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Original Article

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Maternal Vitamin D Level and Rate of Primary Cesarean Section

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Abstract

Background: Vitamin D deficiency has been a worldwide health problem, and pregnant women are considered as a high risk group among whom the prevalence of vitamin D deficiency is increasing to be around 5-40% and to reach a rate of 10-56% in breast fed infants. Recent studies revealed the importance of vitamin D during pregnancy and correlated its level to several pregnancy and neonatal outcomes. We aimed to assess the effect of low level of maternal vitamin D on the progress of labor affecting primary cesarean section (C-section) rate, pregnancy outcomes (such as risk of uterine atony and postpartum hemorrhage, pregnancy-induced hypertension, preeclampsia and gestational diabetes) and neonatal outcomes (such as low birth weight and preterm birth).

Methods: A prospective cohort study was conducted in two university hospitals in Lebanon between September 2016 and January 2017. A questionnaire was used for collecting date after taking informed consent to participate in the study. Demographic data, calcium intake, vitamin D intake including the dose, obstetric history complicating the current or previous pregnancy, mode of delivery and finally maternal and neonatal outcomes were recorded. Blood samples were collected from all patients participating in the study for vitamin D level measurement. Patients were divided into two groups: the control group (vitamin D level > 30 ng/mL) and the deficient group (≤ 30 ng/mL).

Results: A total of 381 patients were included in this study. In total, 40.9% of the deficient group delivered by C-section for failure of induction, failure to progress or failure to descend, compared to 12.8% only of the control group (P value < 0.0001). There was also a significant association between vitamin D deficiency and risk of uterine atony and postpartum hemorrhage (4.7% and 5.6%, respectively in the study group with low level of vitamin D compared to 0.7% and 1.3% in the control group with significant P value of 0.033 and 0.040, respectively).

Conclusion: Low maternal vitamin D level was associated with increased risk of primary C-section, uterine atony and postpartum hemorrhage.

Keywords: Vitamin D deficiency; Primary C-section; Uterine atony; Postpartum hemorrhage; Pregnancy outcomes; Birth weight; Preterm delivery; Pregnancy outcomes

Introduction

Vitamin D deficiency is a global health problem. It affects 5-50% of the pregnant population in the USA [1]. Vitamin D is important for proper contractility function as it plays an important role in calcium hemostasis. Both skeletal and smooth muscles depend on proper vitamin D level for contractility since vitamin D receptor (VDR) is expressed in cell nuclei of muscle cells [2]. In vitamin D insufficiency or deficiency, muscle function and physical activity may be impaired before clinical and biochemical signs of bone disease are evident [3].

Thus, vitamin D deficiency has been related to gestational diabetes, increased risk of preterm birth, uterine atony, pregnancy-induced hypertension and preeclampsia [4, 5]. Other studies showed that maternal vitamin D levels positively correlate with birth weight percentile [6].

Several risk factors lead to vitamin D deficiency or insufficiency such as little or no solar exposure, dress habits, malnutrition, dark skin, malabsorption and abnormal vitamin D metabolism [1].

Since cesarean section (C-section) rate is increasing worldwide and in the United States, the percentage of cesarean deliveries has increased substantially in recent years from 20.7% in 1996 to 31.1% in 2006 [7], we aimed to conduct a prospective cohort study to assess the effect of vitamin D deficiency or insufficiency on the rate of primary C-section due to failure of induction, failure to progress or failure to descend, and to study if there is correlation between low vitamin D level and other maternal and neonatal outcomes (uterine atony, postpartum hemorrhage, gestational diabetes, pregnancy-induced hypertension, preeclampsia, birth weight

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and preterm birth).

Materials and Methods

Study design

After obtaining approval from the Institutional Review Board (IRB) of the Makassed General Hospital, we conducted a prospective cohort study in two university hospitals including 381 pregnant women fitting the inclusion criteria in a time period from September 1, 2016 till the end of January 2017.

Inclusion/exclusion criteria

A total number of 381 women who delivered at the two university hospitals during this period of time were enrolled in the study. The inclusion criteria were: any pregnant women, previously healthy, with singleton pregnancy, nulliparous or multiparous, cephalic presentation with no congenital anomalies who presented to the delivery suite during this period of time and who delivered through normal vaginal delivery or by primary C-section for failure of induction, failure to progress or failure to descend.

