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Umbilical cord serum 25-hydroxyvitamin D concentrations and relation to birthweight, head circumference and infant length at age 14 days

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Abstract

Background: Insufficient supply of vitamin D during early development may negatively affect offspring growth.

Methods: We examined the association between umbilical cord (UC) serum 25-hydroxyvitamin D (25(OH)D) concentrations and infant size in a study of two Faroese birth cohorts of 1,038 singleton infants. In the third trimester, the pregnant women completed questionnaires, and clinical examination included birthweight, head circumference, and infant length at age 14 days.

Results: Fifty-three percent of the newborn population had UC 25(OH)D < 25 nmol/L as determined by LC-MS/MS. Using multiple linear regression models with adjustment for pre-pregnancy BMI, sex, parity, gestational age or infant age at examination, season of birth, smoking, gestational diabetes, examiner, and cohort identity, we found no relationship between birthweight or head circumference and UC 25(OH)D. However, infants with vitamin D status < 12 nmol/L had a 0.49 (95% CI, -0.85 – -0.12) cm lower length than infants with vitamin D status > 50 nmol/L in models further adjusted for birthweight.

Conclusion: Our data suggest that umbilical cord serum 25(OH)D concentrations are positively associated with infant length but not with birthweight and head circumference. Although the pediatric relevance of the observed association is unclear, the possible long-term consequences of late-pregnancy hypovitaminosis D deserve attention.

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Keywords

umbilical cord serum 25(OH)D; prenatal vitamin D exposure; birthweight; infant length

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Introduction

Vitamin D insufficiency is prevalent among pregnant women^{1, 2} and has been related to adverse maternal outcomes such as increased risk of bacterial vaginosis, gestational diabetes, and pre-eclampsia.¹ The most active vitamin D metabolite, i.e. 1,25 dihydroxyvitamin D, is important for calcium homeostasis, and, as the fetus is entirely dependent on maternal vitamin D for its own 1,25 dihydroxy vitamin D production³, maternal vitamin D insufficiency may also influence intrauterine growth and skeletal development. Birthweight is often used as a routine marker of intrauterine growth. However, observational studies looking at the association between the 25(OH)D concentration and infant growth parameters reported inconsistent results for birthweight.¹ The failure to obtain a clear association with fetal development could be in part that the timing of maternal blood sampling is crucial. For instance, dual-energy X-ray absorptiometry has documented that fetal calcium accumulation increases substantially only during the third trimester.⁴ In addition, small sample size and narrow vitamin D ranges may have led to non-informative results in some past studies.

While vitamin D deficiency is known to be prevalent among malnourished populations and dark-skinned or veiled women, women residing at northern latitudes are also at risk.² Hence, the present study focuses on a comparatively large number of deliveries within the Faroese population (62° north). Due to the low cutaneous vitamin D synthesis and the possible increased dietary intake of vitamin D from marine food, this population represents a fairly wide range of 25(OH)D concentrations.⁵ We examined the relationship between the umbilical cord 25(OH)D concentration as a marker of maternal vitamin D status during the third trimester and fetal growth, as indicated by birthweight and head circumference, as well as infant length at age 14 days in healthy, term-born infants.

Materials and Methods

Information was obtained from two Faroese population-based birth cohorts formed from consecutive births during 1997–2000 (Cohort 3) and 2007–2009 (Cohort 5). In birth cohort 3, 656 pregnant women were recruited in gestational week 34–35, and a maternal blood sample was drawn at this time point and cord blood samples at the time of birth. The second birth cohort 5 initiated seven years later was comprised of 490 women who gave informed written consent and had cord blood samples drawn at the time of birth and from the mother two weeks later at the routine pediatric examination. Only singleton births were included.

