time to recommend routine vitamin D supplementation during pregnancy.12 However, identification of specific risk factors for vitamin D deficiency and the additive effects of these risk factors may lead to opportunities for targeted supplementation with improved outcomes. Thus, the primary purpose of this study was to examine the relationship between race, maternal characteristics, cord blood vitamin D levels and SGA status among infants during one winter season in a Midwestern US population. In particular, we wanted to evaluate the additive effects of race and maternal characteristics such as obesity on vitamin D deficiency and SGA. Our goal was to identify specific high-risk subsets of pregnant women who may benefit from vitamin D supplementation in order to mitigate adverse perinatal outcomes such as SGA.

METHODS

Study design and subjects

This retrospective study was conducted at University of Cincinnati Medical Center in Cincinnati, OH, USA. This study was approved by the University of Cincinnati and Cincinnati Children’s Hospital Medical Center Institutional Review Boards. Previously collected cord blood samples from all singleton births from November 2010 to April 2011 (one winter season) served as the study population. Multiple births and major congenital anomalies were excluded. Maternal medical records were reviewed for the following information: race, prepregnancy body mass index (BMI) and BMI at delivery, insurance status, prenatal vitamin use and maternal complications including smoking, hypertension, diabetes, chorioamnionitis, preterm
Figure 1. Distribution of cord blood vitamin D levels by race.

Table 1. Maternal and neonatal characteristics by race

|                        | Black (n = 276) | White (n = 162) | P-value |
|------------------------|----------------|-----------------|---------|
| 25(OH)D nmol l⁻¹        |                |                 |         |
| mean (s.d.)            | 39.95 (18.3)   | 59.3 (25.7)     | 0.01    |
| < 25 nmol l⁻¹           | 63 (22.8)      | 13 (8.0)        | < 0.001 |
| 25–50 nmol l⁻¹          | 138 (50.0)     | 54 (33.3)       |         |
| > 50 nmol l⁻¹           | 75 (27.2)      | 95 (58.6)       |         |
| Medicaid, n (%)         | 232 (84.1)     | 108 (66.7)      | < 0.001 |
| BMI at delivery (kg m⁻²)| 32.4 (6.7)     | 32.2 (7.7)      | 0.80    |
| mean (s.d.)            |                |                 |         |
| Prenatal vitamins, n (%)| 253 (91.7)     | 147 (90.7)      | 0.74    |
| Smoking, n (%)          | 74 (26.8)      | 69 (42.6)       | < 0.001 |
| Hypertension, n (%)     | 39 (14.1)      | 26 (16.0)       | 0.58    |
| Diabetes, n (%)         | 26 (9.4)       | 23 (14.2)       | 0.12    |
| Chorioamnionitis, n (%) | 10 (3.6)       | 5 (3.1%)        | 0.76    |
| Preterm labor, n (%)    | 40 (14.5)      | 23 (14.2)       | 0.93    |
| Gestational age weeks, | 38.2 (2.4)     | 38.6 (2.0)      | 0.05    |
| mean (s.d.)            |                |                 |         |
| Birth weight g, mean (s.d.) | 3064 (603.1) | 3212 (531.1)   | 0.01    |
| SGA, n (%)              | 44 (15.9)      | 12 (7.4)        | 0.01    |

Abbreviations: BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; SGA, small for gestational age.

25(OH)D level for our study population (n = 438) was 46.9 nmol l⁻¹, with a range of 5.0 to 135.8 nmol l⁻¹. Differences in the distributions of cord blood 25(OH)D concentrations by race were evident (Figure 1), with a higher proportion of vitamin D-deficient samples found in the black population. The mean birth weight of our study cohort was 3119 g and 12.8% of our study population was SGA. The mean BMI at delivery was 32.3 kg m⁻². Maternal and neonatal characteristics of our study population, stratified by race, are shown in Table 1. Compared with whites, blacks had a lower mean cord blood 25(OH)D level and higher incidence of SGA (P < 0.01).

Race, Medicaid status, higher BMI at delivery and lack of prenatal vitamin use were all associated with vitamin D deficiency at α = 0.05. SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used to conduct all analyses.