We excluded from the study patients with multiple gestation or those with history of previous C-section. Moreover, patients with preexistent medical illness or chronic medical condition (like osteoporosis, mineral bone disease, liver disease intestinal malabsorption, cancer, thyroid or parathyroid dysfunction) or those who were taking some medications that can affect vitamin D level (anticonvulsants, antituberculosis drugs, etc.) were also excluded. Pregnant women with fetus known to have congenital anomalies or those who underwent elective C-section, or C-section for fetal distress, abnormal presentation (breech, transverse), abnormal placenta (previa, etc.), placental abruption and cephalopelvic disproportion were also excluded. Finally, we excluded patients with missed vitamin D level or withdrawal consent.

Data collection and questionnaire

Upon presentation of the patient to the delivery suite for delivery and after taking a written informed consent, a blood sample was taken for vitamin D level measurement and a questionnaire was completed by the team on call.

Data on socioeconomic status, age, body mass index (BMI), gestational age, ethnicity, parity, personal health, alcohol intake, season of delivery, calcium intake, and vitamin D supplementation during pregnancy including the dose were collected. Patients were also asked about the presence of any obstetrical history complicating the current or previous pregnancies: gestational diabetes, pregnancy-induced hypertension, preeclampsia, postpartum hemorrhage, preterm labor and preterm delivery.

After delivery, the mode of delivery (normal vaginal delivery, instrumental vaginal delivery or primary C-section), cause of the C-section, newborn gender and any complication like postpartum hemorrhage or atony were also documented. Small for gestational age (SGA) and preterm birth were considered as neonatal outcomes and were recorded in the data collection sheet of each patient.

Vitamin D measurement

Blood sample from peripheral venous blood was taken for all patients included in the study during their hospitalization for delivery. Samples were immediately fractionated and stored at 2 - 8 °C until analysis. The Elecsys vitamin D total assay was used for the quantitative determination of total 25OH vitamin D and 3 - 70 ng/mL was the measuring range of this assay. Based on lab standards, we divided patients into two groups: vitamin D level less than or equal to 30 ng/mL and vitamin D level greater than 30 ng/mL (sufficient group).

Statistical analysis

The Statistical Package for Social Sciences (SPSS, VERSION 21) program was used for data entry, management and analysis. Categorical variables were presented as number and percentage, whereas continuous variables were presented as mean and standard deviation. Bivariate analysis was carried out by using the Chi-square for comparing categorical variables, whereas the continuous ones were compared using the Student's *t*-test. A P value of less than 0.05 was used to indicate statistical significance.

Results

A total number of 381 pregnant women delivering at the two hospitals from September 1, 2016 till the end of January 2017 were enrolled in the study after fitting the eligibility criteria. Depending on the lab standards, patients were divided into two groups: the control group (149 patients with sufficient level of vitamin D greater than 30 ng/mL) and the study group (232 patients with vitamin D level less than or equal to 30 ng/mL).

Table 1 presents the socio-demographic characteristics and life style of the studied pregnant women according to their vitamin D level. There was no significant difference between both groups concerning age (mean age 26.91 years), educational status, alcohol intake, gestational age at delivery and newborn gender. Concerning BMI, patients were classified into three groups: underweight (BMI: less than or equal to 18.5), normal (BMI: 18.5 - 25) and overweight patients (BMI more than 25). Overweight women were more common in the control group with vitamin D level greater than 30 ng/mL than those in the study group with vitamin D level less or equal to 30 ng/mL (97.2% vs. 89.8%, respectively with P value of 0.014). With respect to seasons, most of the women delivered during autumn and winter since the study was conducted between September and January, and this period of time has the lowest sun exposure in our country. The percentage of women who delivered

