Original Article

The relationship between Vitamin D deficiency and thyroid function in the first trimester of pregnancy

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Abstract

Aims and Objective: There are few studies about the relationship between vitamin D deficiency and thyroid hormone levels in pregnancy. This study aimed to assess the relation serum vitamin D levels with thyroid hormones in the first trimester of pregnancy in Iran. **Methods:** In this case-control research 430 pregnant women (215 mothers with vitamin D deficiency, and 215 without this deficiency) attending prenatal clinics in Tehran, Iran were studied. 25 hydroxy vitamin D levels and thyroid function tests [free tetraiodothyronine (FT4), thyroid stimulating hormone (TSH), and free triiodothyronine (FT3)] were measured in all mothers. Data were analyzed using SPSS version 22 software. Kolmogorov-Smirnov test was used for normality testing of continuous variables; Student T-Test, and Mann-Whitney U test were used to compare the continuous parametric and nonparametric variables respectively in the 2 study groups; Linear regression model was used to assess the effect of potentially effective variables besides vitamin D on thyroid function tests. **Results:** In Mann-Whitney U test performed**,** T4 levels (mean± SD) were significantly higher in vitamin D deficiency group compared with the control group (20.8 ±32.5 vs.14.4 ± 24.1 ng/dl, P-value: 0.04), but there were no significant differences between the 2 study groups regarding TSH, and free T3 levels. In Linear regression analysis, assessing the effects of vitamin D deficiency plus maternal age, Body Mass Index, and number of pregnancies on thyroid function tests, it was shown that vitamin D deficiency had only a significant direct relation with free T4 levels (β: 0.122, P-value: 0.01), but had no significant relations with the other thyroid function tests namely TSH, and free T3. **Conclusion:** A significant direct relationships were observed between Vitamin D deficiency with the level of thyroxin (T4) during early pregnancy. higher levels of T4 in vitamin D deficient mothers. Due to the negative effects of Vitamin D deficiency and thyroid hormones on the mother and fetus, further studies should be conducted which may help in more accurately screening during pregnancy.

Keywords: Vitamin D, Vitamin D deficiency, Thyroid function, Pregnancy.

INTRODUCTION

Vitamin D is a fat-soluble vitamin and a steroid hormone, which its main role is calcium and bone metabolism. The deficiency of this vitamin is known as a worldwide problem. Evidence has shown that vitamin D deficiency may increase the risk of a wide range of chronic diseases. Also, its deficiency can increase the likelihood of autoimmune diseases, upper respiratory tract infection, diabetes, cardiovascular disease, and cancer . [1]

This vitamin is active in the immune system and its role as a modulator of the immune system has recently been highlighted [2] Several clinical trials have shown that autoimmune diseases such as lupus erythematosus, [3] Multiple sclerosis[4], Rheumatoid arthritis, [5] Hashimoto's thyroiditis, and hypothyroidism are associated with vitamin D deficiency. [6]

Vitamin D receptors are present in various tissues of the body such as pancreas, thyroid gland, and myocardium, etc. [7] The important point here is that both vitamin D and thyroid hormones, attach to similar receptors called steroid hormone receptors. On the other hand, a kind of gene in the Vitamin D receptor has been shown to predispose persons to autoimmune thyroid disease. Therefore, any change in vitamin D levels may increase the risk of thyroid

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abnormalities. For these reasons, it is important in patients with thyroid disease to understand the effects of Vitamin D on health. [8, 9] The main mechanisms of the role of vitamin D in autoimmune diseases have not been fully understood but in a clinical trial with a review of vitamin D receptor (VDR) in patients with thyroiditis, increased thyroid disease risk was shown.[10] Recent evidence demonstrates the relationship between vitamin D and Hashimoto thyroiditis and Graves ' disease. Vitamin D may have a role in thyroid diseases, including thyroiditis and thyroid carcinoma.[11] It was also seen that Vitamin D deficiency, especially the amounts of less than 12.5 ng/ml, was considered as a risk factor for autoimmune disease and thyroid disease.[12] Besides, an increased level of TSH was observed after the administration of vitamin D supplements. [13] Another study reported the effect of pregnancy suppressant on thyroid parameters (thyroxin (T4) hormone triiodothyronine (T3) and thyroid-stimulating hormone (TSH)).[14]

