Original Article

Vitamin D Supplementation in the First Trimester of Pregnancy as an Intervention to Protect against Adverse Gestational Outcomes in the Third Trimester

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Abstract

Background: Vitamin D deficiency (VDD) is thought to be common among pregnant women and is a widespread public health problem. **Objective:** The aim of this study was to know whether the correction of VDD by Vitamin D supplementation given to pregnant women in the first trimester of pregnancy can prevent the development of complications such as preeclampsia (PE), gestational diabetes mellitus (GDM), and small for gestational age (SGA) in the third trimester or not, in a sample of pregnant women. **Materials and Methods:** The study was an experimental design. It was carried out between December 2016 and October 2018. A total 200 healthy pregnant women were included. They were chosen randomly in the first trimester of pregnancy from the Outpatient Clinic in Duhok Governorate of Kurdistan Region, Iraq. A knowledge questionnaire was used to collect information. Blood samples were taken and analyzed for the determination of 25 hydroxyvitamin D (25[OH] D). We did routine investigations which done for every pregnant woman as a part of antenatal care in the form of complete blood count, general urine examination, random blood sugar, and ultrasound. **Results:** Mean serum 25[OH] D concentration before supplementation was 8.41 ± 2.48 and after supplementation was 30.96 ± 9.60. There was a reduction in the risk of GDM and SGA but no change in the risk of PE. **Conclusion:** Supplementation of Vitamin D to pregnant women with VDD in the first trimester may lower the risk of GDM and SGA, but its effects in the prevention of PE need further evaluation. All patients had response to the Vitamin D supplement within 8–10 weeks regardless the outcomes.

Keywords: 25-hydroxyvitamin D , gestational diabetes mellitus, preeclampsia, small for gestational age, Vitamin D deficiency

Introduction

Vitamin D, a secosteroid that is synthesized in skin and sequentially metabolized in liver and kidneys in humans, has been well known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization.[1] Vitamin D is metabolized first to 25 hydroxyvitamin D (25[OH]D), then to the hormonal form 1, 25-dihydroxyvitamin.[2]

The largest source of Vitamin D in adults is synthesis from solar radiation, ½ h of sunlight exposure delivers 50,000 IU of Vitamin D with white complexioned skin. Dietary intake of Vitamin D makes a relatively small contribution to overall Vitamin D status, as there is little Vitamin D that occurs naturally in the food supply.[3]

We categorized plasma 25-(OH)D concentrations according to previously published criteria for Vitamin D sufficiency (>30 ng/ml), insufficiency (20–29 ng/ml), and deficiency (<20 ng/ml).[4]

The United States Institute of Medicine (IOM) has recently defined levels of serum 25(OH)D >50 nmol/L or 20 ng/mL as adequate for pregnant women; however, other investigators argue that optimal levels should be set higher (>75 nmol/L or 30 ng/mL) (to convert nmol/L to ng/mL divide by 2.496).[5,6]

The daily upper safe limit for Vitamin D has been set at 4000 IU by IOM and 10,000 IU by the Endocrine Society.[7]

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Vitamin D toxicity generally becomes evident at doses of 20,000 IU/day and can lead to hypercalcemia, hypercalciuria, and elevated (200 nmol/L) levels of serum 25(OH)D.[5]

The Vitamin D deficiency (VDD) epidemic during pregnancy, it appears that the etiology is multifactorial. The factors that affect this include limited sunlight exposure but also reduced dietary Vitamin D and calcium intake, ethnicity, age, socioeconomic status, repeated pregnancies, obesity, and malabsorption.[8] In addition, the oral intakes that are too low to meet the increased demands of pregnancy, even with regular use of prenatal vitamins containing 400 IU Vitamin D3.[9]

VDD has been associated with increased risk of a number of adverse maternal and child health outcomes. These include an increased risk of preeclampsia (PE) and gestational diabetes mellitus (GDM), bacterial vaginosis, and increased production of maternal inflammatory cytokines, insulin resistance, and primary cesarean section. For the offspring, increased risk of preterm birth, small for gestational age (SGA) babies, neonatal hypocalcemia, rickets in infancy, reduced bone density, asthma, and schizophrenia.[10,11]

PE is a pregnancy-specific syndrome characterized by high blood pressure and proteinuria after 20 weeks gestation that occurs in up to 8% of pregnant women. Increased production of inflammatory cytokines, such as tumor necrosis factor-α, has been reported in pregnancies complicated by VDD. Furthermore, (1, 25[OH]2D) stimulates the activity of T-regulatory cells, which are vital in supporting placental implantation through immune tolerance. In PE, the metabolism of Vitamin D in placental tissue is altered, and these differences may play a role in the abnormal trophoblastic invasion found in these pregnancies.[12]

