Is There Any Relationship Between Maternal Vitamin D and Thyroid Function in Pregnancy With Maternal and Neonatal Outcomes? A Cross-sectional Study

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Research Article

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Abstract

Background: The aim of this study was to evaluate the prevalence of vitamin D deficiency in pregnant women to investigate the relationship between vitamin D level and thyroid function.

Methods: In this cross-sectional descriptive study, a total number of 90 patients during the three trimesters of pregnancy were investigated, 30 pregnant women were studied in each trimester of pregnancy. We evaluated thyroid function test and thyroid auto-antibodies (TPO Ab, Tg Ab) also serum level of 25OHD, to determine the relationship between vitamin D level and autoimmune or non-autoimmune thyroid disease in pregnancy.

Results: Pearson correlation in all subjects showed that vitamin D levels did not have a significant relationship with maternal age. Only in the third trimester, there was a significant difference in maternal age based on their vitamin D status. The mean age of patients with a sufficient level of vitamin D (29.29 ± 3.87) was higher than the moderate vitamin D deficient patient's age (23.4 ± 1.51). There was no significant difference between the trimesters of pregnancy and vitamin D status ($P > 0.05$). Also, there were no significant differences between serum levels of vitamin D within three trimesters. Regarding the pregnancy outcomes, two newborns were admitted to NICU, Meconium Aspiration in one case, and IUFD in another case leads to pregnancy termination. These four cases were related to maternal history of hypothyroidism.

Conclusion: There was no significant relationship between vitamin D and pregnancy trimester. The serum level of vitamin D had no particular effect on the outcome of pregnancy and the thyroid gland function.

Background

Hormonal and multiple metabolic changes during pregnancy, leads in complex effects on the maternal thyroid function (1). Pregnancy increases stimulation and synthesis of steroid hormones, it also increases the thyroxine-binding globulin's (TBG) degradation, TBG levels, Total T3 and Total T4. Studies have shown that TBG levels double in the 16-20th week of pregnancy (1). The level of thyroxin (T4) and triiodothyronine (T3) is regulated by TSH secreted from the pituitary (2)(3). A large percentage of thyroid hormones in the bloodstream (more than 99%) are bound to the carrier proteins. Most of thyroid hormones transmitted by TBG and a lesser extent by Transthyretin and albumin. Binding with these proteins prevents the hormone from entering the cell and provides its effect. (4). So, Thyroid disease is the second most common endocrine disorder affecting women of childbearing age (5)(6). Recently, the evaluations of thyroid function showed that thyroid function tests interpretation depends on the stage of pregnancy (7). Multiple hormonal and metabolic changes during each pregnancy trimester, leads in complex effects on the mother's thyroid function (8). Regarding the high prevalence of women's thyroid diseases in reproductive age, the prevalence of these diseases, including chronic thyroiditis, thyroid dysfunctions, Hashimoto thyroiditis, Graves' disease, etc., it's interesting to investigate considering factors affecting the thyroid functions test(8)(9).

Thyroid disorders affect the reproduction and the Consequence of pregnancy. Pregnancy hyperthyroidism is common (0.2%) but hypothyroidism is more prevalent (2.5%) and can affect the neonatal nervous system development and also increase the incidence of congenital complications (5). Hypothyroidism is associated with fetus nervous system poor evolution (10)(11) and increased the incidence of low birth weight (LBW) (12). Also, the incidence of spontaneous abortions in pregnant women with chronic autoimmune thyroiditis is more prevalent (13).

Recent studies have been revealed that vitamin D deficiency is prevalent worldwide; about one billion people in developing countries have vitamin D deficiency (14). The definition of vitamin D deficiency is different in studies. while the vitamin D deficiency in Asia and the Middle East is more than other parts of the world (15)(16).The prevalence of vitamin D deficiency in Iran is similar to other Middle Eastern countries, about 69% of population(17).

During pregnancy, the vitamin D requirement is increased. Reports indicated a physiological increase in serum 25 OHD levels in the second and third trimesters. Also it was indicated that the active vitamin D metabolite increases in pregnancy and results in more intestine calcium Absorption and higher third trimester level of serum total Calcium (18).

Recent studies indicate vitamin D deficiency in pregnancy, especially in high-risk groups, including: vegetarians, women with low sun exposure or ethnic minorities like blacks (19)(20)(21). Low levels of vitamin D correlates with various maternal complications such as pregnancy induced hypertension , hypertension in diabetic mothers, gestational diabetes, recurrent abortion, preterm labor, and postpartum depression in different studies (22)(23)(24)(25)(26)(27). Vitamin D Receptor is an intracellular, steroid receptor, expressed by multiple organs: the brain, heart, skin, glands, prostate, breast, etc. (28) Thyroid hormones and vitamin D receptors are the same as the steroid hormone receptor, which has various genes involved in its expression, any modification in individual's constructor genes, prone them to autoimmune diseases, including Thyroid autoimmune diseases (such as Hashimoto and Graves). So in each thyroid Immune and non-immune thyroid diseases, the level of vitamin D should be in mind (29) (30).