RESULTS

Of the 506 non-Hispanic white and black infants, 438 with available data on vitamin D status, BMI at delivery, prenatal vitamin use and pre-eclampsia/pregnancy-induced hypertension (PIH) history were included in final analyses. The mean cord blood vitamin D level for our study population (n = 438) was 46.9 nmol l⁻¹, with a range of 5.0 to 135.8 nmol l⁻¹. Differences in the distributions of cord blood 25(OH)D concentrations by race were evident (Figure 1), with a higher proportion of vitamin D-deficient samples found in the black population. The mean birth weight of our study cohort was 3119 g and 12.8% of our study population was SGA. The mean BMI at delivery was 32.3 kg m⁻². Maternal and neonatal characteristics of our study population, stratified by race, are shown in Table 1. Compared with whites, blacks had a lower mean cord blood 25(OH)D level and higher incidence of SGA (P < 0.01).
(25(OH)D < 50 nmol l\(^{-1}\); \(P < 0.01\)). After adjusting for Medicaid status, BMI at delivery and prenatal vitamin use, black infants had a 3.6 greater odds (95% confidence interval (CI): 2.4, 5.6) of having vitamin D deficiency compared with white infants (Table 2). Similarly, infants on Medicaid, a marker of socioeconomic status, had higher odds of vitamin D deficiency (odds ratio (OR) 2.3, 95% CI: 1.4, 3.8), whereas prenatal vitamin use showed a protective effect (OR 0.24, 95% CI: 0.09, 0.62). For every 5-unit increase in BMI, infants had a 1.2 greater odds (95% CI: 1.1, 1.4) of vitamin D deficiency (Table 2). The predicted probabilities of vitamin D deficiency, based on significant predictors in the multivariable regression model, are shown in Figure 2. For instance, at a mean maternal BMI of 32.3 kg m\(^{-2}\), an infant who is black, on Medicaid and no prenatal vitamin use has an 86% (95% CI: 82, 97) probability of vitamin D deficiency, whereas a black infant who is not on Medicaid and with prenatal vitamin use has a 66% (95% CI: 44, 67) probability of vitamin D deficiency.

Blacks had a significantly greater proportion of SGA when compared with whites (\(P = 0.01\); Table 1). As vitamin D levels also differed by race, we stratified the models predicting SGA by race and examined vitamin D deficiency, smoking, pre-eclampsia, maternal age, Medicaid status and BMI at delivery as covariates (Table 3). Black infants with vitamin D deficiency had 2.4 greater odds of SGA (95% CI: 1.0, 5.8) after adjusting for maternal history of PIH and maternal BMI, two significant confounding variables in our model (Table 3). Similarly, infants of black mothers with history of PIH were associated with 2.3 greater odds of SGA after adjustment for confounding variables. Vitamin D deficiency was not significantly associated with SGA for white infants in our study population (Table 3).

We examined several additional models with various cutpoints for 25(OH)D based on clinical guidelines and previous literature, while adjusting for maternal PIH and maternal BMI at delivery. These results indicated that black neonates with 25(OH)D levels < 25 nmol l\(^{-1}\) had an even greater odds of being SGA (OR 3.8, 95% CI: 1.4, 10.6) compared with those with levels ≥ 50 nmol l\(^{-1}\). The OR was 2.2 (95% CI: 0.88, 5.4) for black neonates with 25(OH)D levels 25 to 50 nmol l\(^{-1}\) compared with those > 50 nmol l\(^{-1}\). The small proportion of neonates who were SGA with 25(OH)D levels > 75 nmol l\(^{-1}\) precluded evaluation at higher cutpoints.

Although SGA status was the main outcome of our study, we also evaluated models of 25(OH)D and birth weight percentile after adjusting for maternal PIH and maternal BMI at delivery. Birth weight percentiles for neonates with 25(OH)D levels < 25 nmol l\(^{-1}\) were significantly lower compared with those with 25(OH)D levels ≥ 50 nmol l\(^{-1}\) (adjusted mean weight percentile 0.35 (95% CI: 0.20, 0.50) compared with those > 50 nmol l\(^{-1}\)).

