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Severe Vitamin D Deficiency in HIV-infected Pregnant Women is Associated with Preterm Birth

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Abstract

Background—Low maternal vitamin D has been associated with preterm birth (PTB). HIV-infected pregnant women are at risk for PTB, but data on maternal vitamin D and PTB in this population is scarce.

Methods—In a cohort of Latin American HIV-infected pregnant women from the NICHD International Site Development Initiative (NISDI) protocol, we examined the association between maternal vitamin D status and PTB. Vitamin D status was defined as the following 25-hydroxyvitamin D levels: severe deficiency (<10 ng/mL), deficiency (10–20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (≥30 ng/mL). PTB was defined as delivery at <37 weeks gestational age (GA). Logistic regression was used to assess the association between maternal vitamin D status and PTB.

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Results—Of 715 HIV-infected pregnant women, 13 (1.8%) were severely vitamin D deficient, 224 (31.3%) deficient, and 233 (32.6%) insufficient. Overall, 23.2% (166/715) of pregnancies resulted in PTB [median GA of PTBs =36 wks (interquartile range: 34-36)]. In multivariate analysis, severe vitamin D deficiency was associated with PTB [Odds Ratio=4.7, 95% Confidence Interval: 1.3-16.8)].

Conclusion—Severe maternal vitamin D deficiency is associated with PTB in HIV-infected Latin American pregnant women. Further studies are warranted to determine if vitamin D supplementation in HIV-infected women may impact PTB.

Keywords

Vitamin D; Preterm Birth; HIV; Pregnant women; Pregnancy

INTRODUCTION

Vitamin D status during pregnancy has been linked to maternal and pregnancy outcomes.¹ Preterm birth (PTB) is a pregnancy outcome associated with significant morbidity and mortality worldwide and is the leading cause of neonatal and childhood mortality in those under the age of 5 years.² Low maternal vitamin D status has been demonstrated in observational and clinical trials to be consistently associated with PTB.³⁻¹⁰ HIV-infected pregnant women, particularly those receiving antiretroviral therapy (ART), are at increased risk of PTB,^{11,12} but data regarding maternal vitamin D and PTB in women with HIV infection is scarce.¹³ Because of this increased risk of PTB in HIV-infected women on ART, potential associations involving vitamin D pathways would be important to elucidate as vitamin D supplementation could have increased impact on a population already at increased risk for PTB. The goal of this paper was to investigate the association between maternal vitamin D status and PTB in a large prospective cohort of HIV-infected pregnant women in Latin America and the Caribbean.

MATERIALS AND METHODS

Study Population

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) enrolled a prospective cohort of HIV-infected pregnant woman/infant dyads into the NICHD International Site Development Initiative (NISDI) Perinatal and Longitudinal Study in Latin American Countries (LILAC) protocols in Latin America and the Caribbean from 2002-2009.¹⁴ Seventeen sites across Argentina, the Bahamas, Brazil, Mexico, Peru, and Jamaica participated. The Perinatal protocol enrolled HIV-infected pregnant women 8 weeks gestational age (GA), while the LILAC protocol enrolled those 22 weeks GA. Study visits were conducted antepartum (up to 2 visits), at delivery, and until 6 months (Perinatal protocol) or 2 years (LILAC protocol) postpartum. Data including medical histories, physical examinations, and laboratory assessments (hematology, flow cytometry assays, HIV RNA levels, and biochemistries) were collected during maternal study visits. Plasma specimens were collected from maternal and pediatric participants and stored in a central repository at -80°C for potential future studies. Informed consent was obtained for all

enrolled participants. The study was approved by the NICHD Institutional Review Board (IRB), the Westat IRB, and in-country ethics committees and national review boards (where appropriate).

We restricted our study population to HIV-infected pregnant women enrolled for the first time (subsequent pregnancies were not included) in the NISDI Perinatal and/or LILAC protocols with available antepartum blood specimens collected between 12-34 weeks GA. In addition, only women whose pregnancies resulted in HIV-uninfected singleton live births were included.

