ORIGINAL ARTICLE

High prevalence of vitamin D deficiency in newborn infants of high-risk mothers

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Objective: To determine the prevalence of vitamin D deficiency in newborn infants of mothers at risk of vitamin D deficiency because of dark skin or the wearing of concealing clothes (such as a veil) compared with a group presumed not to be at risk. A second aim was to correlate these newborn infants' vitamin D concentrations with biochemical parameters of vitamin D metabolism and bone turnover at birth.
Design: A prospective study conducted between April 2004 and February 2006 including women delivering during this period and their newborn infants.
Setting: The outpatient clinic of the obstetrics department, Sint Franciscus Gasthuis, Rotterdam, the Netherlands.
Patients: Eighty seven newborn infants of healthy mothers with either dark skin and/or concealing clothing (risk group) or light skin (control group).
Results: We found a significant difference in the prevalence of vitamin D deficiency (25-hydroxyvitamin D_3 <25 nmol/l) between newborn infants of mothers at risk and those of mothers in the control group (63.3% vs 15.8%; p<0.001). Mean alkaline phosphatase concentrations were significantly higher in the at risk group.
Conclusions: Newborn infants of mothers with dark skin or wearing concealing clothes are at great risk of vitamin D deficiency at birth. The clinical implications are unknown. Further research is necessary to determine the long-term consequences of maternal and neonatal vitamin D deficiency so that guidelines on vitamin D supplementation during pregnancy can be issued.

Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D_3. Regulated by parathyroid hormone, additional hydroxylation to 1,25-dihydroxyvitamin D_3 takes place in the kidney. 1,25-Dihydroxyvitamin D_3 is the active metabolite of vitamin D that increases intra- and extracellular calcium concentrations by several mechanisms: it absorbs intestinal calcium, diminishes renal calcium excretion and, in conjunction with parathyroid hormone, mobilises calcium from bone. Of late, the focus of vitamin D deficiency research has shifted from breastfeeding without vitamin D supplementation to the newborn infants of mothers at risk of vitamin D deficiency. Several studies have reported a higher risk of vitamin D deficiency in pregnant women due to ethnocultural factors; dark skin or concealing clothing may lead to limited sun exposure.[9 10]

We conducted a study among a group of pregnant women and their newborn infants in a general hospital in Rotterdam, the Netherlands. This is a multi-cultural city in which residents of Surinamese origin constitute the largest immigrant group (20%), those of Turkish origin the second largest (17%) and those of Moroccan origin the third largest (13%).[11]

The prevalence rates of vitamin D deficiency in these immigrant groups are unknown, and few data are available concerning newborn infants of mothers at risk.

Our first aim in this study was to determine prevalences of vitamin D deficiency in newborn infants born to mothers in different risk groups in the Netherlands. A second aim was to correlate these newborn infants' vitamin D concentrations with biochemical parameters of vitamin D metabolism and bone turnover at birth.

METHODS

The study was reviewed and approved by the medical ethics review board of MCRZ Hospital, Rotterdam, the Netherlands.

All pregnant women visiting the obstetrics outpatient department at Sint Franciscus Gasthuis, Rotterdam, between April 2004 and February 2006 were invited to participate in our study. Those who gave informed consent completed a questionnaire. Hospital interpreters were available. The questionnaire asked about degree of skin pigmentation, country of origin, hours of sun exposure per day, clothing style, use of vitamins, diet (especially dairy products and fish) and medical history including clinical features suggestive of vitamin D deficiency. We aimed to include a ''risk group'' of 50 women with dark skin or veiled clothing and a control group of 50 women with light skin. Colour of skin was determined through self-assessment by the women who participated. The self-assigned skin colour was light, dark or intermediate. Women with intermediate skin colour were assigned to the group with dark skin. Newborn infants born to mothers in the risk group were also considered at risk. Newborn infants of mothers with light skin served as controls. The risk group consisted of 17 newborn infants of mothers with intermediate skin, five infants of mothers with dark skin and 20 infants with veiled mothers. Exclusion criteria were illnesses during pregnancy, chronic diseases, use of glucocorticoids and vitamin D deficiency secondary to hereditary illnesses of vitamin D metabolism. Maternal blood and urine samples were collected at the end of the third trimester. Maternal umbilical cord blood values at birth were taken to represent the newborn infant's values. The infants' birth weight, gestational age, sex and season of birth were documented. Infants presenting with symptomatic hypocalcaemia were admitted to the hospital and treated by the paediatrician on call. Blood samples were taken to evaluate therapy.