Table 1. Demographic Characteristics of Patients in Both Groups

Maternal status	Total (N = 381)	VD level		P-value
		≤ 30 ng/mL (N = 232)	> 30 ng/mL (N = 149)	
Age, mean ± SD	26.91 ± 5.66	26.92 ± 5.86	26.91 ± 5.34	0.984
BMI				0.0137
≤ 18.5 (underweight)	1 (0.3%)	1 (0.5%)	0 (0.0%)	
18.5 - 25 (normal)	25 (7.0%)	21 (9.8%)	4 (2.8%)	
> 25 (overweight)	331 (92.7%)	193 (89.8%)	138 (97.2%)	
Race				1.000
White	377 (99.0%)	229 (98.7%)	148 (99.3%)	
Black	4 (1.0%)	3 (1.3%)	1 (0.7%)	
Season of delivery				0.0003
Autumn	191 (50.1%)	134 (57.8%)	57 (38.3%)	
Winter	186 (48.8%)	97 (41.8%)	89 (59.7%)	
Spring	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Summer	4 (1.0%)	1 (0.4%)	3 (2.0%)	
Educational status				0.0567
Illiterate	8 (2.1%)	8 (3.4%)	0 (0.0%)	
School	219 (57.5%)	130 (56.0%)	89 (59.7%)	
University	154 (40.4%)	94 (40.5%)	60 (40.3%)	
Sunscreen use				0.008
No	272 (71.4%)	177 (76.3%)	95 (63.8%)	
Yes	109 (28.6%)	55 (23.7%)	54 (36.2%)	
Alcohol				0.522
No	379 (99.5%)	230 (99.1%)	149 (100.0%)	
Yes	2 (0.5%)	2 (0.9%)	0 (0.0%)	
Parity				0.008
Nulliparous	125 (32.8%)	88 (37.9%)	37 (24.8%)	
Multiparous	256 (67.2%)	144 (62.1%)	112 (75.2%)	
Gestational age at delivery, mean ± SD	38.63 ± 1.06	38.68 ± 1.20	38.55 ± 0.83	0.218
Current pregnancy complications				0.005
No	302 (79.3%)	173 (74.6%)	129 (86.6%)	
Yes	79 (20.7%)	59 (25.4%)	20 (13.4%)	
Pregnancy-induced hypertension				0.161
No	376 (98.7%)	227 (97.8%)	149 (100.0%)	
Yes	5 (1.3%)	5 (2.2%)	0 (0.0%)	
Gestational diabetes				0.699
No	361 (94.8%)	219 (94.4%)	142 (95.3%)	
Yes	20 (5.2%)	13 (5.6%)	7 (4.7%)	
Preterm labor				0.008
No	331 (86.9%)	193 (83.2%)	138 (92.6%)	
Yes	50 (13.1%)	39 (16.8%)	11 (7.4%)	
Preeclampsia				1.000
No	380 (99.7%)	231 (99.6%)	149 (100.0%)	
Yes	1 (0.3%)	1 (0.4%)	0 (0.0%)	

Table 1. Demographic Characteristics of Patients in Both Groups - *(continued)*

Maternal status	Total (N = 381)	VD level		P-value
		≤ 30 ng/mL (N = 232)	> 30 ng/mL (N = 149)	
Previous pregnancy complications				0.003
No	362 (95.3%)	214 (92.6%)	148 (99.3 %)	
Yes	18 (4.7%)	17 (7.4%)	1 (0.7%)	
Postpartum hemorrhage				1.000
No	379 (99.7%)	230 (99.6%)	149 (100.0%)	
Yes	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Gestational diabetes				1.000
No	377 (99.2%)	229 (99.1%)	148 (99.3%)	
Yes	3 (0.8%)	2 (0.9%)	1 (0.7%)	
Preterm delivery				0.004
No	369 (97.1%)	220 (95.2%)	149 (100.0%)	
Yes	11 (2.9%)	11 (4.8%)	0 (0.0%)	
Pregnancy-induced hypertension				0.283
No	377 (99.2%)	228 (98.7%)	149 (100.0%)	
Yes	3 (0.8%)	3 (1.3%)	0 (0.0%)	
Preeclampsia				1.000
No	379 (99.7%)	230 (99.6%)	149 (100.0%)	
Yes	1 (0.3%)	1 (0.4%)	0 (0.0%)	
New born gender				0.438
Male	191 (50.1%)	120 (51.7%)	71 (47.7%)	
Female	190 (49.9%)	112 (48.3%)	78 (52.3%)	

