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Association of serum 25-OHD concentrations with maternal sex-steroids and IGF-1 hormones during pregnancy

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Abstract

Background—Vitamin D may influence circulating levels of sex-steroid hormones in women during reproductive life, but associations in pregnant women have not been explored.

Methods—Correlation and linear regression models were used to assess the association between sex-steroids, (estradiol, progesterone, 17-hydroxyprogesterone, testosterone and androstenedione), IGF-I and serum 25-hydroxyvitamin D (25-OHD) concentrations during the first trimester of pregnancy in 106 cancer free women from the Finnish Maternity Cohort.

Results—There was no significant association of serum 25-OHD with any of the hormones measured. One unit increase in serum 25-OHD concentration was associated with a non-significant 6% increase in estradiol concentrations. Multiparous women had higher levels of vitamin D (40.4 vs. 32.9 nmol/L, p-value =0.01) than primiparous women.

Conclusion—Our study does not support an association between maternal serum 25-OHD levels and sex steroids or IGF-I concentrations during the first trimester of pregnancy.

Keywords

Vitamin D; estradiol; progesterone; testosterone; androstenedione; IGF-1; sex-steroid hormones; pregnancy

Introduction

Vitamin D is a seco-steroid pro-hormone with a cyclopentanoperhydrophenanthrene ring, which makes it structurally similar to sex-steroid hormones (1). Apart from regulating calcium homeostasis, it may have a myriad of other biological functions based on its immunogenic, apoptotic and anti-proliferative properties (2).

Animal studies suggest that vitamin D may also be involved in the regulation reproductive processes by influencing estrogen synthesis (3–6), but its role in human reproduction and ovarian steroidogenesis has, however, not been extensively studied. In a recent study in young (18–22 years old) non-pregnant women, an inverse association of circulating serum

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25-hydroxyvitamin D (25-OHD) with estradiol and luteal phase progesterone concentrations was observed (7). Exploring the relationship between vitamin D and sex-steroids is of interest, given that high concentrations of this vitamin have been associated with reduced risk of hormonally dependent breast cancer (8, 9).

To further characterize the relationship between serum 25-OHD levels and the sex-steroid hormones, we investigated these associations among women from the Finnish Maternity Cohort (FMC) who had donated blood samples during the first trimester of pregnancy.

Materials and Methods

The FMC serum biobank established in 1983 is a bio-repository of over 1.6 million serum samples donated by almost all pregnant women in Finland predominantly during the first trimester of pregnancy. After screening for intra-uterine infections, the remaining sample is stored for research purposes, at −25°C, in a well protected central bio-repository.

The subjects in this study were 106 cancer free women from the FMC, who were randomly selected among controls of an ongoing nested case-control study on pregnancy hormones, vitamin D and ovarian cancer. Case subjects in the study were women from the FMC who were diagnosed with ovarian cancer after entry into the FMC. Cases were identified after linkage with the population-based Finnish Cancer Registry (FCR). Controls were also women from the FMC who were free of cancer and were matched for cases on (i) age ± 1 year, parity and (iii) date of index blood sampling ± 2 weeks. Information on index pregnancy, maternal and child characteristics was obtained from the FMC and linkage to the Finnish Medical Birth Registry (MBR).

The study was approved by the ethical committee of the National Institute for Health and Welfare, Finland.

Laboratory Analysis

Hormones and 25-OHD were quantified at the Department of Medical Biosciences, University of Umeå, Sweden. Serum 25-OHD was measured by radioimmunoassay, RIA (IDS Ltd, Boldon, UK) with a specificity of 100% for 25-OHD3, 75% for 25-OHD2, 100% for 24, 25-OH2D3, and less than 0.01% or 0.3% for cholecalciferol (D3), and ergocalciferol (D2), respectively. The intra-assay and inter-assay coefficients of variations (CV) of the assay were 7.8% and 9.6% at level 28.4 nmol/L 25-OHD, and 4.1% and 7.4% at 107 nmol/L 25-OHD, respectively.

