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ARTICLE

Vitamin D and associated perinatal–neonatal outcomes among extremely low-birth-weight infants

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Abstract

Objective To evaluate vitamin D inadequacy among extremely low-birth-weight (ELBW, <1000 g) infants and the association between circulating vitamin D concentrations and perinatal–neonatal outcomes.

Study design Prospective cohort study of ELBW infants in the neonatal ICU. Blood was collected within the first 3 days after birth after obtaining informed consent. Circulating 25-hydroxyvitamin D concentrations (25(OH)D) were quantified using liquid chromatography–tandem mass spectroscopy and classified as vitamin D deficient, insufficient, or adequate (< 20, 20–30, or > 30 ng/mL, respectively). Associations between 25(OH)D and perinatal–neonatal outcomes were determined by multivariable regression, adjusted for covariates that differ in the bivariate analysis.

Results Of the 60 ELBW infants enrolled, 13 (22%) were vitamin D deficient, 15 (25%) were insufficient, and 32 (53%) were adequate. 25(OH)D levels were positively associated with fetal growth restriction and prolonged rupture of the membranes.

Conclusions Vitamin D inadequacy was frequent among ELBW infants. Circulating vitamin D concentrations were significantly associated with perinatal outcomes in this contemporary cohort.

Introduction

Extremely low-birth-weight (ELBW, < 1000 g) infants are at increased risk of mortality and multiple morbidities [1]. They miss much or all of the third-trimester placental transfer of macro and micronutrients from the mother [2]. Vitamin D is one such nutrient frequently leading to vitamin D inadequacy [3]. It is unknown whether vitamin D inadequacy contributes to the mortality and morbidities in ELBW infants.

Vitamin D is a fat-soluble metabolite required for the homeostasis of many body systems as well as for normal human growth and development. Many developmental processes, including maturation of the immune system and lung development, are thought to be modulated by vitamin D [4]. Vitamin D inadequacy may have implications beyond infancy, as certain adult-onset diseases have their roots in nutritional insults sustained in early life [5, 6]. This is further supported by enhanced knowledge about vitamin D's role as a preprohormone and its effects on genomic imprinting [7]. Vitamin D is inexpensive and a treatment that is easy to administer. Vitamin D supplementation has been shown to increase 25-hydroxyvitamin D (25(OH)D) concentrations during pregnancy and impacts pregnancy outcomes, including pre-eclampsia, low birth weight, and preterm birth [8].

There is a paucity of data on vitamin D inadequacy in ELBW infants. Currently, there is not sufficient evidence

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showing whether vitamin D inadequacy has harmful effects in ELBW infants. Lack of evidence has resulted in varying practices in the evaluation and management among treating physicians. Hence, the objective of this study was to determine the frequency of vitamin D inadequacy among a recent cohort of ELBW infants and the association between circulating vitamin D concentrations and perinatal–neonatal outcomes in the ELBW infant cohort.

Methods

This prospective observational exploratory study was conducted at Women & Infants Hospital of Rhode Island (latitude 42° North) from December 2012 to March 2015 after approval from the local institutional review board. Inclusion criteria included all live-born ELBW infants admitted to the neonatal intensive care unit (NICU). Exclusion criteria were a decision made for comfort care only, major congenital anomalies, and genetic syndromes. Infants were enrolled after the written informed parental consent was obtained.

Circulating 25(OH)D concentrations were measured quantitatively on scavenged blood obtained within the first 72 h after birth. Blood was collected in tubes (Becton Dickinson Microtainer Systems, Franklin Lakes, NJ, USA) containing EDTA for plasma or plain tubes without anticoagulant for serum. The contents of the collection tubes without anticoagulant were allowed to clot at room temperature for 30 min. Serum and plasma were separated by centrifugation at 2000*g* for 10 min (refrigerated) and immediately transferred into a clean polypropylene tube. The samples were maintained between 2 and 8 °C while handling and frozen at −70 °C during storage. Serum samples were transported frozen to the laboratory of Dr. Michael Holick for measuring the circulating 25(OH)D concentrations by tandem mass spectrometry through a turbulent-low liquid chromatography system (Cohesive Technologies, Franklin, MA, USA) followed by traditional laminar flow chromatography (LC-MS/MS) [9]. Vitamin D status was stratified as deficient (<20 ng/mL), insufficient (20–30 ng/mL), or adequate (>30 ng/mL) as per the Endocrine Society guidelines [10]. The inadequate category included deficient and insufficient circulating concentrations of 25(OH)D. The staff members who performed these assays were blinded to the sample identity.

