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Maternal-Cord Blood Vitamin D Correlations Vary by Maternal Levels

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Vitamin D levels of pregnant women and their neonates tend to be related; however, it is unknown whether there are any subgroups in which they are not related. 25-Hydroxyvitamin D [25(OH)D] was measured in prenatal maternal and child cord blood samples of participants (n = 241 pairs) in a birth cohort. Spearman correlations were examined within subgroups defined by prenatal and delivery factors. Cord blood as a percentage of prenatal 25(OH)D level was calculated and characteristics compared between those who did and did not have ≥25% and ≥50% of the maternal level and those who did and did not have a detectable 25(OH)D level. The correlation among Black children was lower than in White children. When the maternal 25(OH)D level was <15 ng/mL, the overall correlation was \( r = 0.16 \). Most children had a 25(OH)D cord blood level less than half of their mother’s; 15.4% had a level that was <25% of their mother’s. Winter birth and maternal level were associated with the level being less than 25%. Children with undetectable levels were more likely to be Black and less likely to be firstborn. These data suggest mothers may reduce their contribution to the fetus’s 25(OH)D supply once their own level becomes low.

1. Introduction

Vitamin D is important for its many health benefits for adults and children. The best evidence for the role of vitamin D in health is related to its importance to bone health [1, 2]. Vitamin D may also be related to other health conditions. For example, early life supplementation in children has been associated with decreased risks of type 1 diabetes and influenza [3, 4]. Despite its positive role in health, vitamin D deficiency is a pandemic [5].

Given the important role of vitamin D in health, there has been much discussion about the best ways to prevent and treat vitamin D deficiency [3, 6]. Prevention in children is a priority as it may relate to skeletal and immune development. Previous research has demonstrated that the vitamin D levels of women and their neonates are highly related [7–11]. The goal of this work was to examine whether there are any particular subgroups in which the mother’s prenatal 25-hydroxyvitamin D [25(OH)D] level and her child’s cord blood level of 25(OH)D are not strongly related. These analyses could identify pregnant women who need a prenatal vitamin D intervention tailored to them based on the various characteristics, as well as identifying children who may have a lower level of 25(OH)D at birth and may be prioritized for vitamin D screening.

2. Methods

2.1. Study Population. The birth cohort studied here is part of an NIH and institutionally funded cohort study that enrolled pregnant women receiving care at obstetrics clinics in a health system in the Detroit, Michigan, USA, area for longitudinal study of their children through early childhood with the goal of examining early life exposures related to childhood allergies and asthma. These children and their mothers served as the source population for the analyses. Details of cohort creation have been published [12–14]. Briefly, women were enrolled in their 3rd trimester at which time they provided a blood sample and completed an interview about their health. The child’s cord blood was collected at delivery. Only
2.2. Vitamin D. 25(OH)D, representing the sum of 25(OH)D$_{2}$ (ergocalciferol which is diet related) and 25(OH)D$_{3}$ (cholecalciferol which is sun related), was measured in frozen plasma samples (−80°C) in the laboratory of Dr. Neil Binkley at the University of Wisconsin. An HPLC method was used and has been used in previously published research [15–22]. 25(OH)D is expressed in ng/mL. 25(OH)D was measured in the stored samples from pregnancy (3rd trimester) and delivery (cord blood). For those with 25(OH)D levels below the lowest detectable limit of 5 ng/mL, a value of 2.5 ng/mL was assigned. This assignment is a common practice with lab values in research as it allows results to be retained in analyses of continuous measures rather than being removed from analyses due to lack of an actual value.

For the analyses, we examined whether maternal-child correlations in subgroups would vary between those in which maternal 25(OH)D was and was not low. We chose the a priori cutpoints of 20 ng/mL and 15 ng/mL. While 20 ng/mL defines deficiency [3], we knew that many of the mothers in the analyses had even lower levels of 25(OH)D. Thus, we also chose to examine the cutpoint of 15 ng/mL. Although limited by sample size, we also examined the associations when maternal levels were less than 40 ng/mL versus levels at least 40 ng/mL ($n = 218$ and $n = 23$, resp.) as it has previously been shown that 40 ng/mL is the level at which 25(OH)D conversion to 1,25-dihydroxyvitamin D$_{3}$ [1,25(OH)$_{2}$D$_{3}$] is maximized [23].