Primary Outcome

The primary outcome was PTB, defined as delivery occurring at <37 weeks GA. These included both spontaneous and non-spontaneous PTBs. Infant GA at delivery was measured using obstetrical estimation by last menstrual period with or without ultrasound confirmation or by newborn examination.¹⁵⁻¹⁸

Primary Exposure of Interest

Maternal plasma 25-hydroxyvitamin D (25OHD) levels were measured on repository blood specimens using the Abbott Architect® chemiluminescent microparticle immunoassay on the ARCHITECT i2000SR analyzer, according to manufacturer's instructions, at ARUP Laboratories (Salt Lake City, UT).¹⁹ Methods and results of these 25OHD assays have been previously reported.²⁰ Maternal vitamin D status was defined as: severe deficiency (<10 ng/mL), deficiency (10-20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (≥ 30 ng/mL).²¹

Measurements

Data regarding other potential confounders were collected including maternal age, socio-demographics, anthropometrics, previous PTB, pre-eclampsia/eclampsia, CD4 cell count, HIV RNA level, substance use during pregnancy, and cART use during pregnancy. Maternal body mass index (BMI) adjusted for GA at the time of enrollment was calculated.²² CD4 cell count and HIV RNA levels were measured at the time of enrollment, and cART use during pregnancy was defined as the regimen lasting ≥ 28 days. Infant variables such as very low birth weight (VLBW) was defined as <1500 g, low birth weight (LBW) as 1500-2499 g, and small-for-gestational age (SGA) as per INTERGROWTH standards.²³

Statistical Analysis

Characteristics at enrollment were compared between severely deficient, deficient, insufficient, and sufficient vitamin D status using Kruskal-Wallis, chi-square, or Fisher's exact tests as appropriate. Variables at least marginally associated with PTB ($p \leq 0.10$) were considered candidates for multivariable analysis. Logistic regression modeling was used to assess the association between maternal vitamin D status and PTB while adjusting for confounders. Statistical analyses were performed using SAS® 9.3 (SAS Institute, Cary, NC.)

RESULTS

Among the 715 HIV-infected pregnant women included in this analysis, vitamin D status was severely deficient in 13 (1.8%), deficient in 224 (31.3%), insufficient in 233 (32.6%), and sufficient in 245 (34.2%). (Table 1) Severely vitamin D deficient women tended to have higher rates of vitamin D specimens collected during winter months compared to deficient, insufficient, or sufficient women (38.5% vs. 33.0%, 17.6%, and 6.5% respectively, $p<0.01$). Severely deficient women had lower rates of no cART use for 28 days during pregnancy compared to deficient, insufficient, and sufficient women (15.4% vs. 55.4%, 49.4%, and 39.2% respectively, $p<0.01$) and higher rates of non-nucleoside reverse transcriptase inhibitor use (46.2% vs. 17.4%, 17.6%, and 16.7% respectively, $p<0.01$). Maternal age, GA-adjusted BMI at enrollment, substance use during pregnancy, GA at vitamin D assessment, CD4 cell count and HIV RNA level at enrollment, rates of pre-eclampsia/eclampsia, and rates of previous PTB did not differ significantly by groups. In addition, rates of VLBW, LBW, and SGA amongst infants did not differ by maternal vitamin D status.

Overall, 23.2% (166/715) of pregnancies resulted in PTB [median GA of PTBs=36 wks (Interquartile Range: 34-36)]. After adjusting for age, substance use in pregnancy, CD4 count, HIV RNA level, body mass index (BMI), ARV use in pregnancy, pre-eclampsia/eclampsia, and prior PTB, severe vitamin D deficiency was associated with PTB [adjusted Odds Ratio (aOR)=4.7, 95% Confidence Interval (CI): 1.3-16.8]. (Table 2) In stratified analyses, these results remained the same amongst women with vitamin D testing at 22 wks GA (aOR=2.7, 95%CI: 1.1-6.7) and those with vitamin D testing at >22 wks GA (aOR=7.0, 95%CI: 1.6-30.9) (results not shown). In addition, pre-eclampsia/eclampsia (aOR=5.8, 95%CI: 2.3-14.7), underweight maternal BMI (GA-adjusted BMI <19.8 kg/m²) (aOR=1.8, 95%CI: 1.1-3.0), and prior PTB (aOR=2.7, 95%CI: 1.6-4.6) were also associated with PTB.

DISCUSSION

In this large cohort of Latin American HIV-infected pregnant women, we found severe maternal vitamin D deficiency to be associated with PTB. Only one other study has been published to date assessing the association between maternal vitamin D and PTB in HIV-infected women.¹³ This study of 884 HIV-infected Tanzanian pregnant women reported no association. However, maternal vitamin D status was evaluated as a dichotomous variable, where adequate status was defined at a threshold of 32 ng/mL, and none of the women received antenatal ARVs.

