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ORIGINAL ARTICLE

The effects of maternal vitamin D on neonatal growth parameters

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Abstract Vitamin D facilitates calcium absorption and bone building. Presence of vitamin D is highly important in pregnant women due to its effect on the development of the fetal skeleton. The study population comprised 208 low-risk pregnant women of a heterogeneous population. Maternal and fetal serum concentrations of vitamin D were measured using the Liaison 25(OH)D Assay (DiaSorin, Italy).

Conclusion: Maternal vitamin D serum concentrations correlate with neonatal vitamin D serum concentrations but do not affect neonatal weight and/or head circumference.

What is known?
- *Vitamin D is known to be also involved in immunomodulation and cellular proliferation and differentiation.*
- *Vitamin D is highly important in pregnant women for its effect on fetal musculoskeletal and neurological development.*

What is new?
- *No association was detected between maternal or neonatal vitamin D concentration with neonatal growth parameters or obstetrical complications, and no association was found between maternal vitamin D serum concentrations and maternal obstetrical complication rate.*
- *A strong correlation was demonstrated between maternal and neonatal serum vitamin D concentrations.*

Keywords Vitamin D · 25(OH)D · 1,25$(OH)_2$D · Neonatal growth · Bone metabolism

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Abbreviations

CLIA	Competitive chemiluminescence immunoassay
ng/mL	Nanograms per milliliter
nmol/L	Nanomoles per liter
VDR	Vitamin D receptor
25(OH)D	25-Hydroxyvitamin D
1,25$(OH)_2$D	1,25-Dihydroxyvitamin D

Introduction

The traditionally acknowledged function of vitamin D is to maintain appropriate calcium balance and bone health [15]. Vitamin D is known to be also involved in immunomodulation and cellular proliferation and differentiation [1]. Studies suggests Vitamin D effects on fertility, pregnancy [31], autoimmunity [9], insulin mechanism [7], blood pressure equilibrium [36], schizophrenia [18], and mortality in severely ill patients [3]. Many biological functions of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) are mediated by the vitamin D receptor (VDR) [8]. Subjects suffering from vitamin D insufficiency exhibit trace amounts of vitamin D because dietary vitamin D is immediately converted to 25-hydroxyvitamin D (25(OH)D) and then to the active form of 1,25$(OH)_2$D in order to maintain the balance of calcium equilibrium. Vitamin D dissolution occurs through an additional hydroxylation by the D-24-hydroxylase enzyme which is found in most tissues. This dissolution renders it biologically inactive and water soluble (converting it to calcitronic acid). Unlike low concentrations of vitamin D, high concentrations will activate this dissolving enzyme resulting in enhanced vitamin D dissolution [8]. Vitamin D concentration levels in adults, including pregnant women, are currently based on 25(OH)D serum concentration levels. Total 25(OH)D concentration reflects delivery of vitamin D from both cutaneous and oral sources. The 25(OH)D serum concentration is expressed in nanograms per milliliter or nanomoles per liter (1 ng/mL=2.5 nmol/L).

As the most prevalent and stable metabolite of vitamin D in the blood with a half-life time of about 3 weeks, it is considered the best indicator for assessing concentrations of vitamin D [32].

Researchers disagree about the exact level of vitamin D that would be considered optimal. Key opinion leaders established ranges of 25(OH)D serum concentration indicating vitamin D deficiency at [<20 ng/mL (<50 nmol/L)], suboptimal status at [20–30 ng/mL(50-75 nmol/L)], and target concentration for optimal vitamin D effects at [30–50 ng/mL (75–125 nmol/L)] [32] in which PTH levels reach physiological values [28, 34, 35]. Most researchers agree that 25(OH)D serum concentration above 20 ng/mL is probably sufficient for calcium absorption and bone health in adults including pregnant women. On the other hand, it is believed that 25(OH)D toxicity is only possible at exceptionally high levels, beyond 150 ng/mL

Fetal and neonatal vitamin D levels depend on maternal levels of vitamin D during gestation. Neonatal reservoirs of vitamin D begin with the crossing of 25(OH)D through the placenta from the mother to the fetus during the first months of gestation. The active form of vitamin D (1,25(OH)$_2$D) is unable to cross the placenta [16]. Several studies have shown that vitamin D levels in neonates, measured as the concentration of 25(OH)D in umbilical cord blood, correlated with vitamin D maternal levels, amounting to some 60–89 % of maternal concentrations [10, 16, 20].