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[13]

The global prevalence of GDM varies widely, from 1% to 28%, depending on population characteristics (e.g., maternal age, socioeconomic status, race/ethnicity, or body composition), screening methods, and diagnostic criteria,[14] and the amount of GDM varies in direct proportion to the prevalence of type 2DM in a given population or ethnic group.[15] Vitamin D also has a role in insulin homeostasis and resistance. It may improve beta-cell activity and increase insulin sensitivity. Pregnancy is another condition associated with insulin resistance and hyperinsulinemia.[16]

SGA is defined as the estimated weight of the fetus is below the 10th percentile for its gestational age, and abdominal circumference is below the 2.5th percentile.[17] The prevalence of SGA births is approximately 8.6%–9.6% based on the data from several countries.[18] Vitamin D has a key role in fetal growth by its interaction with parathyroid hormone and Ca2+ homeostasis.[19]

Materials and Methods

Study population

We selected pregnant women randomly in their first trimester for this experimental study. The sample size was estimated and 200 participants were included. They attended the clinic at regular interval. Data were collected between December 2016 and October 2018. Verbal consents were obtained from each patient included in this study after explaining the nature of the study.

Ethical approval of this study was obtained from the Scientific Committee of the College of Medicine, University of Duhok, Iraq.

The earliest time of patient's selections following measurement of total circulating 25(OH) D was 7 weeks' gestation, with the target upper limit of gestation of 15 weeks gestation. All participants had singleton viable fetus confirmed by ultrasound at the time of inclusion, and all of them had VDD (<20 ng/ml). Those with preexisting medical diseases (DM and hypertension), metabolic diseases, chronic inflammatory disorders, or receiving long-term therapy for any chronic condition, or had previous history of GDM, PE, and SGA were excluded from the study. Furthermore, those participants who had more than one abortion or who were taking Vitamin D supplementation, multivitamins, aspirin, and metformin also excluded from the study.

Clinical assessment

Anthropometrics included prepregnancy weight (as recalled by the participant), current weight, and height. Body mass index (BMI) = (weight [kg]/height [m^2]) was calculated for each participant according to previously reported by Deore *et al*.[20] Blood pressure checked in each visit.

Assessment of circulating 25 hydroxyvitamin D and biochemical parameters

In our study, we performed random plasma glucose (RPG), it measured in each visit using the routine laboratory analysis. If the patient's RPG is >139 mg/dl (7.7 mmol/L), then the 75 g oral glucose tolerance test was done.[21] We adopt the WHO 2013 diagnostic criteria, (2-h glucose is 153–199 mg/dl [8.5–11 mmol/L] after overnight fasting with 75 g glucose load are classified as having GDM).[22]

Vitamin D status is assessed by measuring the prohormone 25(OH) D or (calcidiol) in serum, which reflect the Vitamin D produced cutaneously and that obtained from foods or supplements.[5] The first reading of blood sugar was taken in the first visit, the second reading at 8–10 weeks, and the third reading in the third trimester. Urine for albumin was done in cases of newly developed hypertension to confirm PE.[12]

Data collection

Gestational age was calculated from the date of the last menstrual period and was confirmed using an ultrasound examination during the first visit. All participants answered a generalized questionnaire, which included information on age (18–35 years), parity (0–3), past medical history, medication treatment history, family history, and employment as either homemaker or employed and student.

Intervention study (Vitamin D supplementation) protocol

All participants instructed to take one tablet a day of 5000 IU of Vitamin D.[23] The formula was Vitamin D_3

(cholecalciferol),[24] (life D3) of Sunlife Company from Germany for 8–10 weeks. A 5 ml of blood was collected in the first visit, and after 10 weeks for determination of serum 25(OH)D.

Patients who completed 8–10 weeks course of Vitamin D supplementation were allowed 2 weeks free of supplementation to be followed by postintervention measurement of serum 25(OH) D values, as 25(OH) D has a half-life of approximately 2–3 weeks.[25] If the level of Vitamin D >20 ng/ml, they maintained on 400–800 IU alone or combined with calcium or multivitamins.[24] Some patients who still had Vitamin D level <20 ng/ml, they continue on the dose 5000 IU for another month until the level increased above 20 ng/L.