3. Results

There were 241 maternal-child pairs who contributed samples to the analyses. Maternal average age was 30.3 (SD = 5.4) years and most of the children were Black ($n = 175, 72.6\%$) and were not born in the winter (81.7%). Almost half the women were obese (46.4%, BMI > 30 kg/m$^2$), about a third of the pregnancies were by c-section (36.5%) and most of the children were not firstborn (81.3%).

Descriptive information about the overall prenatal and cord blood levels of 25(OH)D is provided in Table 1. The mean cord blood 25(OH)D level (10.9 ng/mL) is nearly half of the mean maternal prenatal level (23.6 ng/mL). White children and their mothers tended to have higher 25(OH)D levels compared to Black children and their mothers (Tables 1 and 2). Lower prenatal and cord blood levels were found in those who were not firstborn, those mothers with low 25(OH)D levels (<40 ng/mL, <20 ng/mL, and <15 ng/mL), and those who were obese (>30 kg/m$^2$ and ≥35 kg/m$^2$). Lower prenatal levels were found among mothers who had a low birthweight infant. No statistically significant differences were found between those who were and were not born in the winter and were of preterm or low birthweight, or by delivery mode or by maternal atopic status.

Spearman correlations between the prenatal-cord blood levels are presented in Table 3. The prenatal and cord blood levels were highly correlated, overall ($r = 0.75$) and for most subgroups including those defined by winter birth, firstborn status, maternal BMI, preterm birth, low birth weight status, delivery type, and maternal atopic status. The correlation among Black children was less than that of the White children, although both correlations were quite strong ($r = 0.65$ and 0.87, resp.). However, there was a notable exception. When maternal levels of 25(OH)D were low,
the correlation with the cord blood was weak. For example, when the maternal level was less than 15 ng/mL, the correlation was only 0.16. The correlation was stronger, albeit not as strong as the overall, when the maternal prenatal level was less than 20 ng/mL ($r = 0.29$).

Most of the children had a 25(OH)D cord blood level that was 50% or less of their mother’s prenatal level ($n = 149, 61.8\%$) and 37 children (15.4\%) had a level that was less than 25\% of their mother’s level. No factors were associated with the level being less than 50\% (data not shown); however, there were two factors associated with the level being less than 25\%: winter birth and maternal prenatal level. Those children with the percentage less than 25\% were more likely to be born in the winter months (29.7\% versus 16.2\%, $p = 0.05$) and have a lower prenatal maternal level (mean maternal prenatal level = 18.9 ng/mL versus 24.5 ng/mL, $p = 0.003$).

We also examined the characteristics of those children whose 25(OH)D levels were above and below the lowest detectable limit (Table 4). Children who had levels below the detectable limit were more likely to be Black and less likely to...
be firstborn or have an atopic mother. The mean prenatal level tended to be higher for those who had a detectable 25(OH)D level.

### 4. Discussion

In these analyses of this birth cohort, the correlation between maternal prenatal and cord blood 25(OH)D is quite strong overall. However, the maternal-child correlation is much weaker when the maternal level is low. White maternal-child pairs had higher correlations than the Black maternal-child pairs and Black children had lower percentages of their maternal prenatal 25(OH)D levels. These results are likely due to the generally lower level of 25(OH)D among Black women and suggest that mothers may insufficiently contribute to the child’s 25(OH)D supply once their own level falls too low (lower threshold). The data also demonstrate that it is inappropriate to use a prenatal 25(OH)D level to represent the 25(OH)D in a child’s early life.

Furthermore, these data suggest that children who are not firstborn will have a lower percentage of their maternal level. This could be attributed to the fact that maternal prenatal 25(OH)D levels were higher in women carrying their firstborn child. This could also reflect that (1) maternal stores may be depleted from prior births and have not recovered and (2) prenatal supplementation in parous women may not be sufficient to eliminate low 25(OH)D levels. In a study of 92 pregnant women in Saudi Arabia, women with two or more previous births were significantly more likely to have lower 25(OH)D₃ levels compared with those with one previous birth ($p < 0.05$) [28]. The authors also reported a significant correlation between maternal serum and neonatal 25(OH)D₃ ($r = 0.89$, $p = 0.01$).

