Short Communication: High Prevalence of Vitamin D Deficiency in HIV-Infected and HIV-Uninfected Pregnant Women

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Abstract

Vitamin D deficiency is common in HIV-infected populations. In resource-limited settings, vitamin D deficiency has been shown to affect HIV disease progression and mortality in pregnant women, and also increases mother-to-child HIV transmission and mortality in their infants. This study sought to investigate vitamin D status in HIV-infected women compared to healthy controls in a high-income country setting and determine variables associated with vitamin D deficiency. We prospectively enrolled 40 women/infant pairs (16 HIV-infected women/HIV-exposed infant pairs and 24 uninfected/unexposed pairs). In serum cord blood, 25-hydroxyvitamin D [25(OH)D] concentrations were suboptimal (<30 ng/ml) in 100% of subjects from both groups. White race, non-Hispanic ethnicity was the only variable associated with higher serum 25(OH)D concentrations. This high prevalence of vitamin D deficiency, especially among HIV-infected women and their infants, deserves further investigation, as it may have a negative impact on maternal and infant health.

HIV-INFECTED INDIVIDUALS have a high prevalence of vitamin D deficiency, >90% in our recent studies, as determined by blood concentrations of 25-hydroxyvitamin D [25(OH)D].^{1–3} Low vitamin D status appears to negatively affect HIV progression and mortality in nonpregnant populations.⁴ Similarly, vitamin D deficiency has not only been shown to contribute to HIV disease progression and mortality in HIV-infected pregnant women in resource-limited settings, but also increases the overall risk of mother-to-child transmission (MTCT) by 46%.⁵ The HIV-infected children born from these HIV-infected women with vitamin D deficiency also have a 61% higher risk of death during follow-up.⁶ To date, no studies have evaluated vitamin D status in HIV-infected pregnant women in high-income countries. Thus, the main objective of this study was to determine vitamin D status in HIV-infected pregnant women in the United States and to investigate associations with vitamin D deficiency. A secondary objective was to compare results to a healthy pregnant control group.

This was a multicentered, cross-sectional study evaluating HIV-infected pregnant women and their HIV-exposed infants and healthy HIV-uninfected/HIV-unexposed maternal–

infant control pairs. HIV-infected pregnant women were recruited and enrolled prospectively when they arrived at labor and delivery for imminent delivery of their infants at one of three hospitals in northeastern Ohio: University Hospitals Case Medical Center, Cleveland, Ohio, MetroHealth Medical Center, Cleveland, Ohio, or Summa Health System, Akron, Ohio. Inclusion criteria for the HIV-infected women included documented HIV infection, ≥18 years of age, pregnancy >20 weeks gestation, and stable antiretroviral therapy (ART) for at least 4 weeks. Inclusion criteria for the controls included documented negative HIV test during pregnancy, ≥18 years of age, and pregnancy >20 weeks gestation. Exclusion criteria were the same for both groups and included any acute or chronic illness or a laboratory abnormality that would confound the data. The study was reviewed and approved by the institutional review boards from each site. All parents or legal guardians gave written informed consent to participate in the study.

Umbilical cord blood was obtained at delivery from all mothers. Plasma was extracted and frozen at –70°C without prior thawing until analysis. An extensive medical history collection and chart review were conducted in the mothers

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and infants from both groups. Detailed HIV history and ART history were also collected for the HIV-infected women. All infants underwent a physical examination. The HIV-exposed infants' laboratory results were followed until a definitive determination of HIV infection could be made based on current pediatric guidelines.⁷

