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Relationship of maternal vitamin D level with maternal and infant respiratory disease

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Abstract

Objective—Investigate the association of maternal vitamin D and maternal asthma and infant respiratory infection severity.

Study Design—Cross-sectional analyses of 340 mother-infant dyads enrolled September-May 2004-2008 during an infant viral respiratory infection. Maternal vitamin D levels were determined from enrollment blood specimens. At enrollment, we determined self-reported maternal asthma and infant respiratory infection severity using a bronchiolitis score. We assessed the association of maternal vitamin D levels and maternal asthma and infant bronchiolitis score in race-stratified multivariable regression models.

Results—The cohort was 70% White, 19% African-American, and 21% had asthma. Overall, the median maternal vitamin D level was 20 ng/ml (Interquartile range 14,28). Among White women, a 14 ng/ml increase in vitamin D was associated with decreased odds of asthma (AOR 0.54, 95% CI 0.33-0.86). Maternal vitamin D was not associated with infant bronchiolitis score.

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Conclusions—Higher maternal vitamin D levels were associated with decreased odds of asthma.

Keywords

asthma; infant viral respiratory infections; vitamin D

Introduction

Vitamin D plays an important role not only in bone health but more recently studies have found associations between vitamin D levels and lung function in adults, and with asthma severity and steroid responsiveness in individuals with asthma.¹⁻⁴ Vitamin D plays an important role in fetal immune system development, innate and adaptive immunity,⁵⁻¹⁰ and lung development¹¹⁻¹³; fetal vitamin D levels are dependent on maternal levels.¹⁴⁻¹⁶ Supporting a potential association of *in utero* vitamin D status and childhood respiratory disease, higher reported maternal vitamin D intake during pregnancy has been associated with decreased risk of wheezing in 3 and 5 year old children although no published studies to date have investigated the association of maternal vitamin D levels and infant respiratory infection.^{17;18} Therefore the impact that vitamin D insufficiency or deficiency in women may have on her health and through potential *in utero* effects on the health of her child are areas in need of further investigation. World-wide, vitamin D insufficiency is increasing and affects an estimated one billion individuals.¹⁹ Therefore the potential negative respiratory consequences could be clinically significant and vitamin D would potentially be a low-cost intervention for decreasing respiratory morbidity.

The Tennessee Children's Respiratory Initiative (TCRI) is a prospective cohort of mother-infant pairs enrolled during an infant viral respiratory infection. In this cross-sectional study of baseline data, our objectives were to investigate whether higher maternal vitamin D levels, determined at study entry during the infant's first year of life, were associated with decreased 1) prevalence of self-reported asthma in the women and 2) severity of infant lower respiratory tract illness.

Materials and Methods

Study design and setting

To examine the association of maternal 25-hydroxyvitamin D (25[OH]D) levels and self-reported asthma in young women and viral bronchiolitis severity in their infants, we conducted a cross-sectional study of 340 mother-infant dyads enrolled in the Tennessee Children's Respiratory Initiative (TCRI). The methods regarding establishment of the TCRI have been reported elsewhere.²⁰ In brief, the TCRI is a prospective study of 670 term, non-low birth weight infants (less than one year of age at study entry) enrolled with their biological mothers at the time of an infant acute viral respiratory infection. A convenience sample of mother-infant dyads were recruited in the inpatient, emergency department, and clinic settings during viral respiratory seasons September through May 2004-2008 at a single academic institution. The primary goals of TCRI are to investigate the association of viral respiratory infection during infancy, maternal atopy, and development of early childhood asthma and atopy. This analysis includes the subset of women from whom a blood sample was obtained at study entry (N=340) and their infants. The study was approved by the Vanderbilt University Institutional Review Board. Women provided informed consent for herself and her infant.

