Maternal Vitamin D Status Determines Bone Variables in the Newborn

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Context: Vitamin D regulates 3% of the human genome, including effects on bone health throughout life. Maternal vitamin D status may program neonatal skeletal development. The objective here was to determine the association of mothers' vitamin D status with bone variables of their newborns.

Subjects and Methods: In a birth hospital, pregnant women (n = 125) participated in a cross-sectional study with a longitudinal follow-up of the pregnancy. The mean (SD) values for age, body mass index before pregnancy, pregnancy weight gain, and total vitamin D intake in mothers were 31 (4) yr, 23.5 (3.7) kg/m^2, 13.1 (4.3) kg, and 14.3 (5.8) μg, respectively. All newborns were full-term, 99% were appropriate for gestational age, and 53% were boys. Blood samples were collected from mothers during the first trimester and 2 d postpartum and from umbilical cords at birth for analysis of serum 25-hydroxyvitamin D (S-25-OHD), PTH, and bone remodeling markers. Bone variables were measured by pQCT at the 20% site of the newborn tibia on an average of 10 (11) d postpartum. Bone contour was analyzed with a single threshold of 180 mg/mm^3 for the detection of total bone mineral density (BMD), bone mineral content (BMC), and cross-sectional area (CSA).

Results: Mean S-25-OHD was 41.0 (13.6), 45.1 (11.9), and 50.7 (14.9) nmol/liter during the first trimester, postpartum, and in the umbilical cord, respectively. The median value of the individual means for first trimester and the 2-d postpartum S-25-OHD was 42.6 nmol/liter, which was used as cutoff to define two equal-sized groups. Groups are called below median and above median in the text. Newborns below median were heavier ($P = 0.05$), and 60% were boys. Tibia bone mineral content was 0.047 (95% confidence interval, 0.011–0.082) g/cm higher ($P = 0.01$), and cross-sectional area was 12.3 (95% confidence interval, 2.0–22.6) mm^2 larger ($P = 0.02$), but no difference in bone mineral density was observed, above median compared with below median group. These results were adjusted for newborn Z-score birth weight, maternal height, and newborn age at the measurement. A positive, significant correlation was observed between remodeling markers in mothers at different time points and above median group in the cord.

Conclusions: Although the mean total intake of vitamin D among mothers met current Nordic recommendations, 71% of women and 15% of newborns were vitamin D deficient during the pregnancy. Our results suggest that maternal vitamin D status affects bone mineral accrual during the intrauterine period and influences bone size. More efforts should be made to revise current nutrition recommendations for pregnant women that may have permanent effects on the well-being of children. **(*J Clin Endocrinol Metab* 95: 1749–1757, 2010)**

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Abbreviations: BALP, Bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; CSA, cross-sectional area; CV, coefficient of variation; FFQ, food frequency questionnaire; 25-OHD, 25-hydroxyvitamin D; pQCT, peripheral quantitative computed tomography; S-, serum; TRACP, active isoform 5b of the tartrate-resistant acid phosphatase.

As a result of effective vitamin D supplementation from the age of 2 wk to 3 yr, symptomatic childhood rickets is nowadays rare in Finland (1). On the other hand, asymptomatic vitamin D insufficiency is common in all age groups, including adolescent girls (2, 3) and young adults at childbearing age (4, 5). However, especially critical periods for an individual's development are the intrauterine and neonatal periods (6). Previous studies have shown that maternal vitamin D status, defined by serum 25-hydroxyvitamin D (S-25-OHD) concentration, tightly associates with cord blood vitamin D concentration (*e.g.* Refs. 1, 7, and 8). Vitamin D deficiency in fetal life may have permanent effects on body physiology and metabolism (9, 10). Besides skeletal effects, early life vitamin D deficiency may increase risk for type 1 diabetes (11), asthma, and rhinitis (12). In addition, vitamin D deficiency during pregnancy is also associated with preeclampsia (13, 14) and gestational diabetes (15).