Statistical analysis

The baseline information of the patients was presented in frequency distribution either in frequency and percentage or mean and standard deviation. In addition, the rates of patients' outcome were displayed in frequency and percentage. Paired *t*-test was performed to compare the Vitamin D level and blood sugars before and after Vitamin D supplementation. The comparison of Vitamin D levels in patients with different outcomes were examined in independent *t*-test or one-way ANOVA. The null hypothesis was rejected in a $P < 0.05$. The statistical calculations were performed in Statistical Package for the Social Sciences version 25:00 (SPSS 25:00; IBM, Duhok city, Kurdistan Region, Iraq).

Results

Total number of study participants was 200 individuals who had satisfied inclusion criteria. The mean maternal age was 27.41 ± 4.28 (range 18–35) years, and BMI mean was 25.58 ± 2.69. Among them, 154 were homemakers and 46 were employed and student. Among participant, 20 patients had previous miscarriages (mean 0.20), 36 had a family history of DM, and 58 had a family history of hypertension. All are shown in Table 1.

Regarding the outcomes of our patients, 4 patients (2%) only developed GDM, 14 (7%) developed PE, and 5 patients (2.5%) developed SGA as shown in Table 2.

The Vitamin D level increase from severe deficiency, the mean was 8.41 ± 2.48 to sufficient level of mean 30.96 ± 9.60 after 2 months supplementation of 5000 IU vitamin D_3/day, *P* value was statistically significant. At the same time, the mean blood sugar at the time of deficiency was 97.43 ± 13.84 and after supplementation was 111.18 ± 24.26, this is significant as shown in Table 3.

In spite of the reduction of the risk of the SGA and DM as shown in the Table 2, but the results were insignificant. Furthermore, the development of PE was nonsignificant. All participants with VDD have good response to vitamin D supplimentation as shown in Table 4.

Table 1: Baseline information of the patients

Characteristics (*n*=200)	Frequency distribution, mean±SD
Age range (year)	
18-35	27.41±4.28
18-24.9	56±28.0
25 and above	144±72.0
BMI	
Range: 20.0-30.0	25.58±2.69
Normal (18-24.9)	72±36.0
Overweight (≥25)	128±64.0
Parity/abortion (range)	
P (0-3)	0.96±1.02
A (0-1)	0.20±0.40
Family history of disease (%)	
Type 2 diabetes mellitus	36±18.0
Hypertension	58±29.0
No disease	106±53.0
Occupation	
Homemaker	154±77.0
Employed/student	46±23.0

BMI: Body mass index, SD: Standard deviation

Table 2: Patient's outcomes following Vitamin D supplementation

Outcomes (*n*=200)	Frequency (%)
Gestational diabetes	
Normal BS	196 (98)
Diabetes	4 (2)
PE	
Healthy	180 (90)
PE	14 (7)
PIH	6 (3)
SGA	
SGA	5 (2.5)
Non-SGA	195 (97.5)

PIH: Pregnancy-induced hypertension, SGA: Small for gestational age, PE: Preeclampsia, BS: Blood sugar

Table 3: Comparison of Vitamin D levels and random blood sugar before and after vitamin D supplementation

Vitamin D and BS (*n*=200)	Study steps		*P* (two-sided)
	Before supplement	After supplement	
Vitamin D level (ng/ml)	8.41±2.48	30.96±9.60	<0.0001
Random BS (mg/dL)	97.43±13.84	111.18±24.26	<0.0001

Paired *t*-test was performed for statistical analysis. BS: Blood sugar

Discussion

The prevalence of previously undiagnosed DM in Duhok governorate was 10.9% and impaired glucose homeostasis (impaired glucose tolerance and impaired fasting glucose) was 14.3%. The susceptibility of our

Table 4: Comparison of vitamin D level (after supplementation) in patients with different outcomes

	Vitamin D level (ng/ml)		*P* (two-sided)
Patient's categories	***n***	**Mean±SD**	
Small for gestation age			
SGA	5	27.60±8.26	0.409
Non-SGA	195	31.04±9.64	
PE			
PE	14	31.21±7.01	0.992
Healthy	180	30.94±9.94	
PIH	6	30.67±2.07	
Diabetes mellitus categories			
Healthy	186	31.16±9.88	0.514
Prediabetic	10	27.60±4.45	
Diabetes	4	30.00±2.31	

PIH: Pregnancy-induced hypertension, SGA: Small for gestational age, PE: Preeclampsia, SD: Standard deviation

women to high rates of GDM may be related to increased body weight (69.2%), sedentary lifestyle, and no physical activity.[26] There was no available data on the prevalence of GDM in Duhok.