At enrollment trained research nurses administered an in-person structured questionnaire during the acute infant visit. The questionnaire included questions regarding demographics,

details of the acute illness, previous medical history of the mother and infant, infant feeding method, detailed family history of atopic diseases, maternal responses to the International Study of Asthma and Allergies in Children (ISAAC) questionnaire, and smoking exposure.²⁰

To ascertain the women's vitamin D status at study entry, we measured levels of 25(OH)D, the primary circulating form of the hormone, using whole blood specimens on blood spot cards. 25(OH)D levels were determined by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) performed by ZRT labs (Beaverton, OR).²¹

Self-reported maternal asthma status, “ever asthma”, was determined using the validated ISAAC questionnaire and defined as a positive response to the question have you ever had asthma, asked as part of the ISAAC questionnaire, and/or to the question were you diagnosed with asthma as a child. In addition, we determined if women who reported a history of asthma had prevalent symptoms by their response to the question “have you had wheezing or whistling in the chest in the past 12 months.”

Infant viral lower respiratory tract illness (LRTI) severity was determined using both the physician discharge diagnosis and post-discharge chart review. Infants were considered to have a viral lower respiratory tract illness if they had a physician diagnosis of bronchiolitis or wheezing or if on chart review the infant had signs and symptoms consistent with bronchiolitis or viral lower respiratory tract infection including grunting, nasal flaring and/or chest wall retractions and findings of diffuse wheezing, rales, or rhonchi²² and the absence of alternative diagnoses. LRTI severity was determined using the ordinal bronchiolitis score, which ranges from 0-12 with 12 being the most severe.²³ The bronchiolitis score includes respiratory rate, the presence and extent of flaring or retractions, room air oxygen saturation, and the presence and extent of wheezing.

We included variables that could confound the relationship between maternal 25(OH)D level and maternal asthma and/or infant bronchiolitis severity, including: self-reported maternal race/ethnicity, maternal age, maternal smoking, environmental tobacco smoke exposure, infant birth weight, infant sex, infant age at enrollment, infant feeding method, infant insurance status, year of enrollment (September/October-May 2004-2005 through September-May 2007-2008), season of enrollment (fall, winter, spring), and season of infant birth.

In this study's cross-sectional analyses, the variables of interest included maternal 25(OH)D level and its relationship to 1) maternal asthma prevalence and 2) severity of LRTI in her infant. Power and sample size determinations were conducted for the analyses of the original cohort and not this sub-study. In descriptive analyses, the demographics of the population were determined by maternal 25(OH)D level, which was categorized using the historical categorization as sufficient (>30 ng/ml), insufficient (20-30 ng/ml), or deficient (<20 ng/ml) based on levels important for bone health.^{4;19} Characteristics of mother-child dyads were compared by whether or not blood was available for vitamin D determination. In univariate analyses, chi-square tests were used for categorical variables and the Wilcoxon rank sum or the Kruskal-Wallis test were used as appropriate for continuous variables. Analyses were stratified by maternal race as race is a major determinate of 25(OH)D levels.²⁴ Median 25(OH)D levels were compared in women with and without a history of asthma and by whether women with asthma had prevalent symptoms. In analyses stratified by maternal race/ethnicity, we evaluated the association of maternal 25(OH)D levels and maternal asthma using multivariable logistic regression adjusting for factors including maternal age, cigarette smoking, infant insurance, and season of enrollment. To prevent overfitting of logistic regression models propensity score adjustment was also performed for maternal

25(OH)D levels. The propensity score analysis has gained increasing application because it properly adjusts for many confounding factors simultaneously while preserving analytical power by combining factors into one score.²⁵ For maternal 25(OH)D level outcomes, we used the proportional odds logistic regression model to derive the propensity score using the covariates outlined above for the multivariable logistic regression model. Restricted cubic splines were used to allow for non-linear adjustment between propensity score and outcome. Propensity score adjustment was used as a sensitivity analyses in the subset of white women and as the primary analysis in the subset of African-American women because of the small sample size.

We investigated the association between maternal 25(OH)D level and viral LRTI severity in the subset of the cohort with both maternal blood available for 25(OH)D level determination and an infant with a viral LRTI. In analyses stratified by maternal race, the univariate relationship of maternal 25(OH)D level and infant LRTI severity score were assessed using Spearman correlation coefficient (ρ). Multivariable analyses used proportional odds logistic regression for the outcome of respiratory illness severity. Among white women and their infants, multivariable regression analyses controlled for the following variables: maternal age, infant birth weight, infant age at enrollment, year (2004-2005 to 2007-2008) of enrollment, season of enrollment, season of birth, infant insurance, history of any breastfeeding, and other children in the home. Propensity score adjustment was used as a sensitivity analyses in the subset of white women and as the primary multivariable regression analysis in the subset of African-American women because of the small sample size.

