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# Vitamin D status of early preterm infants and the effects of vitamin D intake during hospital stay

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## ABSTRACT

**Objectives** To evaluate vitamin D (vitD) status in early preterm infants (EPTIs) at birth and during birth hospitalisation on current vitD intake.

**Design/methods** Serum 25-hydroxyvitamin-D [25(OH)D] concentrations, vitD intake and risk factors for low vitD status were assessed in 120 infants born at  $\leq 32$  weeks gestation.

**Results** Mean (SD) serum 25(OH)D at birth was 46.2 (14.0) nmol/L with lower concentrations in infants born  $< 28$  weeks than at 28–32 weeks gestation,  $p=0.02$ . Serum 25(OH)D was  $< 50$  nmol/L in 63% of mothers, 64% of infants at birth and 35% of infants at discharge. Mean daily vitD intake was  $289 \pm 96$  IU at 4 weeks of age and 60% achieved 400 IU/day intake at discharge.

**Conclusions** Serum 25(OH)D  $< 50$  nmol/L was widespread in parturient women and in EPTIs at birth and at discharge. Optimising maternal vitD status during pregnancy and improving postnatal vitD intake may enhance infant vitD status during hospitalisation.

## INTRODUCTION

Low vitamin D (vitD) status is a risk factor for rickets and has been associated with increased prevalence of respiratory infections and other adverse health outcomes in infants and children.<sup>1,2</sup> In response to the concern about widespread childhood vitD deficiency, professional bodies have recommended vitD intake of 400 IU/day for all infants.<sup>1,3</sup> The European Society for Paediatrics Gastroenterology, Hepatology and Nutrition recommends 800–1000 IU/day for preterm infants.<sup>4</sup> Based on biomarkers of vitD status mostly in adults, serum 25-hydroxyvitamin-D [25(OH)D] concentration  $\geq 50$  nmol/L was also recommended.<sup>1,3</sup> However, the functional benefit of this level is controversial. Early preterm infants (EPTIs) are likely at risk of low vitD status because of high prevalence of vitD deficiency in pregnancy,<sup>5</sup> lack of sunlight exposure during hospitalisation and difficulty in ensuring adequate enteral nutrition. We hypothesised that serum 25(OH)D concentrations would be low at birth in EPTIs ( $< 32$  weeks postmenstrual age (PMA)) and that current vitD intake during hospitalisation would be insufficient to achieve a serum 25(OH)D  $\geq 50$  nmol/L at discharge. We assessed the serum 25(OH)D concentrations at birth in EPTIs and the effect of current vitD intake during hospitalisation on vitD status.

## MATERIALS AND METHODS

Infants born at  $\leq 32$  weeks PMA admitted to the newborn intensive care units (NICUs) at the University of Cincinnati Medical Center,

## What is already known on this topic

- ▶ Vitamin D deficiency is common in infants that do not receive vitD supplements.
- ▶ Vitamin D intake of 400 IU/day is recommended for infants to achieve a target serum 25 (OH)D concentrations  $\geq 50$  nmol/L.

## What this study adds

- ▶ Low serum concentrations ( $< 50$  nmol/L) are common in preterm infants during birth hospitalisation and at discharge from the neonatal intensive care unit.
- ▶ Current neonatal nutritional strategies for early preterm infants may be insufficient to achieve recommended vitD intake and target serum 25 (OH)D concentrations.
- ▶ Improving maternal vitD status during pregnancy and neonatal vitD supplementation is warranted to optimise vitD status of preterm infants in early infancy.

Cincinnati, Ohio, the Ohio State University Medical Center or Nationwide Children's Hospital in Columbus, Ohio from December 2010 to February 2012 were enrolled after parental informed consent. The study was approved by the respective Institutional Review Boards. Infants were excluded for lethal congenital malformations, severe illness at birth deemed incompatible with survival or multiple gestation pregnancies.

## Study protocol

Data collected included maternal socio-demographics, perinatal history, prenatal vitD intake and birth season. Daily vitD intake was estimated at 4 weeks of age from the concentrations in parenteral nutrition (160 IU/kg), human milk,<sup>6</sup> human milk fortifier (120 IU vitD per 100 mL milk), and in formula and vitD<sub>3</sub> supplements of 200 IU/day from multivitamin D drops from 2 weeks of age.