Maternal vitamin D status during pregnancy may program skeletal development (10) and body composition in the offspring (16) by influencing the interaction between osteoblasts and adipocytes. Low maternal S-25-OHD is associated with shorter duration of gestation and, consequently, reduced growth of long bones in newborns (17). In vitamin D-deficient mothers, maternal PTH is elevated, probably due to increased mineral demands of larger babies (17). Children of mothers with low vitamin D status during late pregnancy had reduced whole-body bone mineral content (BMC), bone area, and areal bone mineral density (BMD) at the age of 9 yr (18). This suggests that vitamin D has an influence on skeletal programming and the tracking of bone mass lasts throughout childhood. Furthermore, birth weight and growth during the first year of life may contribute to skeletal fragility later in life (19–21).

Namgung *et al.* (22) showed that seasonal variation accounted for 8% of the variation in newborn whole-body BMC in Korea, but not in the United States. Vitamin D is proposed to be the limiting factor of bone mineral accrual in adolescence (23–25) and is also related to muscle mass attainment (24, 26, 27). However, among preterm children, vitamin D did not increase bone mineral accrual in a dose-dependent manner (28). During the fetal period, other hormones, such as PTH-related protein, prolactin, or placental lactogen, may contribute to enhanced calcium metabolism (29).

Finnish people living at northern latitudes are at increased risk of vitamin D insufficiency. Although national fortification of liquid milk products and spreads has improved the situation somewhat (30), women of fertile age remain a concern. Maternal health and nutritional status may have permanent effects on newborn health (9). The Finnish healthcare system provides a unique opportunity to follow pregnancy, fetal growth, and the neonatal period. The objectives of this study were to determine whether maternal vitamin D status is associated with skeletal variables and bone remodeling markers in newborns in a cross-sectional setting that includes longitudinal data obtained during pregnancy.

Subjects and Methods

Families (n = 125) were recruited to this semi-cross-sectional study during the last trimester between October and December 2007 at a prelabor visit to the birth hospital. Only primiparous mothers who were healthy, nonsmoking, aged between 20 and 40 yr, of Caucasian origin, and had an uneventful, singleton, full-term pregnancy (37–42 wk) were included. The study protocol was approved by the Ethics Committees of the Hospital Districts of Helsinki and Uusimaa. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Initial power calculation was based on newborn whole-body BMC, which was reported 8% higher in Korean newborns born in summer compared with winter (22). To detect an 8% difference in whole-body BMC with SD = 0.024 g/cm^2 (31), assuming 90% power with $\alpha = 0.05$, a sample size of 60 was calculated to be adequate. However, in our study, dual-energy x-ray absorptiometry measurements were replaced by peripheral quantitative computed tomography (pQCT), and instead of season we divided the groups by 25-OHD concentration. A retrospective power analysis (assuming 90% power, at the significance level 0.05) confirmed that a sample size of 34 for a group is adequate to detect a clinically significant difference in BMC and cross-sectional area (CSA) in this study.

The pregnancies had initiated in winter between early January and mid-March 2007. First-trimester samples were collected in communal prenatal clinics during the first visit between the 8th and 10th gestational weeks as part of normal follow-up. A second, fasting blood sample from the mother was collected 2 d postpartum during the hospital stay between late October and mid-December 2007. At birth, cord blood (20 ml) was obtained from the umbilical vein after cord clamping for further analysis.

At the time of recruitment at 35 wk, the participants received an extensive questionnaire about their medical history, sunshine exposure, and other lifestyle factors, including use of supplements and physical activity. The questionnaire included a food frequency questionnaire (FFQ) to calculate intake of vitamin D and calcium. The questionnaires were returned before labor and checked by one of the researchers. Records on pregnancy follow-up and the birth report, including birth weight, length, head circumference measured by midwives, and duration of the pregnancy, were obtained. Birth lengths and weights were transformed into Z-scores by using Finnish sex-specific normative data for fetal growth (32). One newborn and her mother were excluded from the initial analysis due to intrauterine growth retardation.

The newborn bone variables were measured with pQCT during the hospital stay.

Laboratory measurements

S-25-OHD was measured with an OCTEIA immunoenzymometric assay (IDS, Boldon, UK). The intraassay coefficient of

variation (CV) was less than 2%. All samples of the mother-newborn pair were measured in the same series to avoid interassay variation (7.9%). Reproducibility was ensured by adhering to the Vitamin D External Quality Assessment Scheme (DEQAS). Standardized concentrations of S-25-OHD are used in the analysis. Vitamin D status in mothers was defined as deficient when S-25-OHD was below 50 nmol/liter, insufficient when it was between 51 and 74 nmol/liter, and sufficient when it was above 75 nmol/liter, according to reference values for an adult population (33, 34). Maternal vitamin D status was determined by the mean value of the first-trimester and postpartum samples.