Maternal 25(OH)D levels will not fluctuate significantly during pregnancy unless dietary intake or endogenous synthesis alters [27]. However, both maternal and fetal serum concentrations of 1,25(OH)$_2$D increase by up to 200 % within the first trimester of gestation [20]. The increase of 1,25(OH)$_2$D levels in maternal serum occurs mostly in the kidney [20] while the increase of 1,25(OH)$_2$D levels in fetal serum is probably related to synthesis occurring within placenta tissues and by the fetus itself [30]. Due to the increased need of calcium in the mother, maternal intestinal calcium absorption is increased at the onset of the pregnancy and is doubled during week 12 of gestation. The increased calcium absorption is facilitated by the doubled synthesis of 1,25(OH)$_2$D in the maternal kidney [33]. Following intestinal absorption, calcium is first stored in maternal bones prior to being transferred at a second stage actively crossing the placenta carried by calcium-binding proteins found within it. This supplies the fetus with calcium for the development of the skeleton as well as other systems.

Vitamin D is highly important in pregnant women due to its effect on fetal skeletal development. One study showed that maternal levels of vitamin D during gestation affect the bone mass of offspring up to 9 years of age at the very least [19]. Vitamin D during gestation has additional long-term effects on both the mother and offspring, for example, with respect to insulin resistance in pregnant women. A study of 741 pregnant women found high prevalence of severe vitamin D insufficiency in women suffering from gestational diabetes in comparison to non-diabetic women as well as a positive correlation between vitamin D levels and insulin sensitivity [23]. Low levels of vitamin D at the onset of pregnancy also correlate with increased risk for preeclampsia [4]. Various studies established a relationship between vitamin D and fetal brain development [13, 21, 26]. A normal concentration of vitamin D in pregnant women was found to enhance fetal brain receptors and seems to ensure normal mental development [14]. Research studying the relationship between asthma in infants and maternal consumption of vitamin D during gestation found that vitamin D intake during gestation reduced the risk of wheezing among offspring [11].

Our study aimed to investigate the relationship between vitamin D serum concentration levels in Israeli women and neonatal weight and head circumference (as reflections of neonatalsize and hence development) in a heterogeneous population. We assessed whether vitamin D concentrations in maternal serum affect vitamin D concentrations in fetal serum as well as its impact on neonatal growth.

Deepening our understanding of this relationship will assist in our ability to determine the importance of monitoring vitamin D levels in maternal serum during gestation and to consider recommendations regarding its relevance in fetal intrauterine growth.

Materials and methods

Study population

The study population comprised 208 healthy, low-risk pregnant women who arrived at the hospital's delivery room between March and June 2011 at full-term active labor (week 37 and later). All women whose basic data matched our criteria were asked to participate in the study. This study was conducted with the approval of the ethics committee at Sheari-Zedek, Jerusalem, Israel. The study objectives were explained to candidates; written consent was obtained from all study participants.

Background data collection

Participants were asked for a set of relevant medical details, comprising general medical and gynecological background information, including age, ethnicity, weight, week of gestation, number of previous births, date of last birth, complications in previous births (including caesarian section), intake during gestation of prenatal, or other food supplements as well as intake of vitamin D or calcium supplements.

Measuring vitamin D levels in maternal and fetal serum

Taking maternal blood As part of the routine blood test of antenatal care in the delivery room, an extra 5 mL were extracted for the purpose of measuring vitamin D serum levels (using EDTA tube).

Taking fetal blood Five milliliters of fetal blood were extracted from the severed umbilical cord subsequent to birth.

Measuring vitamin D serum concentrations Blood samples were centrifuged, and the serum was separated and frozen at −80° in dark tubes until 25(OH)D levels were measured. Measurements took place at our laboratory at Sheba Medical Center, Israel, utilizing direct competitive chemiluminescence immunoassay (CLIA) technology with the kit LIAISON® 25 OH Vitamin D TOTAL Assay (Cat. no. 310600, DiaSorin Inc. Stillwater, MN, USA). Quantitative estimates of 25(OH)D serum levels were taken according to the manufacturer's instructions [2].

Neonatal weight and head circumference measurements After birth, neonatal data was extracted from subject files, including the following: weight at birth, head circumference, and Apgar scores (1 and 5 min) as well as information concerning delivery, complications during childbirth, termination of the current pregnancy, and obstetric complications.