## Vitamin D status during hospitalisation

Blood specimens were obtained within 48 h of birth, at 4 weeks of age and at 36 weeks PMA or at discharge. Serum 25(OH)D concentrations were measured from the dried blood spots using liquid chromatography/tandem mass spectrometry (ZRT

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**Table 1** Demographic characteristics and serum 25-hydroxyvitamin-D concentrations

Characteristics	All infants (n=120)	Infants born <28 weeks PMA (n=67)	Infants born between 28 and 32 weeks PMA (n=53)
n (%) male	51 (43)	27 (41)	24 (45)
n (%) African-American	46 (39)	29 (43)	17 (32)
PMA in weeks	28.1 (1.2)	26.4 (1.0)	30.4 (0.8)
Birth weight in g	1028.1 (236.8)	831.5 (231.7)	1276.6 (245.9)
Maternal 25(OH)D in nmol/L at delivery	49.2 (19.2)	44.0 (12.5)	55.7 (22.7)*
n (%) mothers with 25(OH)D <50 nmol/L	75 (63)	45 (67)	30 (57)
Infant 25(OH)D in nmol/L at birth	46.3 (14.0)	42.0 (9.8)	51.8 (19.5)**
n (%) infants with 25(OH)D <50 nmol/L	76 (64)	47 (70)	29 (55)**
25(OH)D in nmol/L at 36 weeks PMA or at discharge	64 (21.8)	59.2 (20.5)	71 (23.5)***
n (%) infants with 25(OH)D <50 nmol/L at 36 weeks PMA or at discharge	43 (36)	27 (40)	16 (30)

\*p=0.02 for difference between 25(OH)D serum concentrations in mothers that delivered at <28 weeks vs 28–32 weeks PMA.

\*\*p=0.02 for difference between infants born at <28 weeks vs 28–32 weeks PMA.

\*\*\*p=0.04 for difference between infants born at 28 weeks vs <28–32 weeks PMA.

Values are mean (SD).

PMA, postmenstrual age.

laboratories in Beaverton, Oregon). The intra- and inter-assay coefficients of variation were 8.6% and 11%, respectively.

### Statistical analysis

Data were analysed by PMA (<28 weeks versus 28–32 weeks) to account for gestational age-associated differences in hospital course. Relationships between variables were tested using Pearson's correlation coefficient. A multivariable logistic regression model with serum 25(OH)D concentration as an outcome variable was constructed to control for potential confounding variables. p Values of <0.05 were considered significant.

### RESULTS

A total of 120 mother/infant pairs were enrolled. Table 1 shows the demographic characteristics and serum 25 (OH)D concentrations. Mean serum 25(OH)D concentration at birth for the EPTI cohort was 46.3 nmol/L (SD 14.0) with lower concentrations in infants born <28 weeks PMA (42.0±9.8 nmol/L) than at 28–32 weeks (51.8±19.5 nmol/L), p=0.02.

Overall, 64% of infants had serum 25(OH)D concentrations <50 nmol/L at birth. Approximately 70% of infants born <28 weeks and 55% of infants born between 28 and 32 weeks had serum 25(OH)D concentrations <50 nmol/L, p=0.02. Maternal serum 25(OH)D concentration was 49.0±21.3 nmol/L. Sixty-three per cent of mothers had 25(OH)D concentrations <50 nmol/L. Infant serum 25(OH)D at birth correlated with

maternal 25(OH)D (r=0.77, p=0.001) and with infant serum 25(OH)D at discharge (r=0.65, p=0.04).

Following multivariable logistic regression, the factors that were significantly associated with serum 25(OH)D <50 nmol/L were low maternal vitD status (adjusted OR (aOR), 5.2 (95% CI 2.9 to 9.6)), African-American ethnicity (3.2 (1.3 to 7.9)), PMA <28 weeks (2.6(1.1 to 6.2)), lack of maternal prenatal vitD use (4.2 (2.1 to 8.5)) and winter birth (4.3 (2.3 to 9.3)), (table 2).

Mean vitD intake at 4 weeks postnatal age was 289±96 IU/day and was not significantly different in infants born at <28 weeks PMA (232±106 IU) than at 28–32 weeks PMA (316±94 IU), p=0.08. At discharge or 36 weeks PMA, 60% of the entire cohort of preterm infants attained 400 IU per day.

With the current vitD intake during hospitalisation in the NICUs, 40% of infants born <28 weeks PMA and 30% of infants born between 28 and 32 weeks had serum 25 (OH)D concentrations <50 nmol/L at 36 weeks PMA or at discharge.

### DISCUSSION

In this multicentre study, two-thirds of preterm infants and their mothers had serum 25(OH)D concentrations <50 nmol/L, a value considered deficient by some professional bodies.<sup>1</sup> Interestingly, the odds of a serum 25(OH)D level <50 nmol/L was increased 2.6-fold in infants born <28 weeks PMA than at 28–32 weeks. Presumably, the high prevalence of serum 25 (OH)D concentrations <50 nmol/L at birth in our cohort of