Data included maternal, intrapartum, infant, delivery room, and nutritional variables. Fetal growth restriction was defined as weight ≤ 10th percentile for gestational age per the fetal growth curves from Fenton and Kim [11] and prolonged rupture of membranes (PROM) if duration > 18 h. Perinatal outcomes included preterm labor, pre-eclampsia and intrauterine inflammation, infection, or both (triple I) [12]. Neonatal outcomes included sepsis (culture-positive), necrotizing enterocolitis (NEC, modified Bell's stage II or above treated medically or surgically) [13], bronchopulmonary dysplasia (BPD, receipt of supplemental oxygen or continuous positive airway pressure at 36 weeks' postmenstrual age), grade III or IV (severe) intracranial hemorrhage (ICH), and stage 3 or greater (severe) retinopathy of prematurity (ROP) [14]. These perinatal–neonatal outcomes were chosen because vitamin D has been implicated in the pathogenesis of these clinical morbidities in ELBW infants. The staff that collected the data from electronic medical records underwent training for consistency in data entry.

Descriptive statistics characterized the normal distribution of circulating 25(OH)D concentrations among ELBW infants. Associations between vitamin D status and perinatal–neonatal outcomes were initially explored with bivariate analyses. *P* values for categorical variables were calculated using Fisher's exact test and continuous data using the Kruskal–Wallis test. For the perinatal–neonatal outcomes, stepwise forward multiple logistic regression was performed to account for prespecified confounders. Variables significant at the 0.10 level were entered into multivariate regression models to adjust for covariates. Statistical calculations were performed using SAS V 9.4 (SAS Institute, Cary, NC, USA), with P (two-tailed) < 0.05 significant. We decided a priori to evaluate the subgroups of isolated maternal fever and triple I separately, only if the *P* value for the interaction between 25(OH)D and covariate (maternal fever vs. triple I) was < 0.1.

Results

During the study period, 1934 neonates were admitted to the neonatal intensive care unit. Among these, 63 were infants who had a birth weight < 1000 g. Three of the eligible families did not consent to participate. No significant differences emerged between the enrolled families and those that did not consent.

Of the 60 infants enrolled, 13 (22%) were vitamin D deficient, 15 (25%) were insufficient, and 32 (53%) were adequate. Forty-seven percent of infants had vitamin D inadequacy.

Tables 1 and 2 show the comparison of maternal, perinatal, and neonatal characteristics by vitamin D status. After controlling for covariates, the positive associations between circulating 25(OH)D concentrations, and fetal growth restriction and PROM persisted ($P < 0.05$).

Logistic regression analysis for the association between circulating 25(OH)D concentrations (factor count as a continuous variable) and perinatal–neonatal outcomes was performed, adjusting for serum calcium, phosphorus,

Table 1 Maternal and perinatal characteristics by Vitamin D status

Variable[a]	Vit D deficient ($n = 13$)	Vit D insufficient ($n = 15$)	Vit D adequate ($n = 32$)	*P*-value
Race/ethnicity				0.07
White, non-Hispanic	2 (15)	11 (73)	20 (63)	
African American	5 (39)	2 (13)	5 (16)	
Hispanic	6 (46)	2 (13)	5 (16)	
Other[b]	0	0	2 (6)	
Maternal age, years	25.8 ± 5.1	28 ± 5.1	27.3 ± 6.1	0.57
Married	5 (39)	7 (47)	14 (44)	0.91
Medicaid/uninsured	10 (77)	12 (80)	21 (66)	0.64
Body mass index, kg/m^2	30 ± 11	27 ± 8	28 ± 6	0.59
Season, winter	3 (23)	6 (40)	8 (25)	0.66
Multiple gestation	5 (39)	3 (20)	7 (22)	0.49
Smoking	2 (15)	3 (20)	6 (19)	1
Fetal growth restriction	1 (8)	9 (60)	10 (31)	0.01
Diabetes, insulin dependent	1 (8)	0	0	0.22
PROM > 18 h	0	7 (47)	13 (41)	0.02
Maternal antibiotics	8 (62)	7 (47)	22 (69)	0.17
Antenatal steroids	12 (92)	14 (93)	28 (88)	0.83
Inborn	12 (92)	15 (100)	30 (94)	0.79
C-section	10 (77)	12 (80)	21 (66)	0.64

PROM prolonged rupture of membranes, *Triple I* intrauterine infection and/or inflammation

[a]Categorical data are presented as *n* (%). Continuous data are presented as mean ± standard deviation or median (interquartile range)

[b]Other race/ethnicity includes American-Indian or Alaskan Native, Asian, Native Hawaiian, or other Pacific Islander and multiracial

prealbumin, AST, ALT and creatinine, race/ethnicity, fetal growth restriction, and PROM. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each included variable are shown (Table 3). Although there was a higher rate of triple I with vitamin D deficiency in unadjusted analysis, this difference was no longer statistically significant when adjusted for PROM.