Table 2. Independent associations and multivariable regression model predicting vitamin D deficiency

| Race, n (%) | Deficient (n = 268) | Sufficient (n = 170) | P-value | Odds ratio (95% CI) | P-value |
|------------|---------------------|----------------------|---------|---------------------|---------|
| Black      | 201 (75)            | 75 (44.1)            | < 0.001 | Black vs White 3.6 (2.4, 5.6) | < 0.001 |
| White      | 67 (25)             | 95 (58.6)            |         |                     |         |
| Medicaid, n (%) | 228 (85.1) | 112 (65.9)           | < 0.001 | 2.3 (1.4, 3.8)       | 0.001   |
| BMI at delivery (kg m\(^{-2}\), mean (s.d.) | 33.1 (7.3) | 31.0 (6.4)          | 0.002   | For 5-unit increase in BMI: 1.2 (1.1, 1.4) | 0.005   |
| History of pre-eclampsia or PIH, n (%) | 43 (16) | 22 (12.9)           | 0.37    | —                   | —       |
| Maternal age, mean (s.d.) | 25.0 (5.4) | 26.5 (6.0)          | 0.01    | —                   | —       |
| Prenatal vitamin use, n (%) | 236 (88.1) | 164 (96.5)          | 0.002   | 0.24 (0.09, 0.62)    | 0.003   |

Abbreviations: BMI, body mass index; CI, confidence interval; PIH, pregnancy-induced hypertension. *Vitamin D: deficient: < 50 nmol l\(^{-1}\); sufficient: ≥ 50 nmol l\(^{-1}\).
They found that vitamin D status was associated with risk of SGA in white and nonobese women, but that there was no association between vitamin D and SGA in black or obese mothers.

In contrast to the above-mentioned studies, our results show that the combination of black race and vitamin D deficiency was associated with increased odds of SGA, but this relationship was not preserved for white infants. Our results may have differed for several reasons. First, the majority of populations in the studies of Bodnar et al. and Burris et al. were white, whereas the majority of our study population was black. Furthermore, this study was conducted in Hamilton County, Ohio, an area with worse perinatal outcomes than national averages, including higher infant mortality, preterm birth and low birth weight rates, as well as considerable racial disparities in infant mortality and perinatal outcomes. All of cord blood samples were collected over one winter season, thus negating seasonal variations in vitamin D levels that may have been seen in other studies. Finally, we analyzed cord blood vitamin D levels at the time of delivery, rather than maternal serum vitamin D levels during pregnancy. Although cord blood 25(OH)D levels do correlate to maternal levels, factors that affect fetal growth may not be uniform throughout pregnancy and this difference in timing could affect study findings.

In addition, maternal characteristics such as obesity or pre-eclampsia could also affect results that may not have been seen if vitamin D samples were obtained during early pregnancy. Concurrently, we also examined maternal variables known to potentially affect vitamin D levels and SGA in an effort to better understand the role of these risk factors in vitamin D levels and risk of SGA. Our results showed several factors to be significant, including BMI at delivery, pre-eclampsia, Medicaid status (as a measure of socioeconomic status) and prenatal vitamin use. Obesity is well known to be a risk factor for vitamin D deficiency because of a sequestering of vitamin D in adipose tissue. Maternal obesity during pregnancy has also been associated with lower vitamin D levels in neonates at delivery.

Table 3. Independent associations and multivariable regression model predicting SGA stratified by race

| Vitamin D, n (%) | Black infants | White infants |
|------------------|--------------|--------------|
|                  | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| < 50 nmol l⁻¹ | 0.02 | < 50 vs ≥ 50 nmol l⁻¹ | 2.4 (1.0, 5.8) | 0.04 | < 50 vs ≥ 50 nmol l⁻¹ | 1.1 (0.32, 3.9) | 0.86 |
| ≥ 50 nmol l⁻¹ | 14 (25) | 226 (59.2) | 2.3 (1.0, 5.4) | 0.04 | 4.1 (1.0, 16.1) | 0.05 |
| Smoking, n (%) | 20 (35.7) | 123 (32.2) | 0.60 |
| Pre-eclampsia or PIH, n (%) | 14 (25) | 51 (13.4) | 0.02 |
| Maternal age, mean (s.d.) | 25.1 (5.5) | 25.7 (5.7) | 0.46 |
| Medicaid, n (%) | 42 (75) | 298 (78) | 0.61 |
| Maternal BMI at delivery (kg m⁻²), mean (s.d.) | 30.4 (6.5) | 32.6 (7.1) | 0.04 |

Abbreviations: BMI, body mass index; CI, confidence interval; PIH, pregnancy-induced hypertension; SGA, small for gestational age.