in winter is higher in the control group with vitamin D level greater than 30 ng/mL than in the group with low level of vitamin D (59.7% vs. 41.8%, respectively with significant P value of 0.0003). Women who did not use sunscreen were more common in the study group than in the control group (76.3% vs. 63.8%) with significant P value of 0.008. Multiparous women were more common in the sufficient group with vitamin D level greater than 30 ng/mL than in the other group (75.2% vs. 62.1%) with P value of 0.008. For current pregnancy complications,79 of 381 patients had complications and there was a significant difference between both groups with P value of 0.005 (25.4% of women with vitamin D level less than or equal to 30 ng/mL had complications during their current pregnancy compared to 13.4% in the group with vitamin D level greater than 30 ng/mL). This significant difference is mainly for the history of preterm labor (16.8% of patients with vitamin D level less than or equal to 30 ng/mL compared to 7.4% of patients with vitamin D more than 30 ng/mL with significant P value of 0.008). For pregnancy-induced hypertension, gestational diabetes or preeclampsia, there was no significant difference between both groups. This was the same for the history of complications in previous pregnancies. Patients with vitamin D level less than 30 ng/mL had more complications in their previous pregnancies (7.4%) than those with vitamin D level greater than 30 ng/mL (4.7%) with significant P value of 0.003.

Table 2 describes the calcium intake in both groups. In total, 96.6% of all patients took calcium supplementation during pregnancy and there was no significant difference between both groups (95.3% of the study group vs. 98.7% of the sufficient group with P value of 0.075). Regarding the mode of delivery in both groups, of the 381 women enrolled in the study, 256 had normal vaginal delivery, 11 had instrumental vaginal delivery and 114 had primary C-section. Patients who delivered through normal vaginal delivery were more common in the control group (vitamin D level greater than 30 ng/mL), 87.2% compared to 54.3% in the group with low level of vitamin D and this was significant (P value < 0.0001). The rate of primary C-section was around three times more in the group with vitamin D less than or equal to 30 ng/mL than in the control group with vitamin D level greater than 30 ng/mL (40.9% vs. 12.8%, respectively with P value of < 0.0001). The causes of primary C-section were 58.8% (67/381) for failure to progress, 23.7% (27/381) for failure of induction and 17.5% (20/381) for failure to descend. There was no significant difference between both groups concerning the cause of primary C-section.

When comparing vitamin D level between patients who were taking vitamin D supplementation during pregnancy and those who did not take, 96.6% of patients with sufficient level of vitamin D were taking supplementation during pregnancy compared to only 49.6% of patients with low level of vitamin D with significant P value of < 0.0001.

Table 3 presents the percentage of different maternal out-

Table 2. Correlation Between Calcium Intake, Mode of Delivery, and Vitamin D Intake in Each Group With Respect to Vitamin D Level

	Total (N = 381)	VD level		P-value
		≤ 30 ng/mL (N = 232)	> 30 ng/mL (N = 149)	
Calcium intake				0.075
No	13 (3.4%)	11 (4.7%)	2 (1.3%)	
Yes	368 (96.6%)	221 (95.3%)	147 (98.7%)	
Mode of delivery				< 0.0001
Normal vaginal delivery	256 (67.2%)	126 (54.3%)	130 (87.2%)	
Operative vaginal delivery	11 (2.9%)	11 (4.7%)	0 (0.0%)	
Primary C-section	114 (29.9%)	95 (40.9%)	19 (12.8%)	
Cause of primary C-section				0.254
Failure to progress	67 (58.8%)	55 (57.9%)	12 (63.2%)	
Failure of induction	27 (23.7%)	25 (26.3%)	2 (10.5%)	
Failure to descend	20 (17.5%)	15 (15.8%)	5 (26.3%)	
Vitamin D intake				< 0.0001
No	122 (32.02%)	117(50.4%)	5(3.4%)	
Yes	259 (67.98%)	115(49.6%)	144(96.6%)	

comes in both groups. From the total number of 381 women included in the study, 12 had uterine atony (3.1%), 15 had postpartum hemorrhage (3.9%), one had postpartum transfusion (0.3%), four had pregnancy-induced hypertension (1%), one case had preeclampsia (0.3%) and 14 cases had gestational diabetes (3.6%). Women who had uterine atony and postpartum hemorrhage were more common in the group with vitamin D level less than or equal to 30 ng/mL (4.7% and 5.6%, respectively) than in the control group with sufficient level of vitamin D (0.7% and 1.3%) with significant P value of 0.033 and