Before the pediatric examination at infant's age 14 days, the women in cohort 5 completed current health, past medical history and lifestyle questionnaires. For women in cohort 3, this information was obtained from the midwife's records. All women reported summary information on the frequency of marine food intake during pregnancy. Neither type nor portion size of fish was specified. Women were classified with gestational diabetes mellitus

according to clinical guidelines at the time. Gestational age and due date were determined by ultrasound examination at week 18 – 20. The women's pre-pregnancy body mass index was determined by self-reported weight (kilograms) divided by self-reported height (meters) squared. Birthweight (grams) and head circumference (cm) were measured immediately after birth by the midwife. Infant body length (cm) was measured at the pediatric examination approximately 14 days after birth (median infant age, 15 days [IQR: 10 – 21 d]). All of the women were of Caucasian descent. The study was approved by the Faroese Ethical Review Committee and the U.S. institutional review board at Harvard School of Public Health.

Measurement of 25-hydroxy vitamin D concentration

For 1,038 infants (Cohort 3, n=574; Cohort 5, n=464), sufficient umbilical cord (UC) serum was available for determination of vitamin D status.⁶ Following storage at -80°C , UC serum 25(OH)D₂ and 25(OH)D₃ concentrations were assessed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described.² Triple deuterium marked 25(OH)vitamin D₃ was added to serum samples as internal standard and deproteinized with ZnSO₄ in methanol, centrifuged at 4000 rpm for 10 minutes, and 100 μl was injected on the TurboFlow column (Thermo Scientific) on the LC-MS/MS. The LC-MS/MS system consisted of a Thermo Scientific TLX1 system connected to a Thermo Scientific Vantage TSQ. 25(OH)D₂ and 25(OH)D₃ were concentrated on a Thermo Scientific Cyclone P 50 $\times$ 1.0 mm column and back-flushed on the analytical column, Phenomenex Gemini C18 50 $\times$ 3.0 mm and eluted from the analytical column by a gradient. Mobile phases were A: 10 mM NH₄Ac in water and B: 10 mM NH₄Ac in methanol. Human serum was spiked with appropriate amounts of 25(OH)D₂ and 25(OH)D₃ in order to produce six point calibration curves (weighed 1/x²) and 3 levels of QC samples (low, mid, high). The method was calibrated against NIST standard 972² and has been validated through participation in the EQA program.⁷ We report the sum of D₂ and D₃ as total vitamin D (i.e., 25(OH)D) concentration. The lower detection limit was 1.5 nmol/L and the coefficient of variation was < 10 % at 12.5 nmol/L. Values under LOD were imputed to LOD/sqrt2 for 32 samples.

To determine the association between mother-and-infant serum 25(OH)D concentrations, we selected randomly 21 births from cohort 3 among those who had paired blood samples available.

Measurements of PCB and PFOS

Previous studies have demonstrated that environmental chemicals may impact intrauterine growth and we therefore chose to take the maternal level of these into account. Some of these compounds were measured in the maternal serum samples as previously described. Briefly, serum obtained from the mothers was analyzed for polychlorinated biphenyls (PCB's) congeners and a simplified sum (ΣPCB) was calculated from the three persistent congeners that occur in serum at the highest concentrations (PCB138 + PCB156 + PCB180), multiplied by 2 as they make up about 50% of the total PCB in serum. Separation of the congeners and quantitation was performed by gas chromatography using a dual capillary column system with micro-electron capture detection, and the results were adjusted for the total lipid concentration in serum.⁸ Serum concentrations of perfluorooctane sulfonic acid

(PFOS) were determined as the most important perfluorinated alkylate compound using solid-phase extraction and quantification using a gas chromatographic method with a dual column system and electron capture detection.⁹

Statistical analyses

Descriptive statistics are presented as means and standard deviations (SD) for variables showing normal distribution, and medians and quartiles for those deviating from it.

UC 25(OH)D concentrations have not been characterized according to deficiency status, so we chose to use the categories for children and adults, hence categorize vitamin D status at < 12 nmol/L, 12–<25 nmol/L, 25–<50 nmol/L, and ≥ 50 nmol/L according to Danish Health and Medicines Authority recommendations¹⁰ and existing literature.¹¹ Both the categorical vitamin D status and the continuous 25(OH)D concentration were used as exposure variables. For outcomes, three measures of infant size were applied: birthweight, head circumference, and length at 14 days.