Results

25(OH)D levels among enrolled women

In total, 340 of the 670 women in the TCRI cohort had a blood specimen obtained at study entry that was used to determine 25(OH)D. Compared to women who did not have a blood specimen available, in univariate analyses women with a blood specimen available for vitamin D determination were more likely to be enrolled during later study years ($p<0.001$), enrolled during the winter season (63% vs. 54%, $p=0.001$), older (median 26 years vs. 24, $p=0.011$), White (70% vs. 50%, $p<0.001$), to have a younger infant enrolled in the study (median age 11 weeks vs. 15, $p=0.032$), to have a child with a study diagnosis of bronchiolitis (74% vs. 61%, $p=0.001$), and less likely to have breastfed their infant (53% vs. 62%, $p=0.015$). The characteristics of the 340 women are listed in Table 1 for the entire group and by the women's vitamin D status (deficient, insufficient, or sufficient). For the combined group, the mean maternal age at enrollment was 25.8 years (± 5.3) and 31% of the women reported smoking cigarettes (Table 1). The women were White (70%), African-American (19%), Latina (9%), and other (2%) Table 1. Figure 1a demonstrates the distribution of maternal 25(OH)D levels for the women in the cohort. The median maternal vitamin D level was 20 ng/ml (Interquartile range [IQR] 14, 28), and 21% of the women had sufficient levels (>30 ng/ml), 32% insufficient (20-30 ng/ml), and 47% deficient (<20 ng/ml). As depicted in figure 1b, there were differences in median maternal 25(OH)D level by maternal race/ethnicity. Among white women, 29% were sufficient, 37% were insufficient, and 34% were deficient. The majority of African-American women were deficient (81%) or insufficient (8.6%). By maternal vitamin D sufficiency group, there were statistically significant differences in univariate analyses in infant age at enrollment, with women in the sufficient group having the youngest infants, and differences in type of infant insurance and median number of other children in home (Table 1).

Asthma prevalence in the women and relationship to vitamin D status

Overall, 21% of the women reported a history of ever having asthma. Twenty-one percent of white women in the cohort had a history of asthma compared to 28% of the African-American women. The prevalence of smoking in women with asthma was 38% compared to 29% in women without asthma ($p=0.192$). There were no statistically significant differences between women with and without asthma in regards to maternal age at enrollment, maternal educational level, or type of insurance for the child.

When comparing women with and without asthma, there was a statistically significant difference in median 25(OH)D level, 18 [IQR 11,25] and 21 [IQR 14,30], respectively $p=0.01$. Women with prevalent asthma (symptoms within the previous 12 months) had the lowest vitamin D levels (ng/ml) 16 [IQR 11,23] compared to women with asthma without prevalent symptoms 19 [10,22], and women without a history of asthma 21 [14,30], $p=0.018$. In analyses stratified by race (figure 2), an association between history of maternal asthma and lower 25(OH)D levels was seen in white (panel A) but not African-American women (panel B). In white women, a 14 ng/ml increase in maternal 25(OH)D level was associated with decreased odds of asthma (AOR 0.54, 95% CI 0.33-0.86) adjusted for individual characteristics, figure 2, panel C. Results from propensity score adjusted models were consistent. In the African-American women in the study, there was not a statistically significant association between 25(OH)D levels and asthma prevalence (figure 2 panel D).

Maternal vitamin D level and infant bronchiolitis severity

Of the 340 women for whom 25(OH)D levels were determined, 252 had an infant with a viral LRTI, and the other infants had URI or other respiratory illnesses and were not included in this analysis. In infants of white mothers ($N=187$), the median bronchiolitis score by maternal vitamin D level was 7 [IQR 6,8] for the sufficient group, 7 [IQR 4.6,9] for the insufficient group, and 8 [IQR 5,9.8] for the deficient group, $p=0.16$; the Spearman correlation coefficient was $\rho=-0.133$. In the proportional odds model, a 15 ng/ml increase in maternal 25(OH)D level was not associated with bronchiolitis severity (AOR 0.71, 95% CI 0.48-1.04). In propensity score adjusted sensitivity models, maternal 25(OH)D level was not associated with bronchiolitis severity (AOR 0.76, 95% CI 0.52-1.11).