DISCUSSION

In our study population, we found that compared with white infants, black infants had significantly lower cord blood vitamin D levels and a greater proportion of vitamin D deficiency. Although the prevalence of vitamin D deficiency in black mothers and neonates is well known, debate exists as to the relationship between race, vitamin D deficiency and SGA. Review of published literature regarding this relationship revealed several relevant findings. Maternal characteristics such as obesity or pre-eclampsia could also affect results that may not have been seen if vitamin D samples were obtained during early pregnancy.

Concurrently, we also examined maternal variables known to potentially affect vitamin D levels and SGA in an effort to better understand the role of these risk factors in vitamin D levels and risk of SGA. Our results showed several factors to be significant, including BMI at delivery, pre-eclampsia, Medicaid status (as a measure of socioeconomic status) and prenatal vitamin use. Obesity is well known to be a risk factor for vitamin D deficiency because of a sequestering of vitamin D in adipose tissue. Maternal obesity during pregnancy has also been associated with lower vitamin D levels in neonates at delivery.

Our data are consistent and illustrate the inverse relationship between maternal BMI at delivery and vitamin D status after adjusting for confounding variables. The increased odds of vitamin D deficiency in neonates relative to maternal BMI level were seen in both blacks and whites in our study population and supports similar findings seen in a study done by Bodnar et al. Although prenatal vitamin use was not significantly different between blacks and whites in our study, prenatal vitamin use was significant among those with and without vitamin D deficiency. Furthermore, the protective effect against vitamin D deficiency was seen in both blacks and whites in our study, in contrast to a recently published study by Burris et al., who found that lack of prenatal vitamin use...
was associated with vitamin D deficiency in white but not black women.

Importantly, our study illustrates the additive effect of maternal risk factors and their predictive probabilities for vitamin D deficiency and SGA. Black mothers on Medicaid who were obese and did not take prenatal vitamins had the highest probability of having an infant with vitamin D deficiency. Pre-eclampsia is a known independent risk factor for SGA. Pre-eclampsia, coupled with black race and vitamin D deficiency, resulted in significant increases in the predicted probability of delivering an SGA infant. Interestingly, our results show that increasing maternal BMI had a mild protective effect on risk of SGA. This corresponds to the well-known association that women with higher BMI tend to deliver infants with higher birth weights.28

Furthermore, identification and recognition of women and infants at high risk of vitamin D deficiency and SGA can lead to opportunities for risk modification and reduction in adverse outcomes. Specifically, this study supports a need to target supplementation strategies to mitigate the impact of adverse perinatal outcomes such as SGA. Vitamin D supplementation during pregnancy has been shown to positively affect cord blood vitamin D levels at birth.33,44 Studies of vitamin D supplementation during pregnancy thus far have shown conflicting results with respect to birth weight and reduction of SGA.43-48 Adequately powered and randomized controlled trials of vitamin D supplementation during pregnancy are needed to assess the impact of supplementation on SGA as well as the appropriate dose and timing of supplementation. In addition, individuals with the risk factors that we have identified may benefit even more from supplementation or higher dose supplementation. If vitamin D supplementation does not occur during pregnancy, it may be imperative to identify and offer additional supplementation beyond the routinely recommended 400 IU per day for all infants.28

There were several limitations to our study. First, we did not have information regarding exact amounts of dietary maternal vitamin D intake and sun exposure that may affect maternal and cord blood vitamin D levels. We collected samples over one winter season to mitigate the effect of varying sun exposure. Corresponding maternal vitamin D status at different gestations during pregnancy was unknown. This would have allowed for a more expansive definition of the relationship between maternal vitamin D status and perinatal outcomes. Finally, as a retrospective study, we were limited by available data and the amount of cord blood available for further testing.

CONCLUSION

Black obese mothers on Medicaid without prenatal vitamin use were at the highest risk of delivering neonates with vitamin D deficiency. Furthermore, black race and vitamin D deficiency were associated with an increased risk of SGA. We identified additive and modifiable maternal risk factors that would benefit most from risk reduction and targeted vitamin D supplementation. A greater understanding of the variables that influence vitamin D status during pregnancy can have an immense public health impact in the reduction of adverse perinatal outcomes such as SGA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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