To test for differences in baseline characteristics between categories of vitamin D status, ANOVA was used for continuous variables and chi-square-test for categorical variables. The association between vitamin D concentrations, transformed by natural logarithm to approach a normal distribution of the residuals or vitamin D status, and growth parameters were modeled using covariate-adjusted linear regression analyses. The covariates were chosen *a priori* based on previous knowledge including pre-pregnancy BMI, sex, parity, gestational age (birthweight and head circumference) or infant age at examination (chronological age in days corrected for expected date of delivery; length), season (summer: June, July, August; autumn: September, October, November; winter: December, January, February; spring: March, April, May), smoking, gestational diabetes, and examiner. The same set of covariates was used for all analyses except for the regression model of length at day 14, where we further adjusted for birthweight. Finally, we adjusted all models for cohort identity.

Although marine food, i.e. fish and pilot whale meat and blubber, our previous study had shown no association with the 25(OH)D concentration in elderly Faroese.⁵ However, we adjusted for marine food intake in sensitivity analyses as these foods contain both nutrients and contaminants that may influence pre- and perinatal growth in opposite directions.¹² For instance, the Faroese population is highly exposed to PCBs¹³ that may have endocrine disrupting effects and disturb prenatal growth¹² as well as postnatal growth in breastfed infants. Also, perfluorinated compounds, such as perfluorooctane sulfonic acid (PFOS), may also cause endocrine disruption and influence prenatal growth.¹⁴ Therefore, we adjusted maternal serum concentrations for these pollutants in additional sub-analyses.

Model assumptions were tested by visual inspection of residual plots, and collinearity was tested by calculation of the variance inflation factor. A value of $P < 0.05$ (two-tailed) was taken to indicate statistical significance; p-values were not adjusted for multiple comparisons.¹⁵ Stata version 13.1 (Stata Corporation, Texas, USA) was used for statistical analyses.

Results

A total of 1,038 mother-infant pairs had available information on all covariates, vitamin D determination and birthweight. However, a few measures were missing for length and head circumference, thus $n=1,033$ for length and $n=1,032$ for head circumference. Maternal and infant characteristics are given in Table 1. The 25(OH)D concentrations in cohort 3 (geometric mean 21.7, 95%CI: 20.3 – 23.2) were higher than in the more recent cohort 5 (geometric mean 17.6, 95%CI: 15.9 – 19.6) ($p<0.0006$). For 21 mother-infant pairs from cohort 3, the ratio between the newborn and late pregnancy maternal 25(OH)D concentration (gestational week 34–35) was found to average 0.67 (interquartile range, 0.56 – 0.84), with a correlation of $r_p=0.89$ ($p<0.0001$).

A total of 53 percent of the newborns had 25(OH)D < 25 nmol/L. These newborns were on average more likely to have older siblings and mothers with a higher pre-pregnancy body mass index. Also, maternal smoking during pregnancy was associated with dose-dependent decreases in newborn 25(OH)D concentrations ($p_{trend}<0.0001$). Finally, infants from mothers with gestational diabetes were more likely to have 25(OH)D<25 nmol/L as compared with infants from non-diabetic mothers ($X^2=9.0855$, $p=0.003$). As expected, 25(OH)D cord blood concentration varied by season of birth and was significantly higher in summer (June – August) than the other seasons ($p<0.01$).

In multiple regression analyses, all measures of growth were adjusted for potential confounders, i.e., pre-pregnancy BMI, sex, parity, gestational age or age at examination, season, smoking, gestational diabetes, examiner, and cohort identity. Neither categories of vitamin D status nor the continuous cord serum 25(OH)D concentration was associated with birthweight or head circumference (Table 3). Infant length at age 14 days was positively associated with vitamin D status as categories as well as the continuous 25(OH)D concentrations (Table 3).