Cord blood plasma concentrations of 25(OH)D were measured, as 25(OH)D concentrations are considered the best determinant of vitamin D status.⁸ Maternal serum 25(OH)D concentrations are correlated with cord blood and fetal blood concentrations.⁹ Thus, cord blood 25(OH)D concentrations are reflective of both maternal and infant 25(OH)D concentrations. Concentrations of 25(OH)D were measured by ELISA (IDS, LTD, Fountain Hills, AZ) as per the manufacturer's product manual and tested in duplicate. Median intraassay and interassay coefficients of variation were <12%. Quality control was ensured by participation in the vitamin D external quality assessment scheme (DEQAS, site 606). Laboratory personnel were blinded to clinical information. We adopted The Endocrine Society's and Institute of Medicine's (IOM) current guidelines defining vitamin D deficiency as serum 25(OH)D concentrations <20 ng/ml.¹⁰ We also further defined serum 25(OH)D concentrations ≥20–29 ng/ml as vitamin D insufficiency and serum 25(OH)D concentrations >29 ng/ml as optimal vitamin D status, as per The Endocrine Society guidelines.¹¹

Demographics, clinical characteristics, and laboratory parameters are described by study group, and HIV-related characteristics are described for HIV-infected subjects. Comparisons between HIV-infected and uninfected women and between HIV-exposed and unexposed infants were analyzed with non-parametric tests. Continuous variables were analyzed using the Wilcoxon rank-sum test, while comparisons of categorical variables were analyzed using Fisher's exact test. Continuous measures are described by medians and ranges, and nominal variables are described with frequencies and percents.

Plasma cord blood 25(OH)D concentrations were evaluated using both ordinal categories based on vitamin D status (i.e., deficient, insufficient, and sufficient) and by continuous measures. Wilcoxon rank-sum test was used on continuous measures of plasma 25(OH)D concentrations to compare *p* values between HIV-infected and uninfected groups' medians unadjusted and adjusted for time of year of delivery, maternal age, pre-pregnancy body mass index, race, and ethnicity. A multivariable linear regression model was constructed with variables chosen based on clinical significance to determine those associated with 25(OH)D concentrations. The level of significance for all analyses was set at 0.05. All analyses were performed using SAS, version 9.1 (SAS Institute, Carey, NC).

Sixteen HIV-infected women/HIV-exposed infant pairs and 24 healthy HIV-uninfected/HIV-unexposed maternal-infant control pairs were enrolled. Table 1 shows the characteristics of both groups. Groups were similar in age, race, and the time of year of delivery, but the HIV-infected women had a higher pre-pregnancy body mass index (BMI). All women were prescribed prenatal vitamins but the amount of vitamin D in each tablet and medication adherence were not documented. About half of the HIV-infected women subjects were ART-naïve prior to their pregnancies, but all were started on ART at some point during their pregnancies with all but two on a protease-inhibitor (PI)-based regimen with a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone. These other two women were on a triple NRTI regimen. The majority of subjects had HIV-1 RNA levels <1,000 copies/ml at the time of delivery. No women reported tobacco or alcohol use. One HIV-infected woman reported cocaine use. Infants born to HIV-infected women had a significantly lower gestational age compared to controls, but there was no difference between the number of Cesarean sections or infant birth weights. Subsequent HIV RNA/DNA results were negative in all HIV-exposed infants, excluding HIV infection.

TABLE 1. MATERNAL AND INFANT CHARACTERISTICS

Median (range) or no. (%)	HIV ⁺ N=16	Controls N=24
Maternal age, years	26 (19–40)	27 (20–38)
Maternal race/ethnicity		
Black, non-Hispanic	11 (69%)	15 (62%)
White, non-Hispanic	3 (19%)	8 (33%)
White, Hispanic	2 (12%)	1 (5%)
Maternal prepregnancy BMI, g/m ^{2a}	39.8 (29.4–53.5)	31.5 (20.0–46.6)
Delivery during high-sun month ^b	8 (50%)	19 (79%)
Gestational age of infant, weeks ^a	38 (35–40)	39 (36–40)
Delivery by Cesarean section	12 (75%)	12 (50%)
Infant weight, kg	3.1 (2.6–3.9)	3.3 (2.6–4.1)
Time since HIV diagnosis, years	2.0 (0.3–21.2)	—
CD4 count, cells/mm ³	483 (128–1716)	—
Nadir CD4 count, cells/mm ³	345 (1–814)	—
HIV-1 RNA <1,000 copies/ml	13 (81%)	—
ART-naïve prior to pregnancy	9 (56%)	—
Gestational NRTI use, months	5.5 (0–9)	—
Gestational PI use, months	4.5 (0–9)	—
Gestational NNRTI use, months	0 (0–0)	—

^a*p* < 0.05.^bDefined as April 1–September 30.