Serum intact PTH was measured from all samples, but only the postpartum sample was an overnight fasting sample and it was drawn between 0700 and 0900 h. We used an Immulite 1000 automated immunoassay for the detection of serum intact PTH (Siemens Healthcare Diagnostics, Malvern, PA), with intra- and interassay CVs of 4.2 and 7.4%, respectively.

Serum bone-specific alkaline phosphatase (S-BALP) was assayed with an OCTEIA Octase BAP immunoenzymometric assay (IDS) to describe bone formation. Intra- and interassay CVs were 2.0 and 3.0%, respectively. Bone resorption marker, serum active isoform 5b of the tartrate-resistant acid phosphatase (S-TRACP), was determined with a bone TRAP assay (SBA Sciences, Turku, Finland). Intra- and interassay CVs were 2.1 and 3.1%, respectively.

pQCT bone measurement

Peripheral bone variables were determined by pQCT from the left tibia of the newborn infants. One 2.5-mm slice (voxel size, 0.4 mm), at the 20% site, was measured distally from the tibia with a XCT-2000 scanner (Stratec, Pforzheim, Germany). The 20% site was located without scout view. The length of the tibia was defined as the distance between the upper margin of the medial condyle and medial malleolus. The 20% site was marked with a color line to help in the detection of the site.

To stabilize the position of the leg during measurement, footwear was fixed to a holder with a firm Velcro fastening. The researcher supported the horizontal position of the leg during the measurement.

Data were analyzed using version 5.50 of the manufacturer's software package in which the bone contour was analyzed with a single threshold of 180 mg/mm^3 for the detection of total BMD, BMC, and CSA.

The long-term CVs for the phantom BMD and CSA were 1.9 and 1.1, 2.7 and 0.79, and 0.50 and 0.78% in the total, cortical, and trabecular bone. respectively. Short-term precision (CV%) was determined with duplicate measurements of eight subjects. CVs for the total bone BMD, BMC, and CSA were 4.4, 4.1, and 6.2%, respectively. Based on this, we calculated least significant change for total bone BMD, BMC, and CSA to be 13.2, 12.3, and 18.6%, respectively.

Dietary assessment

Dietary vitamin D and calcium intakes were calculated using an FFQ, which is a validated semiquantitative questionnaire covering over 70 foods (2). The nutrient contents of the foods were calculated using the Finnish National Food Composition Database, Fineli, version 2001, which is maintained by the National Public Health Institute of Finland, Nutrition Unit. Total intake

TABLE 1. Baseline characteristics of mothers and newborns below and above median of S-25-OHD

	Below median	Above median	Significance
Mothers			
n	49	49	
Age (yr)	30.1 (3.9)	30.9 (4.0)	0.351
BMI before pregnancy (kg/m^2)	24.1 (4.2)	22.6 (2.6)	0.150[a]
Height (cm)	167.6 (5.2)	168.0 (6.0)	0.766
Weight gain during pregnancy (kg)	14.0 (4.6)	12.8 (3.7)	0.176
Dietary intake of calcium (mg/d)	1780 (520)	1760 (700)	0.882
Total intake of vitamin D (μg/d)	13.7 (5.2)	15.0 (6.2)	0.280
Physical activity (min/d)	76 (63)	62 (79)	0.387
Parental BMI (kg/m^2)	26.5 (3.3)	25.4 (2.9)	0.113
Mean 25-OHD (nmol/liter)	35.6 (4.9)	54.4 (9.1)	$<$0.001[a]
Postpartum PTH (pmol/liter)	4.16 (2.25)	2.69 (1.17)	$<$0.001[a]
Newborns			
Boys (%)	59.6	46.8	0.144[b]
Gestational age (d)	285 (9)	283 (8)	0.491
Cord 25-OHD (nmol/liter)	40.5 (8.6)	59.0 (12.0)	$<$0.001
Head circumference (cm)	35.7 (1.4)	35.5 (1.6)	0.511
Birth length (cm)	51.0 (1.9)	50.5 (1.8)	0.140
Z-score birth length	0.14 (1.0)	−0.20 (0.96)	0.104
Weight (g)	3700 (400)	3520 (440)	0.052
Z-score birth weight	0.12 (0.81)	−0.23 (1.09)	0.082
Age at measurement (d)	12.8 (12.3)	8.1 (9.4)	0.231[a]
Weight at measurement (g)	3920 (620)	3680 (560)	0.055
Tibia BMC (g/cm)	0.34 (0.08)	0.38 (0.08)	0.020
Tibia CSA (mm^2)	76.0 (19.5)	87.5 (33.6)	0.012
Tibia BMD (mg/cm^3)	459 (86)	447 (85)	0.519