Several studies amongst non HIV-infected pregnant women have evaluated associations between low maternal vitamin D status and PTB^{3-10,24,25} with the majority reporting an inverse association between maternal vitamin D levels and PTB.³⁻¹⁰ A joint analysis of two maternal vitamin D supplementation trials in the U.S. revealed a lower risk of PTB in women with vitamin D levels >40 ng/mL compared to those with levels <20 ng/mL [adjusted relative risk (aRR)=0.41, 95% CI: 0.20,0.86].⁷ Another large U.S. case-control study demonstrated increased risk of PTB at maternal vitamin D levels < 50 nmol/L (< 20 ng/mL) and between 50-74.9 nmol/L (20 ng/mL – 30 ng/mL) where increasing risk occurred

at lower vitamin D levels.³ In a large Chinese study of 821 mother-infant pairs mean maternal vitamin D levels differed between those with very PTB (<32 weeks GA) and mild PTB (32-36 weeks GA) ($p=0.01$) as well as between very PTB and term birth ($p=0.001$).¹⁰ A Spanish cohort reported increased risk of PTB with maternal vitamin D levels <20 ng/mL (aOR=3.31, 95% CI: 1.52, 7.19).⁶ Lastly, the results of a meta-analysis demonstrated an overall increased risk of PTB with maternal vitamin D levels <50 nmol/L (<20 ng/mL) (aOR=1.58, 95% CI: 1.08, 2.31).⁹

The fact that we found evidence for increased PTB risk at the most severe levels of vitamin D deficiency and not at all levels of vitamin D deficiency or insufficiency is consistent with other studies.^{3,7,9} Post hoc analyses of the two U.S. randomized clinical trials mentioned above showed that the positive association between maternal vitamin D levels and GA at birth was strongest at levels <20 ng/mL and no association between maternal vitamin D levels of 20-39 ng/mL and PTB were found.⁷ In addition, a large meta-analysis reported associations between low maternal vitamin D levels and PTB when the exposure of interest was dichotomized at 50 nmol/L (20 ng/mL) but not at 75 nmol/L (30 ng/mL).⁹ This demonstrates that there may be a clinically significant and detectable effect of maternal vitamin D status only at the most severe level of deficiency. Of note, when we combined severely deficient and deficient vitamin D HIV-infected women into the same exposure group, we did not see an effect on PTB. (Data not shown).

The mechanisms by which vitamin D may play a role in PTB amongst HIV-infected women remain unclear. The etiology of PTB is likely multifactorial but emphasis has been placed on the role of inflammatory processes.²⁶ Vitamin D and its active metabolite, 1,25 dihydroxyvitamin D (1,25OH₂D), have been reported to have immunomodulatory and anti-inflammatory effects,²⁷⁻²⁹ raising the notion that vitamin D may help mitigate PTB by regulating inflammation. Of note, there was a significantly higher proportion of women receiving non-nucleoside reverse transcriptase inhibitors (NNRTIs) among women with severe vitamin D deficiency, and though ART type was not associated with PTB in our analysis, a potential link between NNRTI use, low maternal vitamin D status, and PTB could be explored.

Our study was limited by the small number of women who had severe vitamin D deficiency and our inability to distinguish between spontaneous and non-spontaneous PTB. As a result, we may have over-estimated the effect of severe maternal vitamin D deficiency on spontaneous PTB. In addition, we could not assess for vitamin D supplementation which may have occurred during the pregnancy. Lastly, the range of GA at which antenatal vitamin D was assessed spanned all three trimesters with the majority occurring after 22 weeks GA, making it difficult to pinpoint a particular time at which maternal vitamin D status is most strongly associated with PTB. However, vitamin D measurements taken closer to delivery have been shown to correlate more strongly with PTB.⁸ In addition, our results were similar even in analyses stratified by GA at the time of vitamin D testing.

PTB results in both significant mortality and morbidity as well as economic burden, particularly for resource-constrained settings.³⁰ These effects may be even more pronounced in HIV-exposed infants given their increased risk for poor growth^{31,32} and

infections³³. Severe maternal vitamin D deficiency appears to be associated with PTB in HIV-infected Latin American pregnant women. As vitamin D is a safe and inexpensive supplement, future studies are warranted to understand mechanisms by which vitamin D may affect PTB, including the ones regulated by vitamin D receptor and its polymorphisms affecting functionality at the placenta-decidua interface³⁴ and the mechanisms by which other micronutrients interact with vitamin D to protect against preterm delivery.³⁵ This will support a future platform for the study of potential vitamin D supplementation interventions in HIV-infected pregnant women.

