Original Article

Vitamin D Status and Response to Vitamin D3 (50000 unit supplementation) in pregnant Iranian woman

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ABSTRACT

Vitamin D deficiency has adverse consequences for both mother and neonate. Most of these conditions are reversible and preventable. Despite taking 600 IU vitamin D per day (recommended dose) during pregnancy, the prevalence of vitamin D deficiency in healthy women still remains high. The aim of this study was to identify the prevalence of vitamin D deficiency in an Iranian pregnant population and to analyze the impact of implementing a screening and treatment protocol among them. This study conducted at a prenatal care clinic in Tehran, Iran. The screening for vitamin D deficiency was typically performed at two points: one at the initial prenatal visit and another at approximately 28 weeks' gestation. If Vitamin D status was insufficient an additional vitamin D3 supplement of 50,000 IU of ergocalciferol was prescribed weekly for 10 weeks. The results of this study confirmed that vitamin D deficiency and insufficiency are quite prevalent in the study population, insufficient (79.6%) or deficient (59.7%), and required an increase in their vitamin D level to achieve sufficiency. Supplementation with less than 50,000 IU per week is insufficient to ensure a vitamin D level above 20 ng/ml in all vitamin D deficient pregnant women. Even larger doses are required to achieve sufficient vitamin D levels (above 30 ng/ml). In conclusion, implementing a screening and supplementing protocol during pregnancy resulted in a significant increase in the percentage of women who were able to achieve a status of vitamin D sufficiency.

Keywords: Vitamin D deficiency, pregnancy, supplementation.

Introduction

Detection of insufficient vitamin D level is ubiquitous. In pregnant population, it affects 20 to 80 percent of women [1]. The skeletal consequences of vitamin D deficiency include decreased intrauterine bone mineral density [2], neonatal craniotabes, congenital and infantile rickets and pregnancy associated osteomalacia [1, 2]. Low levels of vitamin D during pregnancy also harbor detrimental adverse effects, namely, insulin resistance, gestational diabetes mellitus, increased risk of preeclampsia, bacterial vaginosis, primary cesarean section, intrauterine growth retardation, low birth weight [3], small-for-gestational age, preterm birth, and early-onset sepsis in full-term neonates [4]. Fortunately, most of these conditions are reversible and preventable [2].

Biochemically, nutritional vitamin D enters the body as a fat-soluble prohormone and is hydroxylated following light exposure in the skin into 25-hydroxy form (25 (OH) D) which is the main circulatory component of vitamin D (20). In the kidneysVitamin D is metabolized into the active steroid hormone, the calcitriol [1, 25 (OH) vit D]. Calcitriol regulates the absorption and excretion of calcium and phosphate in the intestine and kidneys and cause bone mineralization and skeletal growth [5]. The major source of vitamin D is sunlight exposure that causes cutaneous synthesis [6]. Risk factors of vitamin D deficiency include use of sunscreen, age, darker skin tones,

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seasonal, inadequate sun exposure, lifestyle, taking insufficient vitamins, low intake of fortified food, low compliance with supplements, premature birth, covering the skin with clothing, overweight and living at high altitude [7, 8].

Previous studies in Iran have demonstrated a high prevalence of vitamin D deficiency among pregnant women [9]. The daily recommended dose of vitamin D during pregnancy is 400 to 600 IU [10]. Most prenatal supplements contain 400 IU. However, according to some authors, despite taking 600 IU vitamin D per day, the prevalence of vitamin D deficiency in healthy women still remains high [11]. On the other hand, the exact amount of vitamin D supplementation during pregnancy is not known. The aim of this study was to identify the prevalence of vitamin D deficiency in an Iranian pregnant population and to analyze the impact of implementing a screening and treatment protocol among them.

Materials and Methods

This study conducted at a prenatal care clinic in Tehran, Iran.

Patients' medical records were utilized to create reports of all women who received prenatal care during March 19, 2015, through March 19, 2016. In so doing, 357 cases were identified.