During pregnancy, more than 50 % of the women were eating fish for dinner at least twice a week (information from $N=733$), about 25 % ate pilot whale meat more than once (information from $N=740$), and 10% ate pilot whale blubber at least twice per month (information from $N=735$). The frequency of pilot whale meat and blubber consumption was lower in Cohort 5 than Cohort 3. However, adjustment for marine intake only marginally changed the beta estimates for the association between vitamin D concentration and growth (results not shown). In the sub-groups with information available about maternal serum concentrations of the environmental chemicals PCB ($n=878$) and PFOS ($n=1,004$), again the associations were between vitamin D concentration and growth unaffected after further adjustment for these compounds (results not shown).

Comment

Prevention of maternal vitamin D deficiency during pregnancy remains an important public health goal because of the relatively high prevalence¹⁶, the potential adverse effects for mother and child and it being easy treatable. In this fairly large cross-sectional study of two combined Faroese birth cohorts of singletons with more than 50% newborns with a vitamin

D status < 25 nmol/L, linear growth seemed affected by late-pregnancy vitamin D status, as indicated by the association between UC serum 25(OH)D concentrations and length at 2 weeks of age. Birthweight or head circumference did not show any association with vitamin D status.

While there is no convincing evidence from clinical trials that increasing maternal 25(OH)D concentration increases birthweight, birth length or head circumference¹⁷, a recent meta-analyses of observational studies support a positive relationship between 25(OH)D concentration and fetal growth parameters.¹ Also, a more recent large observational US study demonstrated that low serum vitamin D status (<37.5 nmol/L) at gestational week 26 was associated with a 46 g lower birthweight average and a 0.13 cm lower mean head circumference in comparison with serum concentrations above 37.5 nmol/L.¹⁸ Also a large Australian study suggested that maternal vitamin D status <25nmol/L in the first trimester increased the risk of having an infant diagnosed with SGA, although the authors suggested that this result could be a chance finding.¹⁹ However, all these studies relied upon maternal 25(OH)D concentrations measured from samples drawn in the first or second trimester, thus perhaps explaining the results deviating from ours regarding birthweight and head circumference, as we measured 25(OH)D in cord serum as a reflection of the vitamin D status during late gestation. As a further consideration, the relatively high birthweight in the Faroese birth cohorts (average birthweight, 3,729 grams), possibly linked to the high intake of polyunsaturated fatty acids from seafood²⁰, may obscure the potential influence of a low vitamin D status on birthweight.

As supported by previous observational studies^{21–24}, though not all^{25, 26}, we observed that the infant length was positively associated with the 25(OH)D concentration. Although we did not observe serious manifestations on growth indices even at these low vitamin D levels, the small effect of very low 25(OH)D concentrations could be explained by the fact that the fetal-placental calcium homeostasis may be relatively independent of maternal vitamin D status^{27, 28}. More than 80% of the calcium required for fetal growth and skeleton mineralization is transferred in the last trimester²⁹, and these needs may be met by a vitamin D-receptor independent up-regulation of maternal intestinal calcium absorption²⁷. Thus, the fetus may have some buffering capacity for maintaining the calcium homeostatic balance even at very low maternal vitamin D concentration, as long as the maternal calcium intake is adequate. Furthermore, infant length may not be the most relevant marker for the effects of vitamin D deficiency on fetal growth and bone mineralization as other studies have observed stronger association between low maternal vitamin D concentrations and newborn tibia mineral content and area, but not bone mineral density^{24, 29}.

Traditionally, the Faroese population has consumed a significant amount of marine food, including pilot whale, which contains nutrients, including vitamin D, as well as contaminants that may influence birthweight. A recent review on 12 European birth cohorts which includes a Faroese birth cohort demonstrated a reduced birthweight by exposure to PCBs¹². On the other hand, it has been suggested that fatty fish and marine mammals may increase gestation length and therefore also birthweight due to their high content of *n-3* polyunsaturated fatty acids^{20, 30}. In the present study, adjustment for these variables did not affect the results.