Our results complement and, by adding extensive subgroup analyses, add an additional important dimension to previously published analyses of examinations of prenatal-cord correlations and factors predicting cord blood 25(OH)D levels [7, 29]. Nicolaidou et al. reported that neonatal vitamin D had a positive correlation with maternal vitamin D levels ($r = 0.69$, $p < 0.001$) in those mothers with normal vitamin D levels but not in those with hypovitaminosis ($n = 123$ maternal-child pairs) [29]. Godang found a strong positive association between maternal 25(OH)D and cord 25(OH)D ($\beta = 0.42$, $p < 0.001$) in a subset of 202 Scandinavian women but did not examine the association in subgroups [30]. Bodnar et al. examined whether prepregnancy obesity predicted poor vitamin D status in neonates in their study of 400 women in Pittsburgh, Pennsylvania [7]. Prenatal (4–22 weeks) levels of 25(OH)D were lower for women who were obese before pregnancy compared to women who were lean even after adjusting for season and other factors. This difference likely led to the result in which women who were obese before pregnancy were more likely to have delivered a child with vitamin D deficiency compared to women who had a normal BMI (odds ratio = OR = 2.1, 95% confidence interval = CI 1.2, 3.6). While we did not see differences by antenatal BMI, the work of Bodnar et al. also highlights the importance of examining subgroups.

A limitation of our study is that maternal prenatal 25(OH)D, while measured in the 3rd trimester, was not measured at the same time in the 3rd trimester for all women. We did not have maternal prepregnancy weights and relied on the weight measured at the time of the first prenatal care visit; however, Holland et al. suggest similar BMI categorization based on first measured pregnancy weight and self-reported prepregnancy weight [31]. Furthermore, there may be maternal characteristics that were not collected for these analyses that may identify other subgroups with variable prenatal-cord correlations.

Our goal was to examine whether the maternal-child 25(OH)D correlation varied within subgroups rather than to examine predictors of a child’s cord blood 25(OH)D level as previous studies have already highlighted the importance of the maternal level [8, 9, 11, 30]. The results from this birth cohort suggest that a child’s 25(OH)D level is only a fraction of their mother’s prenatal level. Furthermore, the degree to which the newborn’s level is associated with their mother’s prenatal level varies by several interrelated factors.

### Table 3: Spearman correlations between prenatal 25(OH)D and cord blood 25(OH)D.

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby is Black</td>
<td>0.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby is White</td>
<td>0.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby is firstborn</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby is not firstborn</td>
<td>0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Winter birth</td>
<td>0.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nonwinter birth</td>
<td>0.74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D &lt; 40 ng/mL</td>
<td>0.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D ≥ 40 ng/mL</td>
<td>0.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D &lt; 20 ng/mL</td>
<td>0.29</td>
<td>0.004</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D ≥ 20 ng/mL</td>
<td>0.73</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D &lt; 15 ng/mL</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Maternal prenatal 25(OH)D ≥ 15 ng/mL</td>
<td>0.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal BMI at 1st prenatal visit &lt; 30 kg/m²</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal BMI at 1st prenatal visit ≥ 30 kg/m²</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal BMI at 1st prenatal visit &lt; 35 kg/m²</td>
<td>0.79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal BMI at 1st prenatal visit ≥ 35 kg/m²</td>
<td>0.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 weeks)</td>
<td>0.54</td>
<td>0.015</td>
</tr>
<tr>
<td>Full term birth (≥37 weeks)</td>
<td>0.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low birth weight (≤2500 g)</td>
<td>0.43</td>
<td>0.08</td>
</tr>
<tr>
<td>Not low birth weight (&gt;2500 g)</td>
<td>0.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby born vaginally</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baby born via c-section</td>
<td>0.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mother is atopic</td>
<td>0.73</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mother is not atopic</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
including maternal race, birth order, and the actual maternal level. Not only do these studies indicate that use of the prenatal level of 25(OH)D to represent the child’s early life vitamin D level is not specific, but also the data suggest that a maternal threshold exists below which the mother limits her contribution of 25(OH)D to the fetus. The designs and analytical plans of future studies of prenatal dietary interventions should consider the possibility of a threshold effect when considering the maternal contribution to the fetus. Furthermore, children who are Black and not firstborn and those born to women with very low 25(OH)D may identify a priority group for vitamin D deficiency screening.

5. Conclusions

The degree to which a newborn’s vitamin D [25(OH)D] level is associated with their mother’s prenatal level varies by several interrelated factors including maternal race, birth order, and the actual maternal level. A maternal threshold may exist below which the mother limits her contribution of 25(OH)D to the fetus; low thresholds should be assessed for other prenatal nutrients. The designs and analytical plans of future studies of prenatal dietary interventions should consider the possibility of a threshold effect when considering the maternal contribution to the fetus. Children who are not firstborn, those who are Black, and those born to women with very low 25(OH)D may identify a priority group for vitamin D deficiency screening.

Conflict of Interests

The authors report no conflict of interests.

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