BMI, body mass index; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors.

TABLE 2. MULTIVARIABLE REGRESSION MODEL FOR PREDICTORS OF VITAMIN D STATUS

Variable ^a	β	SE (β)	P
Time of year of delivery ^b	-1.2	3.0	0.70
Maternal age	0.23	0.23	0.33
White, non-Hispanic	6.2	2.5	0.02
White, Hispanic	13.2	7.4	0.08
Prepregnancy BMI	0.02	0.16	0.91
Gestational age of infant	0.34	1.1	0.77
Study group ^c	-0.23	3.2	0.94
Adjusted R ²		0.13	

^aVariables were selected based on clinical significance.

^bApril 1–September 30 vs. October 1–March 30.

^cHIV-infected vs. healthy controls.

BMI, body mass index.

HIV-infected subjects had a median (range) plasma cord blood 25(OH)D concentration of 9 (7–27) ng/ml, whereas control subjects had a median (range) of 11 (8–26) ng/ml. There was no difference between unadjusted medians ($p=0.21$), or after adjusting for the time of the year of delivery, maternal age, BMI, and race and ethnicity ($p=0.85$). Seventy-five percent of the HIV-infected subjects had vitamin D deficiency (<20 ng/ml) and 25% were insufficient (20–29 ng/ml), respectively. Fifty-six percent of the HIV-infected subjects were in the severely deficient range (≤ 10 ng/ml). Similarly, in the control group, 67% of subjects were vitamin D deficient (<20 ng/ml) with 50% of these severely deficient (≤ 10 ng/ml). Thirty-three percent were vitamin D insufficient (20–29 ng/ml) with 13% at a level of 20 ng/ml. In the multivariable regression model, the only variable associated with vitamin D status was white, non-Hispanic group, where this race and ethnicity had higher 25(OH)D concentrations (Table 2).

In this study, we evaluated vitamin D status in cord blood from HIV-infected pregnant women compared to healthy controls and variables associated with vitamin D deficiency. Our study demonstrated a very high prevalence of vitamin D deficiency, including more than half of whom were severely deficient. All of the study subjects, both HIV-infected women and healthy controls, had suboptimal 25(OH)D concentrations. These data are consistent with vitamin D deficiency prevalence from recent National Health and Nutrition Examination Survey (NHANES) data¹² and from studies evaluating other nonpregnant HIV-infected populations.^{1–3} Another NHANES study demonstrated no overall statistical difference between rates of deficiency between pregnant and nonpregnant women.¹³ While the rates are higher in this study compared to some studies of pregnant women, they are consistent with others, depending on the population studied.¹⁴ For example, in the aforementioned NHANES study,¹³ rates of vitamin D deficiency among pregnant U.S. women were 33% <50 nmol/liter (~ 22.7 ng/ml) and 69% <75 nmol/liter (~ 34 ng/ml). These are lower than our current study, but their rates of non-Hispanic blacks were much lower than ours (16% vs. 69%), which likely accounts for the difference.

In this study, there was no discernible difference between groups, even after adjusting for common factors that affect vitamin D status in two statistical methods, similar to larger studies examining nonpregnant HIV-infected vs. uninfected women.¹⁵ The only factors of those examined that were as-

sociated with higher 25(OH)D concentrations were race and ethnicity, likely secondary to the associated degree of skin pigmentation. This is not surprising, and has been shown in other HIV populations,² because increased skin pigmentation decreases the production of vitamin D₃ in the skin.¹⁶ However, in this study, even white, non-Hispanic subjects had a high prevalence of vitamin D deficiency.