Statistical analysis Descriptive statistics included the following: means and standard deviation, percentages, median, and interquartile range. Comparison between continuous variables was achieved using Student's t test. Pearson's correlation coefficients were examined between maternal and fetal vitamin D levels and various factors. A two-tailed approach was employed for statistical tests, where p value <0.05 was considered significant. Statistical analyses were carried out using SPSS software version 18 (SPSS Inc. Chicago, IL, USA).

Results

Demographic data

Mother and childbirth data Average age of birth-giving patients was 28.3±5.8 and their average weight amounted to 74.1 ±11.6 kg. Gestation age averaged at 39.8±1.2 weeks. Of the mothers, 89.3 % were given dietary supplements during pregnancy, but only 20 % were supplemented with vitamin D. For 71.6 %, this was not their first birth; the mean birth number was 2 (range 1–5). A total of 12.7 % had suffered complications during the previous delivery while 12.1 % had suffered complications during the current delivery (lack of progress, meconium, fever, fetal distress, and suspected placenta debris) (Table 1).

Table 1 Characteristics of mothers participated in the study

Characteristics of mothers	
Maternal age (year)	28.3±5.8
Maternal weight (kg)	74.1±11.6
Gestational age (week)	39.8±1.2
No. of births	Median 2 [1–5]
Consumption of supplements during pregnancy	89.30 %
Vitamin D and/or calcium consumption during pregnancy	20 %
Vitamin D concentration (ng/ml)	15.01±51.65
1st birth	28.40 %
Complications during previous birth	12.70 %
Complications during current birth	12.10 %

N=208. Data is presented as average±standard deviation or percentage or as median

Neonatal data Among 208 births, 43.7 % neonates were male. Average weight at birth amounted to 3.3±0.4 kg and average head circumference was measured at 34.6±1.3 cm. A total of 95.2 % newborns achieved a score of 9 at Apgar 1 while 98.6 % achieved a score of 9 at Apgar 5. The average 25(OH)D serum concentration amounted to 11.41±6.59 ng/mL (Table 2).

Vitamin D concentrations in maternal serum

Vitamin D serum concentrations among study participants averaged at 15.0±51.7 ng/mL (Table 1). Most women (93.5 %) were found to suffer from vitamin D insufficiency, defined here as 25(OH)D serum concentration under 20 ng/mL. A total of 5.3 % of the women exhibited vitamin D serum concentrations in the range of 20–30 ng/mL, and only two women (0.1 %) measured 25(OH)D serum concentrations greater than 30 ng/mL (Table 3).

Table 2 Characteristics of newborns participated in the study

Characteristics of newborns	
Males	47.30 %
Newborn weight (kg)	3.3±0.4
Newborn head circumference (kg)	34.6±1.3
Apgar score of 9 after 1 min	95.20 %
Apgar score of 9 after 5 min	98.60 %
Vitamin D concentration (ng/ml)	11.4±6.6

N=208. Data is presented as average±standard deviation or percentage or as median

Table 3 25(OH)D concentration in maternal serum and in newborn

Concentration 25(OH)D	Mothers (%)	Newborns (%)
<20 ng/ml	89.90	88.50
20–30 ng/ml	5.80	5.80
>30 ng/ml	1	2.90
Missing data	3.40	2.90

N=208. Data is presented in percentages

Correlations between maternal and fetal vitamin D serum concentrations

A high correlation was found between maternal and fetal vitamin D serum concentrations (R p=0.85, p<0.001). Respective to 93.5 % of the mothers who exhibited 25(OH)D serum concentrations lower than 20 ng/mL, 95 % of neonates were also found to have 25(OH)D serum concentrations under 20 ng/mL. Mothers who consumed vitamin D supplements during gestation and whose vitamin D levels were high gave birth to neonates who exhibited high levels of vitamin D serum concentration.

Effect of vitamin D concentrations in maternal and fetal serum on neonatal weight and head circumference

No correlation was found between 25(OH)D concentrations in maternal serum and neonatal size as reflected in weight (R p=−0.01, p=0.93) and head circumference (R p=−0.10, p=0.15). Similarly, no correlation was found between 25(OH)D concentrations in fetal serum and neonatal weight (R p=−0.02, p=0.82) and head circumference (R p=−0.11, p=0.14).

We could not detect an association between both maternal or neonatal vitamin D concentrations and complications during delivery.

