Pregnancy in dark winters: implications for fetal bone growth?

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Objective: To prospectively examine the prevalence of hypovitaminosis D in pregnancy and to correlate maternal and fetal vitamin D to fetal anthropometry.
Design: A prospective cohort study.
Setting: Tertiary referral maternity hospital.
Patient(s): Sixty pregnant women.
Intervention(s): Serum 25-hydroxyvitamin D (25OHD) was measured in early pregnancy, at 28 weeks, and in cord blood at delivery.
Main Outcome Measure(s): The prevalence of hypovitaminosis D and the relationship between fetal growth and serum 25OHD concentrations.
Result(s): Two subgroups were analyzed to examine results in the context of seasonal variation in 25OHD: a winter and a summer cohort. Fetal anthropometry was assessed at 20 and 34 weeks, and at delivery the neonatal anthropometry was recorded. There was a high prevalence of hypovitaminosis D ranging from 33% to 97%, with a marked seasonal variation. Fetal 25OHD concentrations correlated with all biometry at 20 weeks. In the winter cohort, a correlation was found between early pregnancy 25OHD and femur length at 20 weeks, and between 28-week 25OHD and femur length at 34 weeks. Infant length was shorter in those with early pregnancy 25OHD less than the median (52.1 vs. 53.6 cm).
Conclusion(s): The high prevalence of maternal hypovitaminosis D during winter months in northern latitudes may have detrimental effects on fetal skeletal growth. (Fertil Steril® 2013;99:206–11. ©2013 by American Society for Reproductive Medicine.)
Key Words: Fetal growth, fetal femur length, pregnancy, vitamin D

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Vitamin D is required for normal calcium homeostasis and bone mineralization, and vitamin D deficiency leads to rickets in childhood or osteomalacia in later adult life (1, 2). Hypovitaminosis D in pregnancy has been linked to a wide variety of additional adverse outcomes, including preeclampsia, low birthweight, gestational diabetes, and an increased predisposition to autoimmune disease in later life (3), but the evidence is inconsistent and inconclusive as regards causality (4). The developing fetus entirely depends on the maternal pool of calcium; as such, there are growing concerns about the implications of hypovitaminosis D during pregnancy (5, 6). Despite the increasing awareness in the medical literature, it appears that the public health message to date is inadequate, with many studies reporting a high prevalence of hypovitaminosis D in pregnant populations (7, 8). This is possibly compounded by the lack of consensus in the literature regarding recommendations for antenatal vitamin D supplementation (9). Risk factors for vitamin D deficiency include dark, pigmented skin, regular use of sunscreen, maternal obesity, and living in high-latitude regions, especially during winter or spring months (3). In northern countries at latitudes above 42° north, endogenous production of vitamin D essentially ceases from November until March (10, 11).

Accurate assessment of the prevalence of hypovitaminosis D is limited in many studies to date by the heterogeneity of populations studied, the effects of seasonal variation, and the reliance on a single assessment of 25OHD at just one time point in pregnancy (12, 13). Our objective was to clarify

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TABLE 1

Baseline patient characteristics and comparison of summer and winter cohorts.

Characteristic	Overall	Winter cohort	Summer cohort	*P* value
Age (y)	31.7 (6.2)	31.2 (7.3)	32.4 (4.8)	.4
Height (cm)	166.8 (5.8)	166.2 (5.5)	167.5 (6.1)	.3
Weight (kg)	73.6 (11.5)	74.5 (11.1)	72.7 (12.1)	.5
BMI (kg/m^2)	26.6 (4.2)	27.1 (4.1)	26.2 (4.4)	.4
Supplemented	37	23	14	.05
Smokers	2	2	0	.5
Early pregnancy 25OHD nmol/L	45.6 (22.6)	57.5 (19.8)	33.8 (18.8)	.000
28-wk 25OHD (nmol/L)	54.38 (33.4)	43.6 (14.8)	65.1 (42)	.012
Cord blood 25OHD (nmol/L)	31.8 (12.6)	31.7 (10.6)	31.8 (14.4)	.98

Note: Baseline patient characteristics including the mean and standard deviation of the age, weight, height, body mass index (BMI), serum 25-hydroxyvitamin D (25OHD) concentrations, number of smokers, and number taking supplements in the entire group, with a comparison of the winter and summer cohorts.