Discussion

This study reports vitamin D status, as reflected by circulating 25(OH)D concentrations, in ELBW infants evaluated prospectively. About half of the ELBW infants had early biochemical evidence of vitamin D inadequacy. With a reported half-life of approximately three weeks, 25 (OH)D is the main circulating metabolite of vitamin D and most informative measure to assess the overall vitamin D status [10]. These data demonstrate a significant difference in the micronutrient levels (circulating vitamin D concentrations) associated with fetal growth restriction and PROM.

We report a high prevalence of vitamin D inadequacy that was not entirely unexpected, given the high latitude (42° North) of the study setting. However, this finding is likely primarily due to the missed third-trimester transfer of vitamin D from the mother to the infant [3, 15]. These ELBW infants received standard hyperalimentation solution with ~160 IU per kilogram per day of vitamin D. This inadequate supplementation of vitamin D, along with other nutrients, as evidenced by low calcium and phosphorus concentrations, could have contributed as well. In a study of 100 pregnant women in Poland (latitude 52° North), maternal and umbilical cord 25(OH)D concentrations were higher in the summer group, but the majority were still noted to have vitamin D inadequacy [16]. Recent studies of preterm infants also reported a high prevalence of vitamin D deficiency [17–19]. The authors acknowledged the differences in multiple methods of quantitative analysis of circulating 25(OH)D concentrations, and large assay coefficients of variation could have limited validity of the these studies. Further, a less biologically active C3 epimer of 25(OH)D, generated within the fetal-placental unit, and detected by quantitative assays of 25(OH)D may limit the

Table 2 Neonatal characteristics by vitamin D status

Variable[a]	Vit D deficient ($n = 13$)	Vit D insufficient ($n = 15$)	Vit D adequate ($n = 32$)	*P*-value
Birth weight, g	834 ± 102	768 ± 156	762 ± 163	0.34
Gestational age, weeks	26.7 ± 1.8	27.4 ± 2.1	26.1 ± 2	0.13
Male	8 (62)	10 (67)	18 (56)	0.79
Apgar, 5 min	6 (3–8)	8 (6–8)	6 (5–7)	0.19
Mechanical ventilation, duration, days	95 (66–110)	87 (39–125)	98 (71–116)	0.89
Diuretics	4 (31)	6 (40)	12 (38)	0.87
Postnatal steroids	7 (54)	7 (47)	14 (44)	0.83
hsPDA	4 (31)	0	6 (19)	0.07
Age at initiation of enteral feeds, days	3 (3–4)	3 (3–4)	4 (3–5)	0.46
Feeding				
Human milk	3 (23)	2 (13)	5 (16)	
Formula	0	0	1 (3)	
Both	10 (77)	13 (87)	26 (81)	
Timing of full enteral feeds, days	44 ± 35	37 ± 28	48 ± 32	0.54
Nutritional labs at d 28–31				
Calcium, mg/dL	9.5 ± 0.9	10.3 ± 1.1	10.1 ± 0.7	0.05
Phosphorus, mg/dL	4.2 ± 0.8	3.8 ± 0.6	4.7 ± 1.3	0.05
Magnesium, mg/dL	2.6 (2.4–2.8)	2.5 (2.2–2.9)	2.3 (2.1–2.6)	0.15
Alkaline phosphatase, IU/L	363 ± 96	346 ± 141	420 ± 188	0.29
Prealbumin, mg/dL	9 ± 1.78	6.9 ± 2.6	8.1 ± 2.6	0.09
Direct bilirubin, mg/dL	0.8 (0.4–1.3)	0.5 (0.4–0.7)	0.7 (0.4–1.5)	0.20
AST, IU/L	19.5 (12–27)	31 (28–40)	39 (32.5–92)	0.08
ALT, IU/L	6 (6–9)	7 (6–8)	7.5 (6–11.5)	0.05
Creatinine, mg/dL	0.4 (0.3–0.8)	0.5 (0.3–0.9)	0.5 (0.4–1)	0.06
Length of hospital stay, days	99 ± 25	107 ± 54	108 ± 41	0.77

hsPDA hemodynamically significant patent ductus arteriosus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

[a]Categorical data are presented as *n* (%). Continuous data are presented as mean ± standard deviation or median (interquartile range)

interpretation of 25(OH)D concentrations in these studies [20, 21].