Methods

This descriptive-cross sectional study was conducted in a community of pregnant women referred to clinics of Jahrom University of Medical Sciences. This study was approved by Research Ethical Committee of Jahrom University of medical sciences (with registration code of IR.JUMS.REC.1396.036). We divide the pregnancy into three 3-month periods or trimesters, and from each trimester, 30 pregnant women with no acute illness, metabolic bone disorders, absorption impairment, history of thyroidectomy or radioactive iodine intake, were evaluated for FT4, TSH, 25 (OH) D and, if necessary, FT3.The level of thyroid antibodies (TPO Ab, Tg Ab) also were checked to identify the relationship between vitamin D and autoimmune thyroid diseases in pregnancy. The results were interpreted based on the pregnancy trimester. After determining the mean serum level of vitamin D in each trimester, patients were divided

into four groups: participants with adequate levels of vitamin D or vitamin D sufficient pregnant, participants with severe, moderate, and mild vitamin D deficiency.

Severe vitamin D deficiency was defined as serum 25OHD levels less than or equal to 8ng/ml; moderate vitamin D deficiency was considered to serum 25OHD levels from 8ng/ml to 15 ng/ml, and mild vitamin D deficiency was 15ng/ml to less than or equal to 20ng/ml. Vitamin D sufficiency is defined with serum 25OHD levels higher than 20ng/ml (31).Pregnancy complications such as preeclampsia, preterm delivery, postpartum abnormal bleeding, or low Apgar score, were recorded based on the patient's report and medical records.

Results

In our study, a total number of 90 patients during the three trimesters of pregnancy were investigated for thyroid function. 30 mothers in the first trimester, 30 in the second and 30 in the third trimester were examined. The mean age of participants was 38.4 ± 34.28 . The mean age of individuals surveyed in each Trimesters is presented in Table1. There was no significant difference between the age of participants in the three trimesters ($P = 0.688$).

The mean serum vitamin D was 29.24 ± 15.72 . The prevalence of vitamin D deficiency was shown in Table 1. Severe vitamin D deficiency was observed in 4 participants (4.44%), moderate vitamin D deficiency in 24 pregnant women (26.67%), mild vitamin D deficiency in 18 cases (20%) and vitamin D sufficient participants were 44 cases (48.89%).

Table 1. Studied population characteristics in different trimesters

		First trimester	Second trimester	Third trimester	p
Age, year, Mean±SD		28.04±4.31	28.04±5.21	29.21±4.52	0.688
Vitamin D levels, ng/mL, Mean±SD		29.21±4.53	28.05±5.21	28.05±4.31	0.381
Vitamin D Status, n(%)	mild	0(0)	1(3/33)	3(10)	0.573
	moderate	7(23/33)	9(30)	8(26/67)	
	sever	5(16/67)	6(20)	7(23/33)	
	normal	18(60)	14(46/67)	12(40)	
T3, median (q1-q3)		15.38(4.07-28.52)	12.33(1.23-13.32)	14.39(10.43-17.55)	0.088
T4, median (q1-q3)		4.95(4.27-5.28)	4.05(3.4-4.5)	4.25(4.03-4.46)	0.074
TSH, median (q1-q3)		2.58(0.58-3.64)	1.59(0.57-3.13)	3.41(1.38-5.12)	0.979
Thyroid function, n(%)	hyperthyroidism	1(3/33)	16(53/33)	11(36/67)	0.305
	euthyroid	1(3/33)	20(66/67)	5(16/67)	
	subclinical hypothyroidism	4(13/33)	14(46/67)	8(26/67)	
	hypothyroidism	1(3/33)	16(53/33)	11(36/67)	

To assess the relationship between age and vitamin D, a Pearson correlation test indicated that vitamin D levels did not have a significant correlation with maternal age ($p = 0.071$). After splitting the data based on Trimesters, only in the third trimester, there was a significant difference between the ages of mothers based on their vitamin D status. The mean age of patients with normal vitamin D (29.29 ± 3.87) was higher than the mean age vitamin D deficient patients (23.4 ± 1.51), as shown in Figure1 ($p = 0.007$).

The status and level of vitamin D in each trimester of pregnancy were examined, as shown in Table1. The mean levels of serum 25OH vitamin D in pregnant women is presented in Table1, based on pregnancy trimester. In order to determine the high risk group, based on vitamin D deficiency, there was no significant difference between the three trimesters of pregnancy and vitamin D status in chi-square test ($p = 0.573$). Also, there were no significant differences between the levels of serum 25OHD D in each trimester compared to the others. ($p = 0.381$)

The results for TSH, T3, and T4 levels are shown in Table3 based on trimesters. Due to the nonparametric tests, these results are reported as median $\pm$ IQR. No differences were observed in three trimesters for TSH ($P > 0.05$). Also, the interpretation of Thyroid function tests for the definition as a thyroid disorders was also reported at the same table, which no significant differences were observed including the distribution of euthyroid, hypothyroid and hyperthyroid individuals in each pregnancy

trimesters ($P = 0.305$) and no statistical differences were observed based on thyroid autoimmunity based on trimesters, too, $p=0.24$ and $p=0.46$ for TpoAb and TgAb, respectively. No significant difference observed in Ab type and levels.