Data are expressed as mean (SD). BMI, Body mass index.

[a] Mann-Whitney *U* test.

[b] Pearson χ^2.

TABLE 2. Distribution of vitamin D status at each time-point for maternal samples

S-25-OHD (nmol/liter)	Vitamin D status	First trimester	Postpartum[a]	Mean[b]
n		124	101	99
<50	Deficient	96 (77.4%)	61 (60.4%)	70 (70.7%)
51–74	Insufficient	25 (20.2%)	36 (35.6%)	27 (27.3%)
>75	Sufficient	3 (2.4%)	4 (4.0%)	2 (2.0%)
Mean (SD)		41.0 (13.6)	45.1 (11.9)	44.8 (11.9)
Range		9.6–82.1	18.0–87.2	17.8–76.9

[a] Vitamin D status improved from first trimester to postpartum (marginal homogeneity test; $P = 0.02$).

[b] Mean value of first trimester and postpartum 25-OHD concentrations.

of vitamin D among mothers during the last trimester included intake from supplements as well.

Statistical analyses

Statistical analyses were performed with SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL). Comparison of two groups was performed with independent samples *t* test; if variances were not equal, the Mann-Whitney *U* test was applied. Pearson and Spearman correlations were used to assess the association between variables. Repeated measures ANOVA was applied to follow the concentrations of S-25-OHD, S-BALP, and S-TRACP in first trimester, postpartum, and umbilical cord samples. Comparison of these time-points was performed with contrasts. Distribution of vitamin D status at each time-point for all samples was tested with marginal homogeneity test.

The S-25-OHD concentrations measured at different time-points were tested for determinants of newborn bone variables with partial correlations. The mean of first-trimester and 2-d postpartum values was chosen as the best determinant for newborn bone variables (data not shown). The median value of 42.6 was used as the cutoff to define two equal-sized groups with "below median" and "above median" maternal vitamin D status. Mean S-25-OHD concentrations in the groups were 35.6 (4.9) and 54.4 (9.1) nmol/liter, respectively. The association of newborn bone variables was tested with multivariate analysis in which birth weight Z-score, maternal height, and age at pQCT measurement were used as covariates.

Results are presented as mean (SD), unless otherwise indicated. Results were considered significant when $P < 0.05$; P values between 0.05 and 0.10 were considered trends.

Results

Vitamin D status

Characteristics of the 124 mothers and their newborns are shown separately for below median and above median in Table 1. The mothers' mean dietary vitamin D intake was 7.8 (3.3) μg, and the mean total vitamin D intake was 14.3 (5.8) μg; 80% used vitamin D-containing supplements with an average of 6.6 (4.8) μg of vitamin D. The mean S-25-OHD concentration during the first trimester was 41.0 (13.6) nmol/liter (n = 124). Vitamin D status improved during the pregnancy (Table 2), the mean increment being 5.6 (14.4) nmol/liter from the first trimester in January-March to the postpartum period in October-December (repeated measures ANOVA; $P < 0.001$). In the umbilical cord, mean S-25-OHD concentration was 50.7 (14.9) nmol/liter, which was 2.0 (7.5) nmol/liter ($P = 0.044$) higher than in the postpartum sample.