Circulating 25(OH)D concentrations were positively associated with fetal growth restriction in our population. Vitamin D is a fat-soluble secosteroid. Higher circulating 25 (OH)D concentrations may reflect its lower "hidden" concentrations in the fat tissue, as body fat dilutes vitamin D. Supporting this concept, Wortsman et al. reported lower circulating concentrations of 25(OH)D in adults, with BMI $> 30\ kg/m^2$ exposed to the same amount of UVB radiation or vitamin D intake compared with age-matched normal weight adults [22]. This finding was thought to be due to decreased bioavailability of vitamin D because of its deposition in body fat compartments. In a study of adolescents with anorexia nervosa who were significantly underweight for their age, there was a lower prevalence of vitamin D deficiency than in healthy controls, as we found with fetal growth restriction [23].

The association between vitamin D and PROM can be explained by several mechanisms. Vitamin D has been shown to alter the microbiome, and low levels were associated with bacterial vaginosis [24]. In addition, this nutrient is a known immune modulator [25]. Vitamin D is also an effective stabilizer of the membrane through non-genomic mechanisms [26]. This membrane stabilization is structurally specific, in that the open B ring and the cis-triene structure of vitamin D are required [7]. Moreover, vitamin D has been implicated in epigenetic alterations through DNA methylation in genes that regulate the extracellular matrix reorganization and affect membrane integrity [27]. Our results that signal the modulation of the intra-amniotic inflammation/infection by vitamin D is mediated through PROM.

Table 3 Adjusted association between circulating 25-hydroxyvitamin D concentrations and perinatal-neonatal outcomes

Outcomes[a]	AOR (95% CI)	*P*-value
Perinatal		
Any morbidity	1.08 (0.96–1.21)	NS
Preterm labor	1.07 (0.99–1.17)	NS
Pre-eclampsia	0.95 (0.88–1.03)	NS
Triple I	1.03 (0.99–1.08)	NS
Neonatal		
Any morbidity	1.03 (0.99–1.1)	NS
Sepsis	0.98 (0.95–1.02)	NS
NEC	1.01 (0.95–1.06)	NS
BPD	1.03 (0.98–1.07)	NS
Severe ICH	0.99 (0.92–1.07)	NS
ROP	1.04 (0.99–1.09)	NS

[a]There were no significant interactions between serum 25(OH)D concentrations and covariates

A combination of various environmental and host factors including possible genetic predisposition, as demonstrated by vitamin D receptor polymorphisms [28], may explain the lack of association between perinatal outcomes including preterm labor in our cohort. Similarly, given that vitamin D plays important roles in the innate immune system and early lung development, the lack of association between vitamin D and both sepsis and BPD supports a multifactorial etiology, as found in recent studies [29–32]. In addition to the immature immune system of ELBW infants, sepsis, NEC, and mortality are affected by multiple other determinants including prenatal factors, delivery room and resuscitation management, and the infant microbiome and infection control practices within the NICU [33, 34]. The association of vitamin D deficiency and respiratory morbidity [35], as seen in older children and adults, may be due to different pathology than that seen in BPD, which is characterized by alveolar simplification and impaired septation.

Study limitations and strengths merit acknowledgment. Maternal 25(OH)D concentrations and neonatal parathyroid hormone were not evaluated in the present study, as sampling was limited to clinical indications. Information on maternal vitamin D supplementation was not available. Measurement of bone mineral content (e.g., dual-energy x-ray absorptiometry) was not possible, given the limited resources available for the study. Additionally, our study was not powered to discern the differences in the outcomes, given the frequency of morbidities such as BPD or NEC. Vitamin D status beyond birth was not evaluated in our study and may have affected the neonatal outcomes. Study strengths include prospective design, predefined morbidities, inclusion of nutritional data, population-based, unbiased collection of samples from almost all ELBW infants in a regional perinatal center during a defined period, and 25 (OH)D quantification by gold standard LC-MS/MS [36].

In conclusion, this prospective cohort study demonstrated that 47% of ELBW infants had inadequate circulating 25(OH)D concentrations, which was associated with fetal growth restriction and PROM. Larger multicenter studies are needed to evaluate the influence of vitamin D on perinatal–neonatal outcomes. Whether or not morbidity and mortality in a subgroup of ELBW infants can be mitigated by vitamin D supplementation requires further investigation. The vitamin D ELBW contemporary cohort supports surveillance of vitamin D status and provides important data needed for planning of future studies to evaluate safety and efficacy of vitamin D supplementation in this at-risk population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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