Even though many studies have evaluated the role of vitamin D in thyroid disease, few studies have investigated the effects of 25-hydroxy vitamin D on thyroid hormones in pregnancy and their effects on maternal and fetal health. [15-17] Pregnancy may be associated with changes in iodine homeostasis and other physiological changes that eventually lead to altered thyroid function. [18] Maternal thyroid function should be maintained normally, especially in the first trimester. In the first trimester, the fetus is fully dependent on maternal thyroid hormones for brain development. [19] Several studies have shown that vitamin D deficiency and thyroid function can lead to a series of adverse complications during pregnancy, including gestational hypertension [20, 21] preeclampsia [22, 23] Preterm delivery [21, 24] intellectual and neurological growth disorder in children [17, 25] and so on. Therefore, to maintain a healthy pregnancy and normal fetal skeletal development and to prevent preeclampsia, an optimal vitamin D level should be maintained to ensure fetal health. [26] Also hypothyroidism is common in pregnant women, and if screening is performed only in high-risk groups, 25% of pregnant women with subclinical and hidden hypothyroidism are not explicitly diagnosed. [27]

Objectives

Given the rather high prevalence of vitamin D deficiency and thyroid disorders in Iran, and their adverse effect on the maternal and fetal outcomes of pregnancy, and also lack of sufficient evidence about the relations between vitamin D deficiency and thyroid function during pregnancy, this study aimed to investigate the relations between serum levels of vitamin D in pregnant women, and also vitamin D deficiency, with thyroid function tests [Thyroid-stimulating hormone (TSH), thyroxin (FT4)) and triiodothyronine hormone (FT3)] in the first trimester of pregnancy in a referral prenatal clinic in Tehran.

Methods

Study design and participants

This case-control study was conducted on 450 pregnant women in their first trimester of pregnancy in a referral prenatal clinic (which admitted patients from all over the city) in Tehran, Iran during September 2017 – 2018. In this clinic measurements of calcium and vitamin D levels were performed as part of routine prenatal laboratory tests for all pregnant women in their first trimester of pregnancy. 215 pregnant women who had vitamin D levels lower than 30 ng/ml were recruited in the study as the case group, and 215 mothers with normal vitamin D levels (equal to or higher than 30 ng/ml) were recruited as the control group.[28]

Inclusion criteria in the study were: age 18-40 years, gestational age less than 14 weeks, not have a chronic disease, and malabsorption, single pregnancy, not taking any supplements except multivitamins, and Iranian nationality.

Controls and cases were matched by frequency matching method in terms of age, number of pregnancies, age of marriage and body mass index (BMI).

Exclusion criteria were, the unwillingness of mothers to continue participation in the study, mothers who had a vegetarian diet or a special diet, mothers who had hypothyroidism before pregnancy and used levothyroxine tablets during Pregnancy.

All eligible mothers were enrolled after being given complete information about the study, and signing the informed consent until the sample size was completed. They also completed their sociodemographic and obstetric questionnaire.

Measurement

Vitamin D was measured by ELISA method using MAN Co Kit. Thyroid function tests (T3, T4, TSH) were conducted by Roche ELISA Modular Analytics Cobas e411 (kit Roche Diagnostics, Mannheim, Germany) at Nilou Laboratory. Mothers' weight and height were measured at the first prenatal visit using unique tools for all participants. Body Mass Index (BMI) was calculated by dividing weight (kg) on height^2 (m^2).

Sample size

Convenience sampling was performed and the sample size was calculated through the Pokak formula,[29] having considered error type 1= 0.05 and, study power 80% for comparing the mean of the two groups, approximately 195 individuals with a 10% rate of loss, per group, were 215 persons. Because the researchers found no similar study, a pilot study was performed on 100 pregnant women (50 with vitamin D deficiency and 50 without deficiency) in the first trimester of pregnancy to assess their TSH levels.

$$n = \frac{S1^2 + S2^2}{(\mu 1 - \mu 2)^2} \times f(\alpha, \beta)$$

S_1=1.8 (group 1 TSH standard deviation) S_2=1.2 (group 2 TSH standard deviation) μ1 =2.3 (mean of the TSH first group) μ2 =2.0 (mean of TSH the second group) $f(\alpha, \beta) = 3.8$

Ethical considerations

This study was conducted after obtaining the Code of Ethics in Tarbiat Modarres Faculty of Medical Sciences (IR. TMU. REC 1395.368), Tehran, Iran.