The total maternal intake of vitamin D correlated positively with S-25-OHD in both the postpartum (r = 0.363; $P < 0.001$) and umbilical cord (r = 0.340; $P = 0.003$) (Fig. 1) without adjusting for birth weight. Maternal postpartum PTH correlated inversely with S-25-OHD in both the postpartum (r = −0.283; $P = 0.006$) and umbilical cord samples (r = −0.315; $P = 0.006$). Mothers below median had on average 1.41 (SEM = 0.37) pmol/liter higher PTH than those above median (independent samples *t* test; $P < 0.001$).

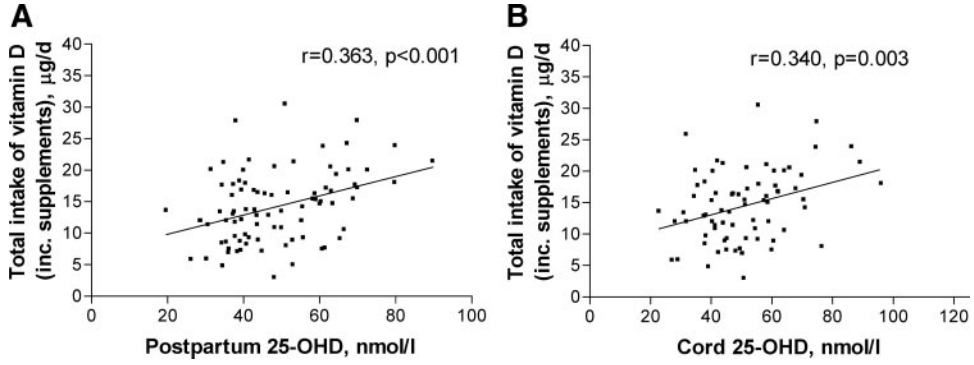

FIG. 1. Total maternal intake of vitamin D correlated positively with S-25-OHD concentration both postpartum (A) (r = 0.363; $P < 0.001$) and in the umbilical cord (B) (r = 0.340; $P = 0.003$).

TABLE 3. Partial correlations between 25-OHD and bone variables for crude values and after controlling for confounding factors

	Crude	Confounding factors		
	log [mean 25-OHD]	+Z-score birth weight	+Maternal height	+log [age of newborn at pQCT measurement]
Tibia BMC	0.149, $P = 0.163$	0.232, $P = 0.034$	0.230, $P = 0.036$	0.192, $P = 0.085$
log [tibia CSA]	0.197, $P = 0.05$	0.214, $P < 0.05$	0.218, $P = 0.048$	0.226, $P = 0.042$
BMD				

Newborn bone characteristics

Crude data showed a tendency for higher tibia BMD in newborn boys than in newborn girls (independent samples *t* test; $P = 0.06$), but no gender difference in BMC or CSA. Partial correlations between maternal S-25-OHD and newborn bone characteristics are shown in Table 3. For multivariate analysis, the newborns were divided into two groups based on maternal vitamin D status (below and above median). Newborns below median tended to be heavier ($P = 0.052$), and 60% were boys. However, crude values showed that the tibia BMC was 0.039 (95% confidence interval, 0.07–0.073) g/cm higher ($P = 0.025$) (Fig. 2A) and CSA was 10.7 (95% confidence interval, 2.6–20.4) mm^2 larger ($P = 0.023$) (Fig. 2B) in newborn above median than below median, whereas no difference was present in BMD (Fig. 2C). After adjusting for birth weight Z-score, differences between groups became more evident in BMC ($P = 0.003$) and CSA ($P = 0.021$), but remained insignificant in BMD.

Both bone formation (S-BALP) and bone resorption (S-TRACP) markers increased during pregnancy (Fig. 3), and the highest levels were measured in the umbilical cord. However, relative bone turnover indicated by the ratio of TRACP/BALP was lower in the umbilical cord than in the postpartum sample. Bone remodeling markers correlated with each other (r = 0.458, r = 0.605, and r = 0.334; $P < 0.01$ for all), in the first-trimester, postpartum, and umbilical cord samples, indicating normal coupling of bone formation and resorption. When testing correlations after stratification into below and above median groups, no correlation was observed in the below median group in the umbilical cord (Table 4). Moreover, no association existed between vitamin D status or PTH and bone remodeling markers, but maternal total intake of vitamin D correlated negatively with umbilical TRACP concentration (r = −0.249; $P < 0.05$).