Sex steroid hormones were quantified by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS), on an Applied Biosystems API 4000 triple stage qua drupole mass spectrometer. The inter-run and intra-run CVs based on the blinded pool of quality controls were; 5.2% and 6.3% at 5.0 ng/mL of estradiol, 3.6% and 7.6% at 0.10 ng/mL of testosterone, 3.8% and 8.1% at 0.25 ng/mL of androstenedione, 5.2% and 8.00% at 5.0 ng/mL of 17-OHP, 3.5% and 6.8% at 75.0 ng/mL of progesterone, respectively.

Insulin-like growth factor-1 (IGF-1) was quantified by immunometric assay on an Immulite 2000 Siemens analyzer with intra-assay CV of 0.8% and inter-assay CV of 4.7% at 57 ng/L.

Statistical analyses

To account for the seasonal variation in serum vitamin D, 25-OHD concentrations were regressed on calendar month. To account for hormonal variation with gestational age, all analyses were adjusted for gestational day at blood donation. The subjects were classified as having high or low 25-OHD concentrations based on the median 25-OHD month-specific

concentration within the cohort. We also compared the hormone concentrations based on tertiles of serum 25-OHD concentrations but the results were not different and thus not presented. The association between vitamin D and the other continuous variables was assessed using Spearman partial correlation. General linear regression models were used to estimate the geometrics means of pregnancy hormones in subjects with low and high 25-OHD. We also estimated the percentage change in hormone concentrations for 1 unit increase serum 25-OHD concentration. The models were adjusted for potential confounders (maternal age, parity and smoking) but these did not influence the observed associations and were not retained in the model. All analyses were performed using the Statistical Analysis System (SAS), software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

The mean age of the women at blood donation was 31.4 years (range; 18 to 44 years). The median gestational age at blood donation was 10 weeks and 26% of the women were primiparous. Serum 25-OHD concentrations were generally low among the women. The mean 25-OHD concentration was 38.5 nmol/L (minimum, 16 nmol/L, maximum 82 nmol/L). Serum 25-OHD concentrations were lowest in April (mean; 25.3 nmol/L) and highest in August (mean; 49.6 nmol/L).

There was a weak correlation between serum 25-OHD concentrations and parity (rs = 0.21, p-value 0.04). Primiparous women had significantly lower mean serum 25-OHD concentrations compared to multiparous women (32.9 vs 40.4 nmol/L, p-value 0.01).

We found weak, non-significant correlations between circulating serum 25-OHD and concentrations of sex-steroids and IGF-I (Table 1). The strongest correlation observed was between 25-OHD and estradiol (rs = −0.13, p-value 0.27). No significant differences in mean hormone concentrations were observed between women with high and low serum 25-OHD concentrations. One unit increase in serum 25-OHD concentration was associated with non-significant 6% decrease in estradiol and 10% increase in 17-hydroxyprogesterone (17-OHP) concentrations (table 2). The results were not different when hormone concentrations were compared based on tertiles of serum 25-OHD concentrations (Table not shown).

Discussion

We observed that, among pregnant women, there was no association between circulating 25-OHD and concentrations of sex-steroid hormones and IGF-I. Parous women had significantly higher levels of 25-OHD than women who were pregnant for the first time.

In the only previous study among young women, an inverse association was observed between serum 25-OHD concentrations and those of estradiol and progesterone (7). We also observed a tendency for an inverse association between serum 25-OHD and estradiol but it was weak and not-statistically significant. These results are biologically plausible, as experimentally, it has been shown that 1,25-dihydroxyvitamin D 1,25-$(OH)_2D$, the active form of vitamin D, can inhibit the synthesis and biological actions of estrogen by downregulating the activity of aromatase enzyme (10). Vitamin D may interact with estrogen action also through additional mechanisms; e.g. vitamin D and estrogens undergo competitive binding for their common cellular membrane receptor, megalin, which is non-recyclable and undergoes lysosomal degradation after hormone delivery (11). In addition, 1,25-$(OH)_2D$ down-regulates the expression of estrogen receptor alpha, thereby attenuating estrogen signaling in breast cancer cells (10, 12).