Statistical analysis

Data collection and analysis were performed using SPSS software version 22. Kolmogorov-Smirnov test was used for normality testing of continuous variables, and Mann-Whitney U test was used to compare the continuous nonparametric variables in the 2 study groups (all continuous variables had non-normal distributions); Liner regression model was used to assess the effect of potentially effective variables besides vitamin D, on thyroid function tests. P-value< 0.05 was considered statistically significant.

Results:

In this study, 430 pregnant mothers were recruited in the study as two groups of case (with vitamin D deficiency) and control (without vitamin D deficiency) (215 in each group). In Mann-Whitney U test performed, there were no statistically significant differences between the two groups in term of distribution of the variable: age, number of pregnancies, age of marriage first trimester BMI and Calcium levels (Table 1).

Also in Mann-Whitney U test, there were significant differences in mean serum levels of vitamin D, and T4 in the 2 groups of case and control (P=0.04); and T4 levels higher in cases (20.8 vs. 14.4 ng/dl). But there were no significant differences about T3 (P=0.39), and TSH (P=0.51) in the 2 study groups (table 2).

Linear regression analysis was performed to assess the impact of vitamin D deficiency, and some potentially effective factors including maternal age, BMI, and number of pregnancies on thyroid function tests (free T3, free T4, and TSH levels). According to linear regression analysis, there was a significant relationship only between vitamin D deficiency and T4 (β: 0.12, P-value: 0.01); T4 level was higher in mothers with vitamin D deficiency (Table 3).

Discussion

This study aimed to investigate the relations between vitamin D deficiency, and thyroid function tests (free T3, free T4, and TSH) in the first trimester of pregnancy in a referral prenatal clinic in Tehran, Iran, during September 2017 – 2018. Normal pregnancy increases thyroxine stimulation and leads to incidence of temporary hyperthyroidism becomes pregnant in the first trimester.

The results showed that there was a significant relationship between serum levels of vitamin D and Thyroxin (T4) in early pregnancy, but there were no such findings about T3, and TSH. The mean level of T4 was higher in mothers with vitamin D deficiency, whereas the mean T3 and TSH levels in this group were lower (insignificantly) and it seems that vitamin D deficiency in the first trimester of pregnancy may increase T4 levels.

The results of the present study were in contrast to the results of a study in Italy. Their results showed a partial correlation, but there was a significant relationship between the sufficient level of 25-hydroxyvitamin D and low TSH level in pregnant women (sufficient vitamin D levels above 30 ng/ml). The study found that during pregnancy there was no evidence of the effect of vitamin D on thyroid hormones such as FT4. However, the correlation between TSH levels with 25-hydroxyvitamin D may reflect the effect of vitamin D on pituitary TSH production, as has been shown in previous studies. [30] But the present study showed the effect of vitamin D on Thyroxin (T4).

A Study in Sudan showed that pregnancy in healthy women had a suppressive effect on all thyroid parameters (TSH, T4, and T3). [14] In the present study, no such effect was found in the group of women with sufficient vitamin D. Another study was conducted among Korean pregnant women which showed that there was no significant difference between the level of 25-hydroxyvitamin D and autoimmune thyroid disease. [31]

A study showed that there was no relationship between 25-hydroxyvitamin D, FT4, and FT3 during pregnancy, however, there was a significant correlation in pregnant women with adequate vitamin D levels (more than 30 ng/ml) between vitamin D and lower TSH. [32] In a study performed during pregnancy, no association was found between 25-Hydroxy Vitamin D and Thyroid function, despite vitamin D deficiency among these women.[33] Different studies have had different results about vitamin D levels and thyroid hormones during pregnancy. Another case-control study among non-pregnant and healthy women showed no significant relationship between vitamin D level and hypothyroidism.[34]

In other studies, there was a significant correlation between vitamin D, Hypothyroidism and its prevalence in women. [35, 36] Furthermore, one other study found there were no significant relationships between vitamin D, Hashimoto's Thyroiditis and Hypothyroidism; this study showed that serum levels of 25-Hydroxy vitamin D were lower in the Hashimoto's Thyroiditis and Hypothyroid group compared to the healthy control group. [37] In the other study, it was observed that serum levels of vitamin D were lower in patients with Hashimoto's Thyroiditis compared to control. [38] The prevalence of vitamin D and zinc deficiency were significantly higher in patients with hypothyroidism compared to healthy controls. [39] Serum vitamin D levels were significantly lower at the beginning of Graves' disease,

but there was no significant association between vitamin D and thyroid hormones.[40] Studies have shown vitamin D deficiency as a risk factor for autoimmune thyroiditis and thyroid function.[41-44]

According to performed studies, researchers have guessed that 25-hydroxy vitamin D and thyroid antibodies act independently and have similar complications in pregnancy.[45] This evidence and the investigation emphasized the role of vitamin D in pregnancy and its relationship with thyroid diseases, but the exact mechanism has not been investigated yet, and explaining the underlying mechanism needs further research.