**Table 2** Factors associated with infant serum 25(OH)D <50 nmol/L at birth in multivariable analysis

Characteristic	Variable	Crude OR (95% CI)	aOR (95% CI)
Maternal 25-hydroxyvitamin-D (nmol/L)	≥50	–	–
	<50	5.8 (3.4 to 9.6)	5.2 (2.9 to 9.6)
Maternal race/ethnicity	Caucasian/other	–	–
	African-American	3.4 (1.6 to 8.2)	3.2 (1.3 to 7.9)
Gestational age	28–32 weeks	–	–
	<28 weeks	2.4 (1.3 to 5.9)	2.6 (1.1 to 6.2)
Maternal prenatal vitamin use	No	–	–
	Yes	0.4 (0.2 to 0.7)	0.24 (0.1 to 0.5)
Season of birth	Summer	–	–
	Fall	1.8 (0.8 to 3.2)	2.1 (1.1 to 4.2)
	Winter	4.7 (2.4 to 9.6)	4.3 (2.3 to 9.3)
	Spring	2.3 (1.2 to 4.2)	1.8 (0.9 to 2.8)

All parameter estimates were adjusted for other covariates. Variables entered from univariate analysis that were not statistically significant in multivariable analysis were maternal age, maternal education, insurance and body mass index.

EPTIs and the higher prevalence in infants born <28 weeks than in infants born between 28 and 32 weeks are reflective of maternal vitD status.

Maternal vitD deficiency predisposes to low vitD status in term infants at birth.<sup>7 8</sup> Similarly, we found that maternal vitD deficiency predicted low vitD status in EPTIs in agreement with our hypothesis. Our data also suggest that vitD status of EPTIs at birth correlated with the vitD status at discharge, underscoring the importance of optimising the vitD status of infants at birth. As reported in studies in term infants,<sup>7 8</sup> African-American ethnicity, lack of maternal prenatal vitD intake and winter birth were predictive of low vitD status at birth in EPTIs. Since EPTIs are usually hospitalised after birth, vitD synthesis from sunlight exposure is lacking. Thus, repletion of vitD status during hospitalisation depends entirely on exogenous sources. There are limited recent reports on vitD intake in preterm infants during birth hospitalisation.<sup>9 10</sup> Our study demonstrated that although total daily vitD intake from all sources increased progressively with age (data not shown), only 60% of this cohort of infants achieved an intake of 400 IU/day of vitD by 36 weeks PMA or at discharge. During hospitalisation, low vitD status at birth and suboptimal vitD intake appear to militate against the achievement of serum 25(OH)D concentrations  $\geq 50$  nmol/L in many preterm infants. Although professional bodies<sup>1 3 4</sup> recommend 25(OH)D concentrations  $> 50$  nmol/L to promote bone health, the effect of target serum 25(OH)D concentration on clinical outcomes in infants is lacking and merits evaluation.

Our study had several strengths. To our knowledge, it is the first reported multicentre investigation of vitD status in infants born <32 weeks gestation and monitored longitudinally from birth until hospital discharge. It provides data on the vitD status achieved by EPTIs born <32 weeks PMA based on conventional nutritional practices in the NICU settings. Thus, our results are likely generalisable to infants in NICUs and will inform future intervention trials to assess the effect of optimising vitD status in preterm infants on short- and long-term clinical outcomes.

## CONCLUSIONS

In this study, neither the vitD intake, nor the recommended serum 25(OH)D concentrations of  $\geq 50$  nmol/L were attained in many EPTIs. The serum 25(OH)D concentrations of infants were directly correlated with maternal vitD status at birth. Therefore, vitD status should be optimised in pregnant women as part of strategy to replete the offspring. In addition, EPTIs require heightened attention to vitD supplementation in the NICU to improve vitD intake and vitD status. In view of potential putative roles for vitD in several biologic functions, studies are needed to test the effect of targeting serum 25(OH)D concentrations of  $\geq 50$  nmol/L on clinically relevant health outcomes.

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**Contributors** NM obtained Institutional Review/Ethical Board approval at University of Cincinnati Medical Center, enrolled subjects at the Cincinnati centre, extracted data from the electronic medical records, collated data on serum 25-hydroxyvitamin-D concentrations and wrote the first draft of the manuscript; JLS obtained Institutional Review/Ethical Board approval at the Columbus centres, enrolled subjects in Columbus, Ohio, collated and analysed the demographic and serum 25-hydroxyvitamin-D data, and contributed to several revisions of the manuscript; CS collated data on dietary intake of vitamin D and contributed to the Methods section of the manuscript; AD developed the concept for the study, supervised the conduct of the study and contributed to the revisions resulting in the final version of the manuscript; HTA developed the concept for the study, supervised the management of the data, supervised the conduct of the study and contributed to the later versions of the manuscript.

**Competing interests** None.

**Ethics approval** University of Cincinnati, Ohio and Nationwide Children's Hospital, Columbus, Ohio (Note: Nationwide Children's Hospital and The Ohio State University have a reciprocity agreement in place. Approval by the Nationwide IRB permits investigations at both institutions).

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**Data sharing statement** The manuscript data, the nutrition data and anthropometric data will be made available to all investigators upon request.

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