Table 3. Maternal Outcomes and Vitamin D Level

Maternal outcome	Total (N = 381)	VD level		P-value
		≤ 30 ng/mL (N = 232)	> 30 ng/mL (N = 149)	
Atony				
No	369 (96.9%)	221 (95.3%)	148 (99.3%)	0.033
Yes	12 (3.1%)	11 (4.7%)	1 (0.7%)	
PPH (postpartum hemorrhage)				
No	366 (96.1%)	219 (94.4%)	147 (98.7%)	0.040
Yes	15 (3.9%)	13 (5.6%)	2 (1.3%)	
Postpartum transfusion				
No	380 (99.7%)	231 (99.6%)	149 (100.0%)	1.000
Yes	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Pregnancy-induced hypertension				
No	377 (99.0%)	228 (98.3%)	149 (100.0%)	0.159
Yes	4 (1.0%)	4 (1.7%)	0 (0.0%)	
Preeclampsia				
No	380 (99.7%)	231 (99.6%)	149 (100.0%)	1.000
Yes	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Gestational diabetes				
No	367 (96.3%)	227 (97.8%)	140 (94.0%)	0.049
Yes	14 (3.7%)	5 (2.2%)	9 (6.0%)	

Table 4. Neonatal Outcomes and Vitamin D Levels

Neonatal outcome	Total (N = 381)	VD level		P-value
		≤ 30 ng/mL (N = 232)	> 30 ng/mL (N = 149)	
Small for gestational age				
No	363 (95.3%)	220 (94.8%)	143 (96.0%)	0.607
Yes	18 (4.7%)	12 (5.2%)	6 (4.0%)	
Preterm delivery				
No	373 (97.9%)	226 (97.4%)	147 (98.7%)	0.490
Yes	8 (2.1%)	6 (2.6%)	2 (1.3%)	

0.040, respectively. The percentage of gestational diabetes was higher in the group with sufficient level of vitamin D (6.0%) than in the group with low level of vitamin D (2.2%) with P value of 0.049. Otherwise, there was no significant difference between both groups concerning other maternal outcomes like pregnancy-induced hypertension, preeclampsia and postpartum transfusion.

Table 4 presents the correlation between neonatal outcomes and vitamin D level. From a total number of 381 patients, 18 cases were SGA and eight cases were preterm delivery. The difference is not significant for these outcomes. Overall, 5.2% of patients with low level of vitamin D had SGA compared to 4% of patients with sufficient level of vitamin D. Only 2.6% of patients with low level of vitamin D had preterm delivery vs. 1.3% of patients in the control group.

Finally, Table 5 demonstrates the mean of vitamin D level for each regimen of supplementation during pregnancy. Patients who did not take any vitamin D supplement during pregnancy had a mean level of 11.44 ± 9.02 ng/mL. This level increased gradually in proportion to the dose of vitamin D taken during pregnancy. It was about 19.28 for patients who were taking 10,000 IU once/week which was increased to a mean of 33.02 when they took 10,000 IU twice per week and to a higher level with a mean of 34.67 when the regimen of supplementation was 25,000 IU once per week.

Discussion

Our prospective cohort study revealed a high prevalence of vitamin D deficiency among pregnant women (60%) and this was similar to other studies [2, 8].

Some studies showed no association between vitamin D deficiency and the incidence of primary C-section or obstructed labor [9]. However, an observational study done by Merewood et al [8] showed four times increased risk of C-section among women with low level of vitamin D less than 37.5 nmol/mL. This significant association between maternal vitamin D level and C-section rate was demonstrated also in another study [2].

Table 5. Vitamin D Supplement Regimen and Maternal Level

Vitamin D supplement and regimen	Vitamin D level, mean ± SD	P-value
No vitamin D intake	11.44 ± 9.02	< 0.0001
Vitamin D 10,000/week	19.28 ± 11.84	
Vitamin D 10,000 twice/week	33.02 ± 4.76	
Vitamin D 25,000/week	34.67 ± 7.44	

In our prospective cohort study, the percentage of primary C-section for failure to progress, for failure to descend and for failure of induction was three times greater among women with vitamin D level less than or equal to 30 ng/mL than in women with sufficient level of vitamin D with significant P value of < 0.0001 (40.9% vs. 12.8%, respectively). One explanation for this significant association is that skeletal and smooth muscle contains vitamin D receptors [2]. So vitamin D deficiency can lead to a decreased muscle performance and strength, with reduced ability of the pregnant women to push to a longer time, thus the difficulty to deliver normally [2].