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Appendix 1

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Table 1

Characteristics of Women and Infants

Characteristics	Maternal Vitamin D Status					p value
	Severe deficiency (<10 ng/ml) (n = 13)	Deficiency (10-20 ng/ml) (n = 224)	Insufficiency (21-29 ng/ml) (n = 233)	Sufficiency (≥ 30 ng/ml) (n = 245)	Total (n = 715)	
<i>MATERNAL</i>						
Age, years						
<20	0 (0.0)	8 (3.6)	12 (5.2)	17 (6.9)	37 (5.2)	0.26
20-29	4 (30.8)	110 (49.1)	121 (51.9)	131 (53.5)	366 (51.2)	
>29	9 (69.2)	106 (47.3)	100 (42.9)	97 (39.6)	312 (43.6)	
Maternal BMI at enrollment, kg/m²						
Underweight (<19.8)	1 (8.3)	29 (13.2)	34 (15.1)	43 (17.9)	107 (15.4)	0.13
Normal (19.8-26.0)	5 (41.7)	129 (58.9)	135 (60.0)	155 (64.6)	424 (60.9)	
Overweight (26.1-28.9)	3 (25.0)	30 (13.7)	30 (13.3)	23 (9.6)	86 (12.4)	
Obese (≥ 29)	3 (25.0)	31 (14.2)	26 (11.6)	19 (7.9)	79 (11.4)	
Substance use in pregnancy	4 (30.8)	59 (26.3)	75 (32.2)	72 (29.4)	210 (29.4)	0.59
Season during vitamin D assessment						
Autumn	2 (15.4)	55 (24.6)	70 (30.0)	96 (39.2)	223 (31.2)	<0.01
Spring	5 (38.5)	70 (31.3)	70 (30.0)	45 (18.4)	190 (26.6)	
Summer	1 (7.7)	25 (11.2)	52 (22.3)	88 (35.9)	166 (23.2)	
Winter	5 (38.5)	74 (33.0)	41 (17.6)	16 (6.5)	136 (19.0)	
Gestational age at vitamin D assessment						
22 weeks	3 (23.1)	86 (38.4)	75 (32.2)	73 (29.8)	237 (33.1)	0.21
>22 weeks	10 (76.9)	138 (61.6)	158 (67.8)	172 (70.2)	478 (66.9)	
CD4 count, cells/mm³ at enrollment						
<200	1 (7.7)	34 (15.2)	32 (13.8)	45 (18.4)	112 (15.7)	0.17
200-499	7 (53.8)	123 (54.9)	113 (48.7)	136 (55.7)	379 (53.2)	
≥ 500	5 (38.5)	67 (29.9)	87 (37.5)	63 (25.8)	222 (31.1)	
HIV RNA level, copies/mL at enrollment						
<1,000	10 (76.9)	108 (48.4)	140 (60.3)	135 (55.6)	393 (55.3)	0.07
1,000-9,999	0 (0.0)	53 (23.8)	41 (17.7)	55 (22.6)	149 (21.0)	
≥ 10,000	3 (23.1)	62 (27.8)	51 (22.0)	53 (21.8)	169 (23.8)	
cART regimen 28 days during pregnancy						
2NRTIs or 1NRTI	1 (7.7)	9 (4.0)	16 (6.9)	15 (6.1)	41 (5.7)	<0.01
2NRTIs+1NNRTI	6 (46.2)	39 (17.4)	41 (17.6)	41 (16.7)	127 (17.8)	
2NRTIs+1PI	4 (30.8)	48 (21.4)	55 (23.6)	88 (35.9)	195 (27.3)	
No ARV ≥ 28 days	2 (15.4)	124 (55.4)	115 (49.4)	96 (39.2)	337 (47.1)	
Other	0 (0.0)	4 (1.8)	6 (2.6)	5 (2.0)	15 (2.1)	