Up to now, vitamin D and thyroid function related studies have shown conflicting results. These conflicting results can be partly due to different study plans, or different definitions of vitamin D deficiency and lack of consensus about the serum levels of 25-hydroxy vitamin D among individuals with vitamin D deficiency. Therefore, it is not easy to conclude that vitamin D deficiency is a risk factor for thyroid abnormalities and vice versa, and for a better conclusion, in the studies, a single protocol should be considered.

T However, if according to previous studies, conclude that vitamin D deficiency is a risk factor for hypothyroidism and autoimmune thyroiditis, and if those conditions coincided together during pregnancy, the imminent harm comes to both the mother and her fetus may be severe. Therefore, the correction of both disorders is recommended to minimize any potential risks. The limitations in the present study were the lack of testing thyroid antibody and parathyroid hormone testing as well as seasonal variations during study.

Conclusion:

The results of this study showed that Vitamin D deficiency had a significant direct relationship with the level of Thyroxin (T4) in pregnant women. T4 levels were higher in mothers with vitamin D deficiency in the first trimester of pregnancy. There was no significant relationship between Vitamin D serum levels with T3, and TSH levels. Due to the negative effects of Vitamin D deficiency and thyroid hormones abnormalities on the mother and fetus, further studies should be conducted which may help in more accurately screening these conditions during pregnancy.

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Table 1: Comparison of the basic characteristic and calcium levels in case (with vitamin D deficiency) and control (without vitamin D deficiency) groups

Variable	Groups[a] (Mean± SD)		P-value[b]
	Case	control	
Age of Mother (year)	31.1 ± 4.7	32.09 ± 4.3	0.08
Age of Marriage (year)	24 ± 4.2	23.5 ± 3.7	0.75
Gravid	2.2 ± 1.2	2.08 ± 1.1	0.26
BMI(Kg/m2)	25.2 ± 4.5	26.2 ± 4.2	0.48
Calcium	9.5 ± 5.3	9.6 ± 5.6	0.60

[a]Data are presented as mean± SD SD: standard deviation [b]Mann Whitney test BMI: Body Mass Index

Table 2: Comparison serum level of vitamin D3 and thyroid hormones in case and control groups

Variable	Groups[a] (Mean± SD)		P-value[b]
	Case	control	
Vitamin D (ng/dl)	16.7 ± 7.1	43.3 ± 14.1	0.001
TSH(mu/l)	2.2 ± 1.5	2.3 ± 2.05	0.51
FT3(ng/dl)	16.8 ± 42.9	20.07 ± 47.4	0.39
FT4 (ng/dl)	20.8 ± 32.5	14.4 ± 38.5	0.04

[a]Data are presented as mean± SD SD: standard deviation [b]Mann-Whitney test BMI: Body Mass Index

Table 3: Logistic regression analysis of effective factors on thyroid test function

Dependent variable	Predictors variable	β[a]	Statistical Test[b]	
			t	p
T3				
	Age of Mother (years)	0.19	0.38	0.7
	Gravid	-0.02	-0.39	0.69
	BMI (Kg/m2)	- 0.01	-0.3	0.75
	Vitamin D deficiency	0.01	-0.28	0.77
TSH				
	Age of Mother (years)	-0.48	- 0.95	0.34
	Gravid	-0.06	-1.29	0.19
	BMI (Kg/m2)	0.08	1.6	0.09

	Vitamin D deficiency	-0.02	-0.54	0.58
T4				
	Age of Mother (years)	-0.01	-0.19	0.84
	Gravid	0.01	0.29	0.76
	BMI (Kg/m2)	- 0.01	-0.28	0.77
	Vitamin D deficiency	0.12	2.49	0.01

β^a: Beta coefficient. [b] Statistical Test: Liner regression