Biochemical analysis

Umbilical cord blood was tested for 25-hydroxyvitamin D_3 in 87 newborn infants using the 25-hydroxyvitamin D_3 kit

(Advantage, Nichols Institute Diagnostics, San Juan Capistrano, CA). Alkaline phosphatase, parathyroid hormone, ionised calcium and phosphorus were tested in 85, 80, 74 and 86 newborn infants, respectively.

Calcium, phosphorus and alkaline phosphatase levels were measured by standard methods (Synchron LX20, Beckman-Coulter, Fullerton, CA). Ionised calcium was determined by ion selective electrodes (Phox Plus, Nova Biomedical, Waltham, MA). Intact parathyroid hormone levels were determined by LIEMA (Immulite analyser, DPC, Los Angeles, CA) at IJsselland Hospital in Capelle a/d IJssel, the Netherlands. Serum levels of 25-hydroxyvitamin D_3 <25 nmol/l in newborn infants were considered to reflect vitamin D deficiency.

Sample size calculation and statistical analysis

Sample size was calculated by a priori power analysis, aiming at a power of 0.80 to allow for determination of a difference in the prevalence of vitamin D deficiency between the risk group and controls. As prevalences reported in the literature vary widely, we aimed at a 20% minimal difference in prevalence. Thus, a minimal sample size of 102 with a power of 0.80 and $\alpha = 0.05$ was calculated. Statistical analysis was conducted using SPSS (version 12.0). Because some of the biochemical parameters showed skewed distribution, the results are presented with medians and quartiles (25th and 75th percentile). In addition, we used logarithmically transformed data for statistical analysis of comparison of means.

p Values, for comparison of log-transformed means for the risk group compared to controls, were tested by one-way ANOVA.

RESULTS

Between April 2004 and February 2006, 166 pregnant women were recruited, and these gave birth to 182 children. Multiple pregnancies (ie, 16 twins) were excluded to prevent a bias. No data were available for 25 newborn infants, either because the mother was transferred in pregnancy to another hospital or because of intra-uterine death (two cases). Of the 125 newborn infants for whom data were available, 25-hydroxyvitamin D_3 was not measured in 38 for various reasons (eg, insufficient material, not requested for testing or loss of samples). Thus, 25-hydroxyvitamin D_3 levels of 87 newborn infants were available for analysis. Paired measurements of both the mother and the newborn infant were available in 73 cases. Data on the use of vitamin D supplements were available for 70 women: five of the 40 of these women (12.5%) in the risk group, and 11 of the 30 in the control group (36.7%) had used vitamin supplements. Table 1 shows the baseline characteristics and prevalences of vitamin D deficiency for both the risk and control groups. Mean gestational age, birth weight and season of birth did not differ between the two groups. The control group included 17 (45%) boys and the risk group 33 (67%) boys.

25-hydroxyvitamin D_3 and the seasons

The mean serum 25-hydroxyvitamin D_3 values did not differ significantly between the seasons of birth in both groups.