Birth measurements and vitamin D status

The birth length and weight Z-scores did not correlate with first-trimester S-25-OHD, but an inverse correlation was observed with the postpartum S-25-OHD (r = −0.261, $P = 0.013$; and r = −0.193, $P = 0.068$, respectively). Similarly, the postpartum PTH correlated with the absolute birth length (r = 0.287; $P = 0.007$) and with the birth length Z-score (r = 0.281; $P = 0.008$). However, in multivariate analysis, after adjusting for parental size, maternal weight gain during pregnancy, solar exposure, total intake of vitamin D, and initial 25-OHD concentration, higher birth weight Z-score (but not higher birth length) was associated only weakly with decreased maternal S-25-OHD ($P = 0.07$) .

Discussion

To our knowledge, this is the first study to examine the effect of maternal vitamin D status on skeletal variables of the newborn. The results show that newborns whose mothers had mean 25-OHD concentration during pregnancy above the median (S-25-OHD at least 42.6 nmol/

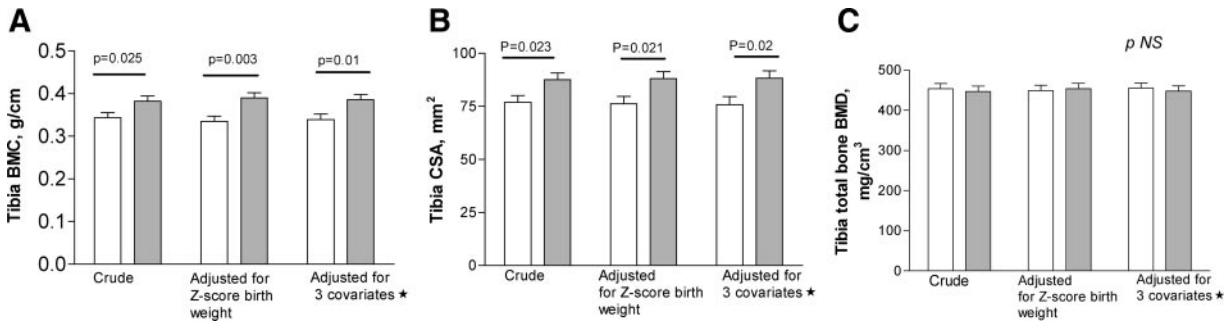

FIG. 2. Newborn BMC (A), CSA (B), but not BMD (C) differed between below median [= mean 25-OHD 35.6 (4.9) nmol/liter] (*white bars*) and above median [= mean 25-OHD 54.4(9.1) nmol/liter] (*dark bars*) of maternal vitamin D status. Results are shown for crude values (unadjusted), after adjustment for Z-score birth weight, and after adjustment for Z-score birth weight, maternal height, and age at pQCT measurement.

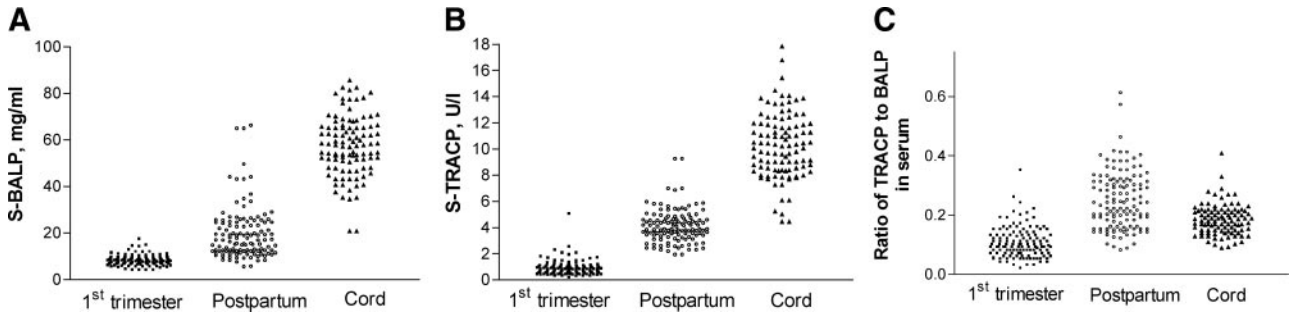

FIG. 3. Both bone formation (S-BALP) (A) and bone resorption (S-TRACP) (B) markers increased during pregnancy, and the highest levels were measured in the umbilical cord (repeated measures ANOVA; $P < 0.001$, for both). The ratio of TRACP/BALP (C) increased from first trimester to postpartum, but in the umbilical cord the ratio was lower than in the postpartum sample.

liter) had 13.9% higher tibial BMC and 16.3% higher CSA compared with those below median. However, tibia volumetric BMD did not differ between these groups. Our study supports the importance of vitamin D in fetal growth.