There were 39 African-American women with an infant with a viral lower respiratory tract infection. Most women had deficient or insufficient levels so we examined the infant bronchiolitis score by tertile of maternal vitamin D level. Median bronchiolitis scores were 5, [IQR 3.5,6] (lowest tertile 5-9 ng/ml), 7, [IQR 5,8] (middle tertile 10-14), and 8 [IQR 7.5, 9] (highest tertile 15-41 ng/ml), $p=0.029$, the Spearman correlation coefficient $\rho=0.35$. In propensity score adjusted proportional odds model, there was not a statistically significant association found between maternal vitamin D level and infant bronchiolitis score (9.12 ng/ml increase in vitamin D associated with adjusted OR 3.02 95% CI 0.90-10.15).

COMMENT

Vitamin D is obtained from dietary sources and endogenous production in the skin through ultraviolet sunlight exposure has historically been the primary source. However, westernized countries have developed behaviors that have contributed to vitamin D insufficiency.¹⁹ Vitamin D is important in the development and functioning of the pulmonary and immune systems and therefore potentially important in illnesses such as asthma and pulmonary infections. Vitamin D levels have been associated with lung function and with airway hyper-reactivity in adults with asthma, although the association with asthma has not been consistent across studies.^{1;3;26} In addition, lower self-reported vitamin D intake during pregnancy has been associated with increased risk of wheezing in children at ages 3 or 5

years of age.¹⁷ This current work investigated the relationship of maternal vitamin D levels with maternal asthma and infant bronchiolitis, two illnesses associated with significant morbidity.

This study confirms a high prevalence of vitamin D insufficiency and deficiency in women of child bearing age.^{27;28} Women were enrolled September to April in the northern hemisphere, which includes seasons during which vitamin D levels are typically the lowest. Overall, 34% of white women and 81% of African-Americans were deficient.

In this cross-sectional analysis, among white women there was an inverse association between vitamin D level and asthma risk. A 14 ng/ml increase in maternal 25(OH)D level was associated with 46% decreased odds of asthma (AOR 0.54, 95% CI 0.33-0.86). An association between maternal 25(OH)D level and asthma in African-American women was not found. However, the majority of African-American women in the study were 25(OH)D deficient (81%) and the sample size of the African-American women was small. Therefore it is possible that an association between maternal vitamin D level and maternal asthma, similar to that seen in the sub-set of white women, would have been found in the sub-set of African-American women if the group had been larger and included a wider range of vitamin D levels.

Viral LRTIs, such as bronchiolitis, are a leading cause of infant mortality in developing countries and infant morbidity in the US.²⁹⁻³¹ In adjusted proportional odds models stratified by African-American and white maternal race we did not detect a statistically significant association between maternal 25(OH)D levels obtained at study entry and infant viral LRTI severity. Among infants of white women there was a non-significant decreased odds of LRTI severity with increased maternal vitamin D levels, although the magnitude of change of LRTI severity may not be clinically significant. Among African-American women there was a positive trend in the relationship of maternal 25(OH)D level and bronchiolitis score. However findings should be viewed with caution as the African-American sub-group was small with a narrow range of maternal 25(OH)D levels and the potential relevance of physiologic differences, particularly between tertiles 1 and 2 would be expected to be limited.

There are several limitations of this work. Maternal asthma was determined by self-report and not by objective criteria such as pulmonary function testing. However, self-reported asthma in young adults in whom there is little overlap with other diseases is specific.³² Maternal 25(OH)D level and self-reported maternal asthma were determined at the same time point, therefore no causal inferences regarding their association can be made. It is possible that individuals with asthma may develop behaviors that predisposes to vitamin D deficiency and have less sunlight exposure. In addition, glucocorticoid use, a treatment for asthma, has been associated with lower vitamin D levels.²⁴ There is seasonal variation in vitamin D levels and a one time assessment of vitamin D can not fully characterize a person's vitamin D status.³³ A recent Norwegian study found a modest correlation between serum 25(OH)D levels collected 14 years apart and over a 12 month period in a second study.³³ Women in the cohort with an available blood specimen for vitamin D determination were more likely to have an infant with higher respiratory virus severity than women without blood available. Whether results of this cohort of women with an infant with an acute lower respiratory illness are generalizable to other populations is not known. Longitudinal studies will help clarify the relationship between vitamin D status and asthma in women of child bearing age.