25-hydroxyvitamin D_3 prevalence

We found a higher prevalence of vitamin D deficiency in the newborn infants of mothers at risk (63.3%) compared with the control group (15.8%). Within the risk group, we identified the newborn infants of mothers wearing veils to be at highest risk of vitamin D deficiency with a prevalence of 90.9%. 25-Hydroxyvitamin D_3 values in pregnant women and their newborn infants showed a positive correlation ($r = 0.88$), as shown in fig 1. The Pearson correlations of neonatal 25-hydroxyvitamin D_3 with ionised calcium, phosphorus, alkaline phosphatase and parathyroid hormone were non-significant at −0.172 ($p = 0.14$), 0.17 ($p = 0.28$), −0.12 ($p = 0.28$) and −0.18 ($p = 0.12$), respectively.

Table 1 Baseline characteristics of newborn infants and prevalence rates in the control and risk groups

	Control group	Risk group	p Value
Gestational age			
n	38	48	0.400
Mean (weeks)	39.7	39.4	
(min–max) (weeks)	(34–42)	(34–42)	
Birth weight			
n	37	47	0.790
Mean (g)	3382	3416	
(min–max) (g)	(1775–4250)	(2250–4750)	
Season of birth			0.560
Spring, n (%)	10 (26.3)	13 (26.5)	
Summer, n (%)	9 (23.7)	18 (36.7)	
Autumn, n (%)	14 (36.8)	13 (26.5)	
Winter, n (%)	5 (13.2)	5 (10.2)	<0.001
Vitamin D deficient, n (%)	6 (15.8)	31 (63.3)	

Mean cord blood ionised calcium concentrations were not significantly lower in the risk group. However, mean alkaline phosphatase concentrations were significantly higher in the risk group (table 2).

DISCUSSION

Our study provides data on the prevalence of vitamin D deficiency in newborn infants born to mothers from risk groups in the Netherlands. The most important finding was a higher prevalence of vitamin D deficiency in newborn infants of mothers at risk of vitamin D deficiency (63.3%) as compared with a control group (15.8%). The prevalence of vitamin D deficiency in the total group (with vitamin D deficiency defined as 25-hydroxyvitamin D_3 levels <25 nmol/l) was 42.5%. Cut-off

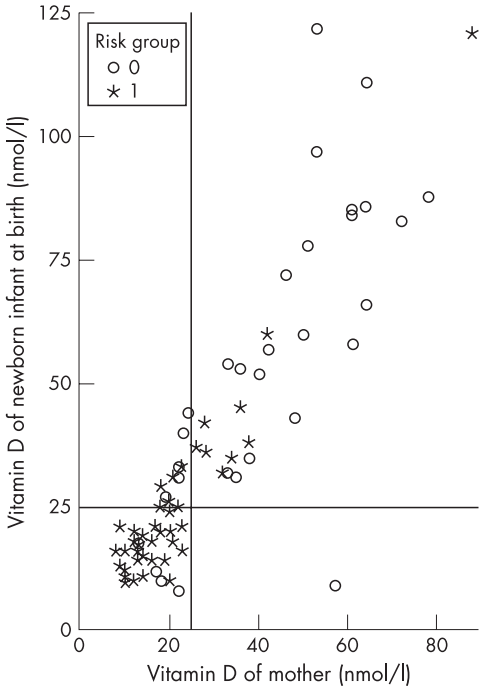

Figure 1 Positive correlation between 25-hydroxyvitamin D_3 values in mothers and newborn infants.

Table 2 Newborn (cord blood) laboratory values in the control and risk groups

	Control group		Risk group		p Value
	n	Median (25th-75th percentile)	n	Median (25th–75th percentile)	
25(OH)D_3 (nmol/l)	38	52.5 (31.8–79.0)	49	20.0 (15.5–30.0)	<0.001
iCa (mmol/l)	34	1.29 (1.21–1.38)	40	1.34 (1.28–1.43)	0.061
P (mmol/l)	38	1.74 (1.58–1.91)	48	1.66 (1.55–1.88)	0.453
AP (U/l)	38	161 (124–213)	47	177 (156–217)	0.050
PTH (pmol/l)	35	0.10 (0.10–0.40)	45	0.20 (0.10–0.80)	0.143