Dietary intake of vitamin D and sunshine exposure determine vitamin D status (2). The average maternal total intake of vitamin D was 14.3 μg, which is in line with current Nordic recommendations (35) for pregnant women (10 μg, or 400 IU). Of the mothers, 80% used vitamin D supplements, which are currently recommended for pregnant and lactating women during the winter (36). All supplements contained only D_3 which is favored in supplements in Finland. Despite the recommended dietary intake, most of the mothers were vitamin D deficient throughout the pregnancy. At the individual level, FFQ may overestimate actual intake of vitamin D somewhat, but at the group level the results are in accordance with 4-d food records. Together with repeated S-25-OHD measurements, the retrospective assessment of vitamin D intake adds to the value of this study (37). The total intake of vitamin D strongly correlated with S-25-OHD in postpartum and cord samples. The cord blood S-25-OHD was 103 (16)% of the maternal postpartum level, and a strong positive correlation existed between the two, in accordance with a review by Greer (8). In earlier Finnish studies, cord 25-OHD has been at least 20% lower than maternal 25-OHD concentration (7, 38), possibly due to differences in vitamin D status and the analytical methods used.

Based on umbilical cord 25-OHD concentration, 14.8% of newborns were categorized as having deficient (S-25-OHD <37.5 nmol/liter), 37.5% as insufficient (37.5 nmol/liter ≤ S-25-OHD < 50 nmol/liter), and 48.2% as sufficient (S-25-OHD >50 nmol/liter) vitamin D status when using pediatric reference values (39). Similarly, of the mothers, 71 and 27% had deficient and insufficient vitamin D status, respectively, during the pregnancy. We used a mean value of the first trimester and d-2 postpartum 25-OHD concentrations to describe the overall maternal vitamin D status. Vitamin D status here improved from first trimester to postpartum by an average of 6 nmol/liter, probably due to seasonal variation. The cumulative effect of 25-OHD on bone development is displayed by using the mean maternal value. As proposed by Namgung and Tsang (40), first-trimester 25-OHD is related to newborn bone variables, but the physiology of bone mineral accrual (17, 29, 41) supports focusing on postpartum 25-OHD.

Newborns of mothers above median had higher BMC and larger CSA in the tibia than newborns of mothers below median. The difference between the groups was significant and clinically relevant, based on least significant change. Our results are independent of birth weight, gender, maternal height, or age at measurement, and they suggest that maternal vitamin D status affects both bone mineral accrual and bone size during the intrauterine period. In previous studies, maternal vitamin D status has been linked to long bone growth in newborns (17), and seasonal variation has been shown to account for 8% difference in whole-body BMC in newborns in Korea, but not in the United States (22). However, animal models exploiting knockout mice (vitamin D receptor, 1-α hydroxylase) yield inconsistent results regarding the role of vitamin D in growth of the fetus or bone mineral accrual (29). In earlier studies, 25-OHD concentration during late pregnancy has been associated with whole-body and lumbar

TABLE 4. Correlation between TRACP and BALP at each time-point divided into below and above median groups

Sample	Below median [mean 25-OHD = 35.6 (4.9) nmol/liter]	Above median [mean 25-OHD = 54.4 (9.1) nmol/liter]
First trimester	r = 0.347* (n = 60)	r = 0.390** (n = 62)
Postpartum	r = 0.496** (n = 49)	r = 0.546** (n = 47)
Umbilical cord[a]	r = 0.155, ns (n = 36)	r = 0.501** (n = 38)

ns, Not significant. * $P < 0.05$; ** $P < 0.01$.