Women were included in the study if: (1) maternal age of 16 years or greater at the time of consent, (2) confirmed singleton pregnancy of less than 16 weeks' gestation at the time of consent, (3) planned to receive ongoing prenatal care in our prenatal clinic in Tehran, (4) they had at least two measurements of vitamin D levels in the first or second trimesters and in the third trimester. Exclusion criteria included twin pregnancy, maternal immune deficiency disease, and a history of gastric bypass surgery.

Of total 714 pregnant women, 498 patients had first trimester and 556 had third trimester vitamin D level. The final sample size of this study was 432. Subjects began vitamin D supplementation at the start of the 12 weeks' gestation, as defined by their last menstrual period. Vitamin D supplements were avoided before 12 weeks'gestation.

BMI was based on weight and height as measured at 12 weeks' gestation. All participants were asked about their use of vitamin and mineral supplements at each time-point, and any multivitamin supplementation were noted in their record. The screening for vitamin D deficiency was typically performed at two points throughout prenatal care: one at the initial prenatal visit and another at approximately 28 weeks' gestation.

All patients received one pill daily: a standard prenatal multivitamin containing 400 IU of vitamin D. If Vitamin D status was insufficient an additional vitamin D3 supplement of 50,000 IU of ergocalciferol was prescribed weekly for 10 weeks. In order to maintain 25 (OH) D levels above 30 ng/ml, 50,000 IU vitamin D was prescribed monthly [12, 13].

Vitamin D status (deficient, insufficient, or sufficient) was also included, and the classification was based on the US Endocrine Society guideline recommendations (≤20 ng/ml (50 nmol/liter) as deficiency, 21-29 ng/ml (525–725 nmol/liter) as insufficiency, and ≥30 ng/ml as sufficiency).

We also recorded the complications of the pregnancy, such as gestational diabetes mellitus, status of thyroid function, anemia, and maternal weight gain as well as the outcomes of the pregnancy in terms of congenital malformations and neonatal birth weight.

Vitamin D level for mothers was assayed on the serum collected by 25-hydroxy vitamin D IDS GmbH Immunodiagnostic Systems, Sunrise, Tecan Co Salzburg, Austria. The method was enzyme immunoassay (EIA). Samples were placed in serum separator anticoagulant-free tubes (SST) II with separation gels and immediately sent to the laboratory, where they were centrifuged for 5 min at 3500 rpm to obtain serum. Serum aliquots were then frozen at _70 _C until they were ready for testing. The Immunodiagnostic System GmbH had intra- assay CV%: 2.6%, interassay CV%: 2.8%, and its sensitivity was 5 nmol/lL (2 ng/ml).

The study was approved by the ethics committee of the Imam Khomeini hospital (No: 1396.3435), Tehran University of Medical Sciences, Tehran, Iran. Its registration reference in Iranian Registry of Clinical Trials (IRCT) is IRCT20170714035077N3. A written informed consent was obtained from all patients and they were informed that participation was anonymous and voluntary. They were also ensured that the results would be confidential and advantageous to them.

The statistical analysis was accomplished by SPSS version 18.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Descriptive statistical techniques were used to determine the prevalence and the means. The Pearson correlation test was used to examine the correlation between the variables. P-values less than 0.05 were considered to be statistically significant. The Paired-Samples T-Test was used for comparing the means between groups.

Results

The mean age of the participants was 31.26 ± 4.82 years (range from 19 to 45 years). The mean Maternal BMI was 24.53±3.76 (range from 16.66 to 42). The baseline characteristics of the 432 included women are shown in Table 1. Initial measurements of serum 25 (OH) D at the beginning of the second trimester revealed that 340 participants (78.7%) had a serum level below 30 ng/ml and 264 participants (61.1%) had initial levels below 20 ng/ml. The mean serum 25 (OH) D level in the initial measurement was 21.22 ± 15.89 ng/ml (minimum: 3 ng/ml, maximum: 109 ng/ml). Second measurements of serum 25 (OH) D in the third trimester revealed that 138 participants (31.9%) had a serum 25 (OH) D level below 30 ng/ml and 40 participants (9.3%) had initial levels below 20 ng/ml. The mean serum 25 (OH) D level in the third trimester was 35.89 ± 13.48 ng/ml (minimum: 6.34 ng/ml, maximum: 89 ng/ml) (Table 2). The difference between the level of vitamin D in the second and third trimesters was statistically significant (P=0.01).