Ideally we would have determined maternal 25(OH)D levels during pregnancy to investigate the association of *in utero* vitamin D status and infant respiratory illness. Although we

adjusted for infant birth month and infant age at enrollment, the specimens used for 25(OH)D determination were taken in the year following the women's pregnancy and may not include prenatal vitamin supplement use during pregnancy. However, a recent description of 25(OH)D levels in women during pregnancy found that approximately 50% of women in the third trimester had insufficient vitamin D levels even though over 80% of the women reported taking prenatal vitamins.³⁴ Our sample size was small, particularly for infants of African-American and Latino mothers, therefore conclusions for those of non-white race are limited. Infant 25(OH)D levels at study entry were not available to assess their association with severity of the acute respiratory illness. Infant viral LRTI and asthma are strongly linked and children are being followed until age 6 years to determine asthma outcomes.²⁰ Importantly, vitamin D has potential as an affordable public health intervention to improve respiratory health. Future and current studies of maternal vitamin D levels during pregnancy will help further delineate the association between *in utero* vitamin D levels with susceptibility and severity of infant viral respiratory illness and subsequent childhood asthma.

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Figure 1.

In 340 women enrolled in the Tennessee Children's Respiratory Initiative, September-May 2004-2008, the distribution of maternal vitamin D levels (ng/ml) (A) and median [interquartile range] levels by self-reported maternal race (B).

Figure 2.

In 340 women enrolled in the Tennessee Children's Respiratory Initiative, September-May 2004-2008, median vitamin D level by asthma history in white (A) and African American (C) women. Probability, with 95% confidence intervals represented in gray, of asthma by vitamin D level in white (B) and African American (D) women.

Table 1

Infant and Maternal Characteristics by Maternal 25(OH) Vitamin D Level (ng/ml) among Dyads Enrolled in the Tennessee Children's Respiratory Initiative, 2004-08)

Characteristic	Deficient (<20) N=161	Insufficient (20-30) N=109	Sufficient (>30) N=70	All N=340
Median maternal age, years[IQR] *	25 [22,30]	27 [23,31]	28 [22,31]	26 [22,30]
Maternal race, n (%)				
White	80 (50)	89 (82)	68 (97)	237 (70)
African-American	57 (36)	7 (6)	1 (1)	65 (19)
Latino	20 (12)	9 (8)	0 (0)	29 (9)
Other	3 (2)	4 (4)	1 (1)	8 (2)
Maternal smoking, n (%)	52 (32)	33 (30)	21 (30)	106 (31)
Median maternal educational, [IQR] (N=317)	12 [11,13]	13 [12,16]	13 [12,16]	12 [12,15]
Maternal Asthma, n (%)	41 (25)	22 (20)	9 (13)	72 (21)
Median EGA[†], weeks [IQR] (N=337)	39 [38,40]	39 [38,40]	39 [38,40]	39 [38,40]
Median infant birth weight, grams [IQR] (N=339)	3289 [2948, 3629]	3402 [3118,3657]	3345 [3175, 3629]	3345 [3033, 3657]
Infant sex, n (%)				
Male	107 (66)	58 (53)	37 (53)	202 (59)
Median infant age, weeks [IQR][‡]	13 [7,29]	11 [6,26]	9 [5,15]	11 [6,25]
Any breastfeeding, n (%)	78 (49)	60 (55)	42 (60)	180 (53)
Infant insurance, n (%) **				
Private	32(20)	39 (36)	32 (46)	103 (30)
Medicaid	122 (76)	62 (57)	35 (50)	219 (64)
None	7 (4)	8 (7)	3 (4)	18 (5)
Day care attendance, n (%)	39 (24)	33 (30)	16 (23)	88 (26)
Other children in home, n [IQR][‡]	1 [1,2]	1 [0,2]	1 [0,2]	1 [1,2]
Secondhand smoke, n (%) (N=336)	90 (57)	61 (56)	43 (61)	194 (58)

* interquartile range

[†] estimated infant gestational age

[‡] p<0.05

** p<0.001