In the current study, the risk of GDM was 2%, which is compatible to the study done by Zhang *et al*. who confirmed that the maternal plasma 25(OH) D concentrations in early pregnancy were significantly and inversely associated with GDM risk.[1]

Eighty-seven observational studies and 25 randomized controlled trials involving 55,859, and 2445 women, respectively, were included. These studies concluded that the low blood Vitamin D level during pregnancy was associated with a higher risk of GDM.[27]

In cohort study of 515 pregnant women by Al-Ajlan *et al*. concluded a significantly higher risk of development of GDM among pregnant women having deficient Vitamin D status.[15]

In a study of Iranian women at high risk for VDD, Hossein Nezhad *et al*. found that 29% of 741 women had 25(OH) D levels <15 nmol/L and the prevalence of GDM in this subgroup was higher compared to women with 25(OH) D levels ≥35 nmol/L. Another study by Wei *et al.* included 12 studies with 5615 participants and concluded that among women with 25(OH) D levels <50 nmol/L (20 ng/ml), there is a modest increase in odds of GDM.[28]

A meta-analysis of 20 observational studies that comprised 9209 participants showed that women with VDD experienced a significantly increased risk for developing GDM with a little heterogeneity.[29] A systematic review and meta-analysis to study the link between Vitamin D and gestational diabetes (2012) indicated a significant inverse relationship between serum 25(OH)D and the incidence of GDM and VDD. Furthermore, a systematic review and meta-analysis of 24 observational studies (2013) found that women with circulating 25(OH)D level <50 nmol/L (<20 ng/ml) in pregnancy experienced an increased risk of PE and GDM.[15]

In a large population-based prospective cohort study of 655 pregnant women done by Lacroix *et al*. found that the low levels of 25OHD at the first trimester are an independent risk factor for developing GDM and associated with insulin resistance at the second trimester.[30]

However, in a prospective cohort study (Spain, 2015) involving 2382 pregnant women, showed no association between maternal 25(OH)D3 concentration and risk of GDM.[15]

Another study by Farrant *et al*. found Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size.[31]

American College of Obstetricians and Gynecologists does not specifically list GDM as being associated with VDD, but the scientific literature suggests that women with GDM are at higher risk than normoglycemic women of low 25(OH)D levels even if the causality of the VDD – GDM association is not yet clear.[28]

Regarding SGA, the risk was 2.5% compared to the data from several countries. In consistent to our results, Aghajafari *et al*. indicated a significant association between SGA infants (with small fetal growth indices) and mother's Vitamin D insufficiency.[19] Another study done by Gernand *et al*. concluded that the maternal Vitamin D status in the second trimester is associated with risk of SGA among all women and in the subgroups of White and nonobese women. In observational studies, maternal VDD has been associated with risk of SGA in several general obstetric populations across the US and Europe.[32] Another study by Wang *et al*. suggested that the maternal Vitamin D insufficiency is independently associated with low birth weight and high risk of SGA in term infants.[33]

A Cochrane review reported that there is limited evidence to assess the impact of Vitamin D supplementation on SGA.[34]

Regarding PE, in our study, there was no reduction in the risk of PE. A similar study from the USA also failed to demonstrate an association between maternal first-trimester Vitamin D levels and the subsequent development of PE after controlling for BMI.[3]

Another study by Shand *et al*. found no difference in the rates of PE, gestational hypertension, preterm birth, or composite adverse pregnancy outcomes by 25OHD concentration.[35]

Our study was incompatible with the study done by Behjat Sasan *et al*. who suggests that the Vitamin D supplementation therapy in pregnancy could help in reducing the incidence of gestational hypertension/PE.[36]

Two meta-analyses including 8 and 31 studies found significantly higher risks PE in women with VDD.[3,37]

A nested case–control study conducted by Bodnar *et al*. found maternal VDD may be an independent risk factor for PE.[9]

Conclusion

The findings of our study highlight the need for Vitamin D supplementation among women during pregnancy. In this study, we found the supplementation of 5000 IU of Vitamin D/day for 8–10 weeks continuously is enough to elevate the serum level of 25(OH)D >20 ng/L. The response to Vitamin D supplementation was not affected by PE and GDM. There was a decrease in the risk of GDM and SGA but no change in the risk of PE. However, VDD is a correctable state, if proven effective; Vitamin D supplementation would be substantial and likely to impact the health of both mother and offspring.

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Conflicts of interest

There are no conflicts of interest.

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