AP, alkaline phosphatase; iCa, ionised calcium; 25 (OH)D_3, 25-hydroxyvitamin D_3; P, phosphorus; PTH, parathyroid hormone.

values for vitamin D deficiency in newborn infants are still being debated. However, 25-hydroxyvitamin D_3 concentrations below 25 nmol/l are considered deficient in children.[12 13]

Vitamin D deficiency in pregnant women at risk because of ethnocultural factors has been widely reported.[9 10 14–19] Prevalences in the various study groups range from 50% to 84%. Vitamin D deficiency as described is becoming a major problem and although the prevalence rates for newborn infants are unknown, they may be high. Very few studies have reported the prevalence of vitamin D deficiency in newborn infants. One report, however, found a high prevalence of vitamin D deficiency in newborn infants and pregnant women from India, a country with abundant sunlight.[15] The newborn infants' mean cord blood 25-hydroxyvitamin D_3 level was low (8.4±5.7 ng/ml) and most of the newborn infants (95.7%) were vitamin D deficient (serum 25-hydroxyvitamin D_3 <20 ng/ml≈50 nmol/l). However, the cut-off value was lower than that used in our study.

In a Dutch study, severe vitamin D deficiency (25-hydroxyvitamin D_3 <13 nmol/l) was found in 54% of newborn infants of non-European origin compared with 6% of Dutch/West European newborn infants.[20] This study did not report data on pigmentation or clothing habits and their possible associations with vitamin D deficiency. Our study found a comparable prevalence (63.3%) of vitamin D-deficient newborn infants from the risk group defined by intermediate/dark skin or veiling. In addition, the newborn infants of the veiled mothers showed an extremely high prevalence of vitamin D deficiency (90.9%).

In our study, mean alkaline phosphatase concentrations in the risk group were higher than in controls, which may indicate increased bone turnover. Nevertheless, as values remained within the normal range, this finding may not be clinically relevant.

Few studies have reported on the consequences of maternal and neonatal vitamin D deficiency for fetal growth and bone development. Data from randomised trials of oral supplementation during pregnancy in women with vitamin D deficiency showed inconsistent results regarding offspring size at birth.[4] A recent study showed that low maternal 25-hydroxyvitamin D_3 values in late pregnancy were associated with decreased knee–heel length, which is a measure of intrauterine long bone growth at birth.[21] Javaid *et al* showed an association between reduced concentration of 25-hydroxyvitamin D_3 in white mothers during late pregnancy and reduced whole-body and lumbar-spine bone mineral content in their children at the age of 9 years.[22]

Further studies are needed to provide more conclusive evidence of the long-term consequences of fetal and neonatal vitamin D deficiency. The lack of evidence so far has led to contradictory recommendations on vitamin D supplementation during pregnancy in many countries. In the Netherlands the Health Council advises that pregnant women at risk should receive vitamin D supplements; however, this is not common practice.[12 23–27]

In conclusion, we found a high prevalence of vitamin D deficiency in newborn infants of mothers at risk. The higher mean alkaline phosphatase levels found in the newborn children of these women might reflect an effect on bone mass. Further research, preferably by randomised controlled trials, is needed not only to establish the effects of vitamin D supplementation during pregnancy, but also the long-term consequences of neonatal vitamin D deficiency for long bone growth and health. The results of such trials would enable clear-cut guidelines on vitamin D supplementation to be issued.

What is already known on this topic

- 25-Hydroxyvitamin D_3 values in the mother's blood and cord blood are strongly correlated.
- High prevalence rates of vitamin D deficiency in dark skinned and veiled pregnant women have been described in countries at the same latitude as the Netherlands.

What this study adds

- High prevalence rates of vitamin D deficiency are found in newborn infants of dark skinned or veiled mothers from a Northern European population.
- Newborn infants of mothers at risk of vitamin D deficiency showed higher mean alkaline phosphatase concentrations than controls, which suggests increased bone turnover. However, as values were still within the normal range, this finding may not be clinically relevant.

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