We measured cord blood 25(OH)D as a measure of fetal 25(OH)D exposure in late gestation, and we used the recommended cut-off points for deficiency classification.¹¹ However, our own results suggest that maternal concentrations of vitamin D in late pregnancy are higher than in cord blood. Other studies also found that third-trimester maternal concentrations are higher than cord concentrations^{31–34} while others have found the opposite, i.e. higher concentrations in the cord blood than in maternal blood^{35, 36}. Hence, it could be questioned whether the same cut-off points should be used for newborns as for infants, children and adults. IOM and most other recommendations, including the Danish, are not specific in this regard. However, even if we used our cord-maternal ratio of 0.67 to recalculate the cut-off points or the predicted maternal concentrations, we still find an association between 25(OH)D and length at age 14 days. The estimates changed only marginally but, of course, the adjusted prevalence of severe deficiency (i.e., 25(OH)D<25nmol/L) decreased (from 53% to 32% < 25 nmol/L).

The present study has important strengths in that the cohorts are population based and had a very high participation rate, thus likely being representative for Faroese births. Furthermore, the vitamin D exposure range was wide and included a high prevalence of newborns with vitamin D concentrations lower than 25 nmol/L. Still, the observational cross-sectional nature of the study design prevents us from causal inferences. Although low vitamin D status in late pregnancy is likely associated with a low vitamin D concentration earlier in pregnancy,²⁹ we cannot rule out reverse causality, i.e., the possibility that fetal growth may influence maternal and consequently infant vitamin D status.³⁷ Additionally, though we adjusted for several known confounders, we cannot entirely exclude residual confounding. Lastly, although the measure of 25(OH)D is suggested to be the best available marker of vitamin D status, it may not be the best biomarker examining the physiological effect of vitamin D. For instance, several recent studies demonstrate that it is the concentrations of free and bioavailable 25(OH)D that is of biological importance. Their concentrations are affected by the vitamin D binding protein, the amount of which is dependent on a common genetic polymorphism.³⁸ Also other common gene variants are associated with 25(OH)D concentrations in Caucasians.³⁹ Our study did not measure free 25(OH)D or these potentially relevant genotypes.

In the present study we observed an approximately ½ centimeter longer length in infants with vitamin D concentrations>50 nmol compared with infants with vitamin D concentrations < 12 nmol/L at age 14 days. Although this difference is statistically significant, it may be of doubtful clinical relevance. However, these differences may track into adulthood where lower height is associated with adverse health, including cardiovascular disease.⁴⁰ Furthermore, we observed a very high prevalence of newborns with vitamin D concentrations below 25 nmol/L. This may be a significant public health concern, as low vitamin D status at birth may have adverse health consequences, including increased risk of rickets or osteomalacia, but also non-skeletal health outcomes later in life,⁴¹ especially if it persists into the perinatal period. The current findings therefore underscore the importance of increased focus on vitamin D in ante- and perinatal care, also in populations with an anticipated high intake of vitamin D from marine food.

In conclusion, this study supports the hypothesis that low prenatal vitamin D status contributes to a diminished intrauterine linear growth, such that higher cord 25(OH)D concentration, as an indicator of last trimester maternal vitamin D status, is associated with greater infant body length. The clinical relevance is uncertain, and long-term follow-up studies are needed to elucidate the impact on infant growth and development associated with a high prevalence of late-pregnancy vitamin D deficiency.

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Table 1

Information from questionnaires and examinations in 1,038 mother-child pairs among two Faroese birth cohorts according to vitamin D categories^a