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the prevalence of hypovitaminosis D in pregnancy by assessing 25OHD concentrations in early pregnancy, at 28 weeks' gestation and in fetal blood from the umbilical cord at delivery in two cohorts of healthy Caucasian women pregnant at opposite times of the year to account for seasonal variation. We also sought to assess the possible implications of vitamin D deficiency for fetal growth, in particular fetal bone.

MATERIALS AND METHODS

This was a prospective cohort study of 60 mother and infant pairs at the National Maternity Hospital, Dublin, Ireland, with institutional ethics approval and written maternal consent. At our institution, routine screening for vitamin D deficiency is not performed. All women were Caucasian and were recruited to the study at first antenatal consultation. Women were excluded if they had an underlying medical condition, if they were younger than 18 years of age, or if they were unable to give full informed consent.

Two specific cohorts were recruited. The first group (winter cohort) consisted of 30 women who were recruited in early pregnancy in September/October and delivered in March/April. A further 30 women were recruited in March/April who delivered in September/October (summer cohort). All women had 25OHD measured in early pregnancy (mean 14.3 ± 2.6 weeks), at 28 weeks' gestation and in fetal blood from the umbilical cord at delivery. At 20 weeks' gestation (range: 19 + 1 to 21 + 5), a routine fetal anomaly ultrasound was performed, and fetal biometry including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) was recorded. Fetal biometry was assessed again ultrasonographically at 34 weeks' gestation (range: 33 + 4 to 34 + 5 weeks).

Serum 25OHD concentrations were measured by competitive radioimmunoassay (Immunodiagnostic Systems Limited). The coefficients of variation (CV) for the 25OHD assay are as follows: interassay CV at a concentration of 29 nmol/L was 6.2% and at a concentration of 106 nmol/L was 7.7%; intra-assay CV at a concentration of 29 nmol/L was 3.0% and at a concentration of 74 nmol/L was 2.7%. To ensure a high standard of analysis, we participate in the Vitamin D External Quality Assessment Scheme (14).

At delivery infant birthweight, the length and head circumference were recorded. Serum 25OHD concentrations of above 50 nmol/L were classified as sufficient, and concentrations of <30 nmol/L were considered at high risk of deficiency as per the recent Institute of Medicine (IOM) report (4).

Dietary vitamin D intake was assessed using a 3-day food diary, which was completed 1 to 2 weeks after the first antenatal consultation. Women were asked to record their usual food and beverage intake over 3 consecutive days, including a weekend day. Dietary data were entered and analyzed using Weighed Intake Software Program (WISP) (Tinuviel Software), which uses food composition data from the Food Standards Agency (15).

Data were assessed for normality using Shapiro-Wilk and P-P plot. Bivariate correlations were assessed using Pearson's correlation coefficient for normally distributed data and Spearman's rho for nonparametric data. Further analysis was performed by comparing outcomes for those patients above and below the median for 25OHD concentrations, namely 41.0 nmol/L in early pregnancy, 45.7 nmol/L at 28 weeks, and 30.8 nmol/L in cord blood. Comparison of means within groups of patients was accomplished with the independent samples *t*-test. $P<.05$ was considered statistically significant. Statistical analysis was performed using SPSS Windows's version 18.0 (SPSS, Inc.). Sample size calculation based on a significance level set of 5% and power set at 90% suggested that 26 in each group would be required to detect 1 standard deviation difference in 25OHD between the two groups.

RESULTS

Vitamin D Status and Season

The baseline characteristics of the cohort are shown in Table 1. Within the total study population, the mean 25OHD concentration was 45.7 ± 22.6 nmol/L in early pregnancy, 54.4 ± 33.4 nmol/L at 28 weeks' gestation, and 31.8 ± 12.6 nmol/L in fetal blood at delivery. All pregnancies resulted in healthy term deliveries ranging from 37 + 1 to 42 + 1 weeks' gestation.

A marked seasonal variation in 25OHD was observed (Tables 1 and 2). In women in the summer cohort whose early pregnancy sample was taken in March/April, the prevalence

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