[a] Partial correlations after controlling for Z-score birth weight and length were r = 0.147, $P = 0.465$; and r = 0.544, $P < 0.001$, for below and above median groups, respectively.

spine BMC, bone age, and BMD at the age of 9 yr (18). Maternal vitamin D status during gestation is suggested to program skeletal development (10) and body composition in offspring (16). Tracking of bone mass occurs throughout life (18, 20, 42), emphasizing the importance of our results.

The highest levels of bone remodeling markers were measured in the cord sample, as also reported by others (7, 43, 44). Högler *et al.* (45) showed that the concentrations of bone remodeling markers (carboxy-terminal collagen crosslinks, osteocalcin, and BALP) in the cord at birth were similar to those in peripheral venous samples at d 2, proving that bone remodeling markers in the cord reflect bone turnover in neonates. We found that bone remodeling accelerated during pregnancy, but similar to findings of other studies (44, 46), maternal bone turnover was not associated with newborn bone turnover. The effect of growth *per se* on bone turnover is minimal in full-term neonates (46, 47). However, turnover time of the remodeling markers in the fetus and newborn may be altered, which may complicate the prediction of results. Maternal smoking (43) and winter season (22) increase resorption markers in cord blood.

Interestingly, maternal intake of vitamin D correlated inversely with TRACP in the cord. Vitamin D supplementation tends to decrease bone resorption in vitamin D-inadequate newborns (48) and adolescents (24). In otherwise healthy adults, vitamin D maintains coupled bone turnover, which is reflected in the significant positive correlation of bone formation and resorption markers (49, 50). The correlation is a robust model that does not take into account the time lag between resorption and formation. In the present study, we used cell-specific bone remodeling markers derived from active osteoblasts (BALP) and osteoclasts (TRACP). A coupled bone turnover was observed in mothers at different time points and above median group in the cord. In newborns whose mothers were below median of vitamin D status, bone turnover was not coupled in umbilical cord, suggesting altered bone turnover. Daily vitamin D supplementation (25–30 μg) during the last trimester to Indian immigrants in England resulted in a lower level of alkaline phosphatase in the umbilical cord relative to the placebo group (48).

A positive correlation was observed between maternal postpartum PTH and newborn Z-score birth length. Furthermore, the change in maternal vitamin D status during pregnancy and the infant's birth length and birth weight Z-scores correlated negatively, suggesting that mothers with larger babies had lower vitamin D status during the postpartum period than mothers with smaller babies. Brooke *et al.* (48) reported less small-for-gestational-age babies in the vitamin D-treated group compared with the placebo group. It is proposed that higher maternal PTH occurs due to increased mineral demands of bigger babies (17, 51). Thus, greater fetal growth may influence maternal vitamin D status, which is supported by findings of Holmes *et al.* (52). We observed that lower maternal vitamin D status was associated with a slightly higher birth weight Z-score ($P = 0.07$), but not length, after adjusting for confounding factors (parental size, maternal weight gain during pregnancy, solar exposure, total intake of vitamin D, and initial 25-OHD concentration). Our study was, however too small to allow any final conclusions to be drawn about whether fetal growth affects maternal vitamin D status.

Our findings indicate that more efforts should be directed toward correcting vitamin D status during pregnancy—first, to achieve full genetic growth potential of the offspring (9), and second, to maximize bone mineral accrual during the fetal period (41). Effective vitamin D supplementation of infants aged between 2 wk and 3 yr of age, which started in the 1940s, has overcome rickets in Finland. However, a discrepancy in vitamin D status between the intrauterine and early postnatal periods may still interfere with skeletal development (9).

Conclusions

Although total intake of vitamin D among mothers met current Nordic recommendations, the majority of the women throughout the pregnancy and newborns at birth had vitamin D status below 50 nmol/liter. Maternal vitamin D deficiency is associated with adverse outcomes during pregnancy (13–15). Our results suggest that maternal vitamin D status affects fetal bone mineral accrual during the intrauterine period and influences bone size and mineral content at birth. Besides bone health, impaired maternal vitamin D status is hypothesized to modify long-term risk for several chronic diseases. More efforts should be made to revise current nutrition recommendations for pregnant women. In addition, intervention studies targeted to pregnant women are warranted.

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