In addition, serum calcium level which is regulated by vitamin D has a role in the initiation of labor as some studies showed [10]. So it is possible that vitamin D deficiency by lowering the level of serum calcium can affect skeletal and smooth muscle strength and thus the initiation of labor.

Because vitamin D deficiency decreases the serum calcium level which will affect the uterine muscle contractility [10], this deficiency can be a main contributing factor for uterine atony and so postpartum hemorrhage. In our study, the findings were similar to other results reported by Khan et al who found a significant association between vitamin D deficiency and uterine atony (4.7% of patients who developed uterine atony were among women with vitamin D level less than or equal to 30 ng/mL compared to 0.7% among women with sufficient level of vitamin D with significant P value of 0.033) [11].

And as we all know, uterine atony is one of the most leading causes of postpartum hemorrhage [11]. In our analysis, we also demonstrated a strong association between vitamin D level and the risk of postpartum hemorrhage since most of the causes of postpartum hemorrhage were due to uterine atony (nine cases out of 12).

The diagnosis of preeclampsia and gestational hypertension was based on the American College of Obstetrics and Gynecologists (ACOG) guidelines [12]. Some studies have demonstrated that maternal vitamin D level can affect the risk of preeclampsia and pregnancy-induced hypertension [13, 14]. This association can be explained by the way in which the implantation of trophoblastic cells in the endometrium occurs where an exacerbated maternal immune response can lead to a

superficial implantation and so decrease the mother tolerance to the fetus [15]. In addition, recent researches reported that vitamin D was found to have immunomodulation effects and this may have essential role in the implantation process [16]. So deficiency in vitamin D can cause imbalance between pro and inflammatory cytokines, vascular endothelial dysfunction (lower level of VEGF) and increase the risk of preeclampsia [16, 17]. On the other hand, previous studies have related vitamin D deficiency to pregnancy-induced hypertension by the activation of the renin angiotensin aldosterone system [18] or by increasing the vessels resistance by direct effect or indirectly by the effect of secondary hyperparathyroidism [19]. In our cohort study, we did not find any association between maternal vitamin D level and these pregnancy complications: preeclampsia and pregnancy-induced hypertension. From a total number of 381 patients, only four cases of preeclampsia and one case of pregnancy-induced hypertension were detected and all were among patients with inadequate level of 25OH vitamin D. These results were similar to previous findings reported by other studies, where no correlation between vitamin D level and hypertensive disorders of pregnancy was found [20, 21]. This lack of association can be due to the overall limited number of patients having preeclampsia or gestational hypertension (only five cases) from our relatively small sample size. It has been speculated also that the most important time for vitamin D supplementation to have an effect on preeclampsia risk is during the first trimester when the placenta is still developing [21]; however, in our study samples were taken later at term. Another explanation is that the effect of low vitamin D level on hypertensive disorders in pregnancy is a result of its effect on BMI [22]. Future researches with larger sample size and further interventions may be needed for better explanation.

Some studies showed that pregnant women with low level of vitamin D are at higher risk of developing gestational diabetes [23]. Others did not find any association between maternal 25OH vitamin D status and risk of gestational diabetes [24]. In our prospective study, women with vitamin D level less than or equal to 30 ng/mL did not have greater percentage of gestational diabetes than women with sufficient level.

Vitamin D plays a role in bone metabolism, placenta sex steroids production and therefore in fetal growth, development and newborns outcomes [25]. Several studies were done to assess the relationship between maternal vitamin D status and the risk of being SGA [13, 26-29]. Three studies showed a significant association between vitamin D deficiency and SGA [12, 26, 29]. Leffelaar et al [26] reported that mothers with inadequate level of vitamin D had a significant high risk of giving birth to SGA infants. Bodnar et al showed that the correlation between maternal vitamin D status and the risk of SGA varied according to race where he demonstrated no association among black women and U-shaped association among white women [29]. Finally a case-control study was done by Robinson et al and the result was that maternal vitamin D level was significantly lower in cases with SGA infants than with controls [13]. In our analysis, the results were similar to those done by Akcakus et al [27] and Mehta et al [28] where they did not find any significant association between maternal vitamin D level and SGA (5.2% of patients with low level of vitamin D had SGA babies compared to 4% among women with sufficient level of vitamin D level with insignificant P value of 0.607). The reason for the lack of association might be due to the relatively small sample size. One of the explanations is that the effect of maternal vitamin D deficiency on infant growth can be affected by fetal VDR gene polymorphism as demonstrated recently by Morley et al [6]. However, future studies with large samples are needed to confirm or reject our results.