In 264 participants who initial levels was below 20 ng/ml the mean serum 25 (OH) D levels in the initial measurement was 11.63± 4.32, their mean serum 25 (OH) D level in the third trimester was 35.52± 4.52. The difference between the level of vitamin D in the second and third trimesters was statistically significant (P<0.01).

Considering gestational diabetes mellitus (GDM), there was no significant difference between vitamin D levels in the diabetic and non-diabetic population after supplementation (29.16 ± 16 and 33.85 ± 12 respectively, P=0.061)

participants by initial 25 (OH) D levels below 20 ng/ml have significantly higher TSH (thyroid stimulating hormone) level (2.53± 1.72 mU/l versus 2.07±1.40 mU/l; P=0.005).

We found no association between the level of vitamin D and conditions such as anemia, maternal BMI, weight gain during pregnancy, neonatal birth weight, and congenital malformations.

During the prenatal follow-up plan, no report regarding side effects or the difficulty of supplement consumption was noted.

Table 1. Demographic and reproductive characteristics of participants

Variables	Amount
Maternal age (year)	31.26±4.28 (19-45)
Infant's gender	Male: 53.8%
Infant's birth weight (grams)	3254.06±436.65 (1200-4400)
Infant's gestational age at birth (<37w)	0
Delivery type (Cesarean)	87.3%
Maternal BMI (kg/m^2)	24.53±3.76 (16.66-42)
Weight gain during pregnancy (Kg)	14.47±5.51 (1-37)
Initial status of vitamin D (ng/ml)	21.22±15.89 (3-109)
Secondary status of vitamin D (ng/ml)	35.89±13.48 (6.34-89)

Table 2. The status of vitamin D in pregnant women

			Secondary status of vitamin D		**total**
			Deficient	Non deficient	
Initial status of vitamin D	Deficient	Frequency	32	232	264
		Percent	12.1%	87.9%	100%
	Non deficient	Frequency	8	160	168
		Percent	4.8%	95.2%	100%
Total		Frequency	40	392	432
		Percent	9.3%	90.7%	100%

Discussion

The results of this study confirmed that vitamin D deficiency and insufficiency are quite prevalent in the study population. Previous studies have numerated some factors influencing vitamin D deficiency such as skin pigmentation and inadequate dietary intake [14, 15]. It also has been postulated that inadequate sun exposure for extended periods would lead to vitamin D deficiency [16].

Previous studies have revealed prevalence of vitamin D deficiency in different countries from 18 to 84 percent according to ethnicity, region, culture and customs [17]. Also, a number of studies have demonstrated that vitamin D deficiency is frequent among Iranian pregnant women [9]. Kazemi et. al observed a high prevalence of physiologically significant hypovitaminosis D among Iranian pregnant women in winter (86%) and in summer (46%) [16]. A study of pregnant women in 2002-2003 in Tehran has found that 60% in the first trimester, 48% in the second trimester, and 47% in the third trimester had either severe (25 (OH) D level below 10 ng/ml) or moderate (25 (OH) D level below 20 ng/ml) Vitamin D deficiency. Another study in Tehran (1997) found 80% prevalence of vitamin D deficiency (25(OH) D level below 10 ng/ml) in women at the time of delivery [18, 19].

According to ACOG Guidelines there is no recommendation for universal screening of pregnant women for vitamin D deficiency. For pregnant women at high risk of vitamin D deficiency (including vegetarians, dark skin tones, limited sun exposure, residents of cold climates, high altitudes, or those who wear sun and winter protective clothes) maternal serum 25-OH-D levels should be interpreted [20, 21]. Thereby Iranian women are at high risk of vitamin D deficiency because of their body covering, and screening could be beneficial.