	Total (n=1,038)	25(OH)D 12 nmol/L (n=222)	25(OH)D >12-25 nmol/L (n=328)	25(OH)D >25-50 nmol/L (n=376)	25(OH)D > 50 nmol/L (n=112)	P-value ^b
<i>Maternal characteristics^c</i>						
Age, y	29.5 (5.4)	29.4 (5.6)	30.0 (5.5)	29.4 (5.3)	28.7 (4.9)	0.112
Height, m	165.7 (5.8)	165.3 (6.3)	165.7 (5.9)	165.8 (5.5)	165.8 (5.5)	0.788
Pre-pregnancy BMI, kg/m ²	24.0 (4.2)	25.0 (5.1)	24.4 (4.3)	23.5 (3.5)	22.8 (3.3)	<0.001
Smoking, % (n)						<0.001
No smoking	77.8 (808)	19.2 (155)	32.2 (260)	38.2 (309)	10.4 (84)	
1-10 cig/day	17.1 (177)	28.8 (51)	24.3 (43)	32.8 (58)	14.1 (25)	
>10 cig/day	5.1 (53)	30.2 (16)	47.2 (25)	17.0 (9)	5.7 (3)	
Parity, % (n)						0.025
0	28 (291)	15.8 (46)	30.9 (90)	40.9 (119)	12.4 (36)	
1	72 (747)	23.6 (176)	31.9 (238)	34.4 (257)	10.2 (76)	
Gestational Diabetes, % (n)	5.3 (55)	27.3 (15)	45.5 (25)	20.0 (11)	7.3 (4)	0.027
<i>Infant Characteristics</i>						
Gestational age, days	277.8 (9.6)	278.0 (9.4)	277.4 (9.4)	278.6 (9.6)	276.3 (9.9)	0.126
Gender, % (n)						0.642
Boys	52.1 (541)	22.7 (123)	30.7 (166)	36.4 (197)	10.2 (55)	
Girls	47.9 (497)	19.9 (99)	32.6 (162)	36.0 (179)	11.5 (57)	

^aUmbilical cord serum 25 hydroxy vitamin D was categorized according to the recommendations by the Danish Health and Medicines Authority¹⁰ and others.¹¹

^bAnova or Chi² whenever appropriate.

^cAll numeric data are mean (SD).

Table 2

Growth parameters among Faroese infants according to categories of umbilical cord serum 25-hydroxy vitamin D^a

Vitamin D status	No. of subjects (%)	Birthweight, gram ^b (n=1,038)	Length at 2 week, cm ^{2b} (n=1,033)	Head circumference, cm ^{2b} (n=1,032)
25(OH)D nmol/L				
>50	112 (10.8)	3682 (475)	55.2 (2.0)	36.8 (1.3)
25-50	376 (36.2)	3734 (519)	55.2 (2.7)	36.9 (1.4)
12-25	328 (31.6)	3730 (479)	54.9 (2.1)	36.9 (1.4)
< 12	222 (21.4)	3746 (514)	55.0 (2.4)	36.7 (1.4)
<i>p-trend</i>		0.5741	0.3353	0.6825

^a Umbilical cord serum 25 hydroxy vitamin D (25(OH)D) was categorized according to the recommendations by the Danish Health and Medicines Authority¹⁰ and others.¹¹

^b All numeric data are mean (SD).

Table 3 Adjusted difference between indicators of infant growth and vitamin D categories^a

Vitamin D status	Birthweight, gram ^b		Length at 2 week, cm ^c		Head circumference, cm ^b	
	beta	95% CI	beta	95% CI	beta	95% CI
25(OH)D mmol/L						
>50		Reference		Reference		Reference
25-50	-26.0	-117.5 – 65.4	-0.20	-0.53 – 0.13	0.12	-2.60 – 2.85
12-25	-21.4	-115.7 – 72.8	-0.41	-0.75 – -0.07	-0.45	-3.26 – 2.36
<12	-29.8	-130.3 – 70.6	-0.49	-0.85 – -0.12	-1.53	-4.53 – 1.47
<i>p-trend</i>		0.686		< 0.003		0.177
continuous	0.41	-1.1 – 1.9	0.008	0.002 – 0.013	0.01	-0.03 – 0.06

^aUnbilical cord serum 25 hydroxy vitamin D (25(OH)D) was categorized according to the recommendations by the Danish Health and Medicines Authority¹⁰ and others.¹¹^bAdjusted for maternal pre-pregnancy BMI, sex, parity, gestational age, season, smoking, gestational diabetes, examiner, and cohort identity.^cAdjusted for all the above but gestational age exchanged for age at examination plus birthweight.