In our study, preterm birth was defined by delivery at less than 37 week of gestational age based on LMP or ultrasound. Some studies suggests that vitamin D deficiency can increase the risk of preterm birth [30] and others reported that this complication can be reduced by an adequate supplementation of vitamin D early during pregnancy [31]. The exact mechanism by which vitamin D regulates hormonal factors of pregnant women is still unclear. Possible explanation is that vitamin D deficiency can induce preterm birth by increasing the risk of other pregnancy complications like hypertension, preeclampsia, gestational diabetes, premature rupture of membrane and bacterial vaginosis [32]. Recent studies also showed that maternal calcium level which is regulated by vitamin D plays a role in both preterm labor and initiation of labor [33]. Others reported that adequate level of vitamin D can prevent preterm birth by reducing the bacterial infections through inducing cathelicidin in maternal and fetal cells of the placenta [16]. In our analysis, there was no significant difference in the percentage of preterm birth between both groups (2.6% in patients with low level of vitamin D less than or equal to 30 ng/mL vs. 1.3% in patient with vitamin D level more than 30 ng/mL). So our study did not report any significant association between vitamin D level and incidence of preterm birth. This was comparable to other studies done previously [28, 31].

Several studies have demonstrated the role of vitamin D supplementation in the prevention of many maternal and neonatal outcomes [31, 34]. It has been reported also that the level of 25OH vitamin D in serum is increasing by supplementation which reduces the prevalence of vitamin D deficiency [35]. This was confirmed in our study where the majority of patients with sufficient level of vitamin D were taking vitamin D supplementation during their pregnancy (96.6% of patients with vitamin D level greater than 30 ng/mL were on vitamin D supplements). It is important to mention that at the end of pregnancy about 90% of the patients who were taking vitamin D supplements were still deficient for vitamin D. This is because the debate concerning the optimal dose of vitamin D supplementations is still ongoing and varies between societies. For example, UK recommends daily 400 IU of vitamin D supplementation during pregnancy [36]. This is different from the recommendations given by the WHO [37], Endocrine Clinical Practice [38], Institute of Medicine [39] and the Canadian Pediatric Society [40]. In our collected data, there were three types of regimens used (10,000 IU/week, 10,000 IU twice/week and 25,000 IU once weekly). Our analysis found that the mean level of serum 25OH vitamin D is 11.44 for patients who did not take vitamin D supplementation and this level increased in proportion with respect to the dose given to reach a mean of 34.67 for a high dose given 25,000 IU once per week. In fact, even with a high dose of supplementation, we did not have in our study a markedly elevated level of serum 25OH vitamin D. This can be because vitamin D is depend-

ent on many factors (race, sun exposure, genetics or seasons). Also, this relatively low level of 25OH vitamin D according to the high dose given can be explained by the different time at which the patients started to take vitamin D supplementations or by the non-compliance of the patient. Finally, more research is needed for an optimal vitamin D supplementation dose during pregnancy and for the safety of a high dose.

Strengths and limitations

Our study has several limitations that should be taken into consideration in future investigations. Maternal serum 25OH vitamin D concentrations were not longitudinally measured throughout the gestational period which could have affected the results. Moreover, our study was limited by small sample size. Finally, the low rate of adverse pregnancy and neonatal outcomes may limit the statistical power to detect significant differences. On the other hand, one of the strengths of this study was the power of our study. Moreover, this is the first study done on the Lebanese population to assess the effect of vitamin D on the rate of primary C-section, uterine atony and postpartum hemorrhage. Finally, this was a prospective multicenter study, which is another strength.

Conclusion

Our prospective cohort study showed a high prevalence of vitamin D deficiency among pregnant women and demonstrated a strong association between maternal vitamin D level, increased rate of primary C-section and other pregnancy outcomes like uterine atony and postpartum hemorrhage. This reflects the importance of vitamin D screening during pregnancy and the effect of supplementation in the prevention of maternal morbidity and mortality.

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Conflict of Interest

The authors did not declare any conflict of interest.

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