The degree of vitamin D deficiency observed in this study is concerning. While this study was not designed to evaluate the impact of 25(OH)D concentrations on maternal HIV progression, mortality, or MTCT, as has been previously shown in other HIV populations,^{4–6} this level of vitamin D deficiency may have a negative impact on maternal and infant health. Vitamin D is a steroid hormone that has long been known to play a critical role in the immune system, including effects on innate immunity, adaptive immunity, and levels of inflammatory cytokines.^{17–20} Many tissues throughout the body, including cells of the immune system, can respond to the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)₂D]. In fact, 1,25(OH)₂D binds to the vitamin D receptor in cells and enters the nucleus to bind to vitamin D response elements on DNA to regulate transcription of hundreds of genes. To date, >900 regulated genes have been identified.²¹ Vitamin D receptor expression is found in monocytes, stimulated macrophages, dendritic cells, natural killer cells, and T and B cells. Thus, vitamin D receptor activation elicits potent immunomodulatory effects.

More recently, studies have shown that vitamin D's effects on the immune system derive in part from its upregulation of the antimicrobial peptide cathelicidin, LL-37.^{22–25} In response to endogenously produced 1,25(OH)₂D, cells produce LL-37, which in turn inhibits bacteria through the disruption of the cellular membrane, but also has broad antimicrobial activity against gram-positive and gram-negative bacteria, as well as certain viruses and fungi. LL-37 also exerts chemotactic, immunomodulatory, and angiogenic effects, and affects serum levels of proinflammatory cytokines. Moreover, LL-37 has been shown to increase autophagy in macrophages to enhance innate immunity against viral infections,²³ and *in vitro* LL-37 inhibits HIV replication in peripheral blood mononuclear cells including in CD4⁺ T cells.^{24,25}

Thus, the high prevalence of vitamin D deficiency in this study establishes the fact that additional studies are needed to better evaluate its impact on maternal and infant health in HIV, including in high-resource settings. For example, in the general pregnant population, lower 25(OH)D concentrations are associated with an increased risk of gestational diabetes and increased risk of Type I diabetes in the offspring.^{26–28}

Insulin resistance and diabetes are very well-described disorders among HIV-infected individuals, including during pregnancy.^{29–35} Similarly, maternal vitamin D deficiency is associated with a number of complications in the infant, including abnormalities in fetal skeletal development, tooth enamel formation, and general fetal growth and development.^{36–41} Maternal vitamin D deficiency has also been shown to increase the risk of acute viral infections and respiratory syncytial virus (RSV) bronchiolitis in infants.^{42–44} It has even been suggested that maternal vitamin D deficiency may “imprint” infants, thereby increasing their subsequent risk of other diseases, including cancer.⁴⁵ While most infants born to HIV-infected mothers in the United States will not acquire HIV infection, *in utero* ART exposure may increase their

cancer risk later in life.⁴⁶ Thus, maternal and therefore infant vitamin D deficiency should not be disregarded.

There were limitations to this study. Foremost, there was a relatively small number of subjects, which limited our ability to adequately evaluate subtle differences between subject groups and variables associated with vitamin D deficiency. Furthermore, a large number of variables was included in the multivariable regression given the overall *N*; therefore, it must be interpreted with caution. Likewise, as a cross-sectional study, it was impossible to evaluate HIV progression in the HIV-infected women and/or subsequent complications in the HIV-exposed infants. Given the interventions to minimize the risk of MTCT, such as planned Cesarean sections, it is difficult to adequately compare infant groups. Finally, the amount of vitamin D in the prescribed prenatal vitamins and the regularity with which they were taken by subjects were not documented. However, in this exploratory study, these data show that vitamin D deficiency is very common in HIV-infected women and their infants, and, given the implications of vitamin D deficiency in other HIV-infected populations, may negatively affect the health of HIV-infected women and their infants. Further investigation, especially longitudinal studies, is needed to better understand the implications of vitamin D deficiency in HIV-infected pregnant women.

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