The results of the current study showed that a high percentage of pregnant women were initially insufficient (79.6%) or deficient (59.7%), and required an increase in their vitamin D level to achieve sufficiency. Although most women achieved sufficient levels of vitamin D by our supplement protocol, still 7.4% remained vitamin D deficient, and 34.7% remained vitamin D insufficient after the intervention. It appears that weekly doses of vitamin D (50,000 IU) are required during the pregnancy for vitamin D deficient women in order to achieve serum 25 (OH) D levels above 20 ng/ml. Supplementation with less than 50,000 IU per week is insufficient to ensure a vitamin D level above 20 ng/ml in all vitamin D deficient pregnant women. Even larger doses are required to achieve sufficient vitamin D levels (above 30 ng/ml).

While there are numerous studies reporting a high prevalence of vitamin D deficiency among pregnant women, few studies have examined different doses of vitamin D supplementation during pregnancy. However, there is a lack of agreement about the need for vitamin D supplementation during pregnancy [22]. We have no global protocol on the exact doses of vitamin D supplementation that is appropriate to either maintain or achieve sufficient 25 (OH) D levels. ACOG said that for vitamin D deficient pregnant women, 1000–2000 IU/day is safe [21]. However, our results revealed that this dose is not enough to achieve sufficient levels. Cooper in his study demonstrated the overall safety of vitamin D supplementation during pregnancy, but he found that supplementation of pregnant women with cholecalciferol 1000 IU/day from 14 weeks' gestation until delivery was not sufficient [23].

Most experts agree that vitamin D supplementation in doses up to 4000 IU/day is safe during pregnancy [10]. Hollis et. al showed vitamin D supplementation with 4000 IU/d was more effective in achieving vitamin D sufficiency throughout pregnancy [24]. In their survey, Yap et. al demonstrated safety of high dose supplementation (5,000 IU daily) in women with baseline plasma 25 (OH) D levels below 32 ng/ml [25].

We found no association between the level of vitamin D and maternal weight gain, maternal anemia, neonatal birth weight, and congenital malformations. Interestingly, an association was detected between the level of vitamin D and gestational hypothyroidism. Although there are reports of such a correlation in non-pregnant population, no study has yet reported this in pregnant population. Significant low levels of vitamin D were documented in patients with autoimmune thyroid disease, attributable to the presence of antithyroid antibodies [26, 27].

Some studies have shown a higher rate of vitamin D deficiency in GDM [28]. However, our findings did not confirm this. Hypponen found dietary vitamin D supplementation was associated with reduced risk of type 1 diabetes. Maghbooli et. al reported prevalence of severe vitamin D deficiency (<12.5) in GDM patients was higher than in normoglycaemic pregnancies. They postulated that vitamin D deficiency could be a confirmative sign of insulin resistance [29].

The limitation of our study was the lack of information about confounding variables, such as diet, season, use of sunscreen and sun exposure [30]. Because the study was retrospective, only documented information in the patients' medical charts was available. Therefore, so non-compliance with prescribed supplements could not be assessed for sure. Further prospective studies would help evaluate the proper dose needed to maintain or raise vitamin D levels during pregnancy.

Conclusion

In conclusion, this study demonstrated a high rate of vitamin D deficiency during pregnancy. Implementing a screening and supplementing protocol during pregnancy, resulted in a significant increase in the percentage of women who were able to achieve a status of vitamin D sufficiency, however, some remained vitamin D insufficient. Further investigation is needed to find the exact causes and factors that contribute to vitamin D deficiency in pregnant women. The exact dietary vitamin D required to maintain vitamin D sufficiency during pregnancy should be determined in future studies, and a guideline for providing adequate supplementation during pregnancy should be devised in order to decrease the rate of vitamin D insufficiency in pregnant women.

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Disclosure Statement

The authors have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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