Characteristics	Maternal Vitamin D Status					<i>p</i> value
	Severe deficiency (<10 ng/ml) (n = 13)	Deficiency (10-20 ng/ml) (n = 224)	Insufficiency (21-29 ng/ml) (n = 233)	Sufficiency (≥ 30 ng/ml) (n = 245)	Total (n = 715)	
Pre-eclampsia/Eclampsia	2 (15.4)	8 (3.6)	5 (2.1)	7 (2.9)	22 (3.1)	0.12
Prior preterm birth	1 (7.7)	19 (8.5)	21 (9.0)	33 (13.5)	74 (10.3)	0.26
<i>INFANT</i>						
Preterm Birth	8 (61.5)	59 (26.3)	43 (18.5)	56 (22.9)	166 (23.2)	<0.01
Birth weight						
VLBW (<1500 g)	0 (0.0)	2 (0.9)	1 (0.4)	5 (2.0)	8 (1.1)	0.26
LBW (<1500 - 2499 g)	3 (23.1)	22 (9.8)	32 (13.7)	36 (14.7)	93 (13.0)	
Normal (≥ 2500 g)	10 (76.9)	200 (89.3)	200 (85.8)	204 (83.3)	614 (85.9)	
Small-for-gestational age	2 (15.4)	24 (10.7)	32 (13.7)	34 (13.9)	92 (12.9)	0.67

BMI=Body Mass Index; cART=combination antiretroviral therapy; LBW=Low Birth Weight; VLBW=Very Low Birth Weight

Table 2

Logistic Regression Results for the Relationship Between Maternal Vitamin D Status and Preterm Birth

Effect	Unadjusted OR	Unadjusted 95% CI	Adjusted OR ^	Adjusted 95% CI
Maternal Vitamin D Status				
Severe Deficiency (<10 ng/mL)	5.4	1.7 – 17.2	4.7	1.3 – 16.8
Deficiency (10-20 ng/mL)	1.2	0.8 – 1.8	1.3	0.8 – 2.1
Insufficiency (21-29 ng/mL)	0.8	0.5 – 1.2	0.8	0.5 – 1.3
Sufficiency (≥ 30 ng/mL)	Ref	---	Ref	---
Maternal Age, years				
<20	0.9	0.4 – 2.1	0.9	0.4 – 2.2
20-29	Ref	---	Ref	---
>29	1.1	0.8 – 1.5	1.0	0.7 – 1.5
Maternal BMI (GA-adjusted), kg/m²				
Underweight (<19.8)	1.7	1.0 – 2.7	1.8	1.1 – 3.0
Normal (19.8-26.0)	Ref	---	Ref	---
Overweight (26.1-28.9)	1.1	0.6 – 1.8	1.0	0.6 – 1.9
Obese (≥ 29)	1.3	0.7 – 2.2	1.0	0.6 – 1.9
Substance Use in Pregnancy	1.0	0.7 – 1.5	1.1	0.7 – 1.7
Pre-eclampsia/ Eclampsia	6.2	2.6 – 15.1	5.8	2.3 – 14.7
Prior Preterm Birth	2.5	1.5 – 4.2	2.7	1.6 – 4.6
CD4 cell count, * cells/mm³				
<200	0.9	0.5 – 1.6	0.9	0.5 – 1.7
200 – 499	1.1	0.7 – 1.6	0.9	0.6 – 1.5
≥ 500	Ref	---	Ref	---
HIV RNA level, * copies/mL				
<1,000	Ref	---	Ref	---
1,000 – 9,999	1.1	0.7 – 1.7	1.1	0.7 – 1.8
≥ 10,000	1.0	0.7 – 1.6	1.1	0.7 – 1.9
ARV Regimen *				
2 NRTIs (dual)/1 NRTI (mono)	1.5	0.7 – 3.1	1.5	0.7 – 3.4
2 NRTIs + 1 NNRTI	1.1	0.7 – 1.8	1.1	0.6 – 1.9
2 NRTIs + 1 PI	1.3	0.9 – 2.0	1.2	0.7 – 1.9
Other	0.6	0.1 – 2.6	0.6	0.1 – 3.0
No ARV	Ref	---	Ref	---

ARV=Antiretroviral; BMI=Body Mass Index; CI=Confidence Interval; GA=Gestational Age; NRTI=Nucleoside Reverse Transcriptase Inhibitor; NNRTI=Non-Nucleoside reverse Transcriptase; Inhibitor; OR= Odds Ratio; PI=Protease Inhibitor;

* At enrollment,

^ Model adjusted for all variables listed in the table.