Discussion

During gestation and lactation, mothers are required to transfer large quantities of calcium to the developing fetus and breastfeeding infant. Given the correlation in adults between vitamin D and calcium levels as well as bone metabolism, we would expect that an optimal level of vitamin D would be crucial during gestation and lactation. We hypothesized that vitamin D concentrations in maternal serum would affect certain parameters of intrauterine growth. We therefore examined whether 25(OH)D concentrations in maternal serum correlated with 25(OH)D concentrations in neonatal serum as well as with neonatal size.

Various studies have shown strong relationships between maternal and fetal 25(OH)D serum concentrations [5, 6, 17, 25, 37] demonstrating that insufficiency in mothers resulted in similar status in newborns. The present study confirms this finding as we found a high correlation between maternal and fetal serum concentration levels of 25(OH)D. We have established that mothers who consumed vitamin D supplements during gestation gave birth to neonates with higher levels of vitamin D whereas mothers suffering from vitamin D insufficiency gave birth to neonates exhibiting lower serum levels of 25(OH)D.

It is well known today that gestational vitamin D insufficiency is a globally prevalent phenomenon. The present study has also found a high rate of gestational vitamin D insufficiency among the studied population. This finding may be explained by the heterogeneous population of the study population, many of them originating from religious Jewish and Muslim communities in which women traditionally cover their bodies with long clothes preventing appropriate sun shine exposure, resulting with low in vivo vitamin D production.

Despite the high correlation between vitamin D levels in maternal and fetal serum, we found no relationship between maternal vitamin D levels and neonatal size as reflected in weight and head circumference. Some previous studies, but not all, find maternal vitamin D status during pregnancy to be associated with fetal growth [37]. In contrast to our findings, comparing neonatal growth parameters with maternal consumption of milk and vitamin D during gestation, Manion *et al.* [24] found neonatal weight to be related to gestational vitamin D consumption. They reported that every increase in maternal consumption of 401 units of vitamin D correlated with an approximate increase of 11 g in neonatal weight. Similarly, studying 108 women and their newborn, Pawley and Bishop [29] found a significant correlation between umbilical cord 25(OH)D levels and infant head size at the age of 3–6 months. Leffelaar *et al.* [22] conducted a community-based longitudinal study (multi-ethnic cohort of 3730 women) in the Netherlands and found that women with deficient vitamin D levels had infants with a higher small-for-gestational age (SGA) risk and lower birth weight. The current study was unable to corroborate such a relationship, possibly due to genetic differences. The discrepancy between our results and previous observational studies emphasizes the need for well-designed randomized vitamin D supplementation trials during pregnancy.

Our study has several limitations; it is possible that the analysis of data originating in more homogenous groups with respect to pigmentation or lifestyle would have resulted in a stronger correlation for specific populations. Additionally, we have differentiated in this study between the consumption of dietary prenatal supplements to that of calcium and/or vitamin D, but we did not differentiate between women consuming calcium supplements and those consuming pure vitamin D supplements. Since the combination of vitamin D and calcium affects the mother and neonate [12], it is possible that differentiating between the two would have resulted a clear distinction. Another limitation of the study is the fact that neonatal length was not measured in addition to weight and head circumference. Finally, the majority of women in this study had low levels of vitamin D. Hence, it is possible that if we had a significant number of women with satisfactory concentrations of the vitamin D, we would be able to record a significant difference comparing them to the majority of vitamin D-deficient women.

In conclusion, vitamin D insufficiency (25(OH)D <20 ng/mL) characterizes a large group of women. Vitamin D levels in maternal serum are tightly related to the neonatal serum concentrations. No relationship was found between vitamin D levels in maternal serum and neonatal weight or head circumference at birth. Results of this study give way to the hypothesis that gestational vitamin D dietary supplementation will increase 25(OH)D concentrations in both maternal and fetal serum. According to the presented data, supplementing pregnant women suffering from vitamin D insufficiency with vitamin D will indeed increase neonatal 25(OH)D maternal concentration levels but probably will not enhance fetus growth.

Conflict of interest Dana Ben-Ami Shor, Joseph Barzel, Ernest Tauber, and Howard Amital report no conflict of interest.

Author's contributions Dana Ben-Ami, Shor-preparation of the manuscript. Joseph Barzel, Defining concepts and aims, materialization of the study and conducting the serum samplecollection and execution of tests. Ernest Tauber, MD, Defining concepts and aims, materialization of the study design Study. Howard Amital, MD, MHA - Defining concepts and aims, materialization of the study design, preparation of the manuscript.

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