In contrast to the results by Knight et al. (7), we did not observe a decrease in progesterone concentrations with increasing serum 25-OHD concentrations. Of note is that the major

production sites of progesterone differ in pregnant and non-pregnant women. In non-pregnant women, the corpus luteum is the main determinant of progesterone concentrations during the luteal phase of an ovulatory cycle, while during the first trimester of pregnancy, circulating progesterone predominantly comes from the placenta (13, 14). Thus, it is possible that vitamin D may affect ovarian progesterone synthesis but not the placental synthesis of the hormone.

Finally, it is possible that vitamin D may have an influence on estrogen and progesterone synthesis but given the very low 25-OHD concentrations among the study subjects and the very high concentrations of these hormones during pregnancy, the effect may not be apparent during pregnancy.

The positive effect of parity on serum 25-OHD levels is in line with previous reports among pregnant women (15). One possible explanation is improved nutritional practices in subsequent pregnancies compared to the first pregnancy (16).

In summary, in this cross-sectional study, no association of serum 25-OHD concentrations with sex steroids and IGF-I concentrations was observed, but a potential inverse association with estrogens warrants further investigation.

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Table 1

Spearman partial correlation coefficient (adjusted for gestational age) between 25-hydroxyvitamin D and hormones and maternal and child characteristics among 106 women from the Finnish Maternity Cohort, 1983–2006

Characteristic/Hormone	25-OHD	Estradiol	Progesterone	17-OHP	Testosterone	Androstenedione	IGF-1	Maternal Age	Parity	Child weight	Child length
25-OHD (nmol/L)		−0.13	0.09	0.10	0.02	0.11	0.04	0.07	**0.21**	0.15	0.07
Estradiol (ng/mL)			**0.42***	0.16	**0.36***	**0.29***	−0.05	0.05	0.00	0.08	0.01
Progesterone(ng/mL)				**0.37***	0.04	0.11	0.14	0.07	0.07	−0.17+	−0.13
17-OHP (ng/mL)					**0.47***	**0.56***	**0.21***	−0.07	−0.07	−0.03	−0.01
Testosterone(ng/mL)						**0.83***	0..16	−0.09	−0.12	0.09	0.01
Androstenedione (ng/mL)							0.19+	−0.19+	−0.11	0.08	−0.01
IGF-1 (ug/L)								−0.18+	−0.10	−0.07	−0.02

*P-value < 0.05

+P-value > 0.05 < 0.10

Table 2

Geometric means* of maternal hormones by 25-hydroxyvitamin D concentrations and percentage change in maternal hormone concentrations per unit increase in serum 25-OHD concentrations among 106 women from the Finnish Maternity Cohort, 1983–2006

Characteristic/Hormone	Estradiol ng/mL	Progesterone ng/mL	17-OHP ng/mL	Testosterone ng/mL	Androstenedione ng/mL	IGF-1 ug/L
25-OHD concentration+						
Low 25-OHD (< 34.9 nmol/L)	2.04	23.5	2.30	0.78	1.74	119.7
High 25-OHD (≥ 34.9 nmol/L)	1.84	24.1	2.29	0.75	1.74	126.3
P-value	0.34	0.69	0.99	0.64	0.98	0.48
Percentage change in maternal hormone concentrations per unit increase in serum 25-OHD concentrations						
Changes (%)	−6.0	5.8	9.8	3.4	6.7	4.1
P-value	0.30	0.51	0.19	0.64	0.30	0.62

*Adjusted for gestational age

+Cut-off based on the median 25-OHD concentrations among the women