After split of the data based on the trimesters, examination of thyroid function tests during pregnancy in relation to vitamin D showed that there was no significant Spearman correlation between thyroid function status and serum vitamin D level ($P > 0.05$). Mother's thyroid function tests are summarized in Table 2. There was no significant difference in mean level of serum 25OHd vitamin D in each subgroup of thyroid status ($P < 0.05$)

Table -2: Results of Thyroid tests and vitamin D level in each group

Subgroups	N	Vitamin D level	TPOAb (n)	TGAb (n)
hyperthyroidism	6	22.07±11.13	3	3
euthyroid	50	23.84±12.42	18	15
subclinical hypothyroidism	24	18.17±5.94	7	5
hypothyroidism	10	50.43±51.6	5	5
p-value	-	0.589	0.249	0.463

Table-3: Neonatal outcomes

According to pregnancy outcomes, two newborns were admitted to NICU, a case of meconium aspiration and a case of IUFD were observed. These four cases were related to maternal history of hypothyroidism. According to Table3, there was no relationship between delivery type and vitamin D status ($P = 0.398$). There was no significant differences in mean of serum 25OHD levels between pregnancy termination by cesarean section or normal delivery ($P = 0.811$).

maternal serum vitamin D	Neonatal weight	height	Head circumference	gestational age of birth	Apgar	bilirubin level
sever vitamin D deficiency	2550±129.83	47±2.3	34±1.7	36±2.5	9±0	6±0.7
moderate vitamin D deficiency	3323.33±427.76	51.83±2.5	33.81±1.22	37.5±1.04	9±0	6.78±0.73
Mild vitamin D deficiency	3204.55±346.74	51.18±2.99	33.83±1.47	36.91±2.3	9±0	7.45±1.13
vitamin D sufficient	3160.56±325.51	51.97±2.95	33.17±1.65	37±1.37	9±0	7.34±1.45
p-value	0.133	0.335	0.497	0.538	-	0.258

The relationship between vitamin D status and new-born outcomes studied such as height, weight, head circumference, bilirubin, Apgar score, and gestational age were analyzed by ANOVA. There were no significant differences in neonatal outcomes based on maternal vitamin D status during pregnancy ($P > 0.05$).

Discussion

The aim of this study was to investigate the relationship between serum vitamin D level and thyroid function tests in pregnant women referring to Jahrom University of Medical Sciences clinics during the years 2018-2019. In this study, 51.11% of studied pregnant women had vitamin d deficiency. In a meta-analysis study in Iran, the prevalence of vitamin D deficiency among pregnant women was found to be 68.8 percent based on a cut-off point of 20 ng/ml (32). This, as like as our study, was a very high prevalence. However, in each pregnancy trimesters, this study showed that the highest prevalence was in the third trimester. While our study found the highest prevalence of vitamin D deficiency in the first trimester, according to the importance of first trimester in fetal organogenesis, attention to vitamin D status is crucial. Our study showed that mothers of older age had a higher level of vitamin D in the third trimester; it seems to be related in higher level of education and better socioeconomic level of older mothers in this study. As well as our study, Ates et al stated no relationship between maternal age and vitamin D levels in the first trimester (33).

Different factors such as hijab, residence place and lower maternal age affect this process (34). While in our study in the third trimester, women with higher age had higher vitamin D levels. In our study, there was no significant difference in serum levels of vitamin D comparing trimesters. Also, there was no significant difference between the trimesters of pregnancy and the prevalence of vitamin D deficiency.

F.Azizi and his colleagues concluded that during pregnancy, significant changes in the regulation of thyroid function in healthy women are observed. Increasing estrogens increases total TBG and T4. Increased hCG stimulates the thyroid gland so TSH concentration decreases. Thyroxine metabolism is accelerated and urinary iodine excretion is increased. In areas with iodine deficiency, there is a greater reduction in thyroxin levels and goiter during pregnancy. The prevalence of thyroid dysfunctions in pregnancy was about 2 to 3%, but subclinical hypothyroidism was about 10%. Hyperthyroidism intensifies in the first trimester. Then, during the second and third trimester, the relative recovery is increased and rebounded after delivery. Infant and fetal hyperlipidemia can be caused by the passage of stimulant antibodies from the mother's TSH receptor from the paw, causing tachycardia, accelerating bone growth, and delaying intrauterine growth. Failure to pay attention to thyroid disorders during pregnancy causes irreversible lesions in pregnancy outcomes, physical and mental development of fetuses and newborns. Therefore, the diagnosis, evaluation and proper care of thyroid activity and its diseases during pregnancy is very important (35).

Our study demonstrated the incidence of thyroid disease was not related to vitamin D levels. There was also no difference in the incidence of thyroid diseases in pregnancy trimmers. The levels of TSH, T3, and T4 did not differ significantly comparing between the trimesters.

Previous studies have confirmed the same findings. A study by Musa et al. Showed that there is no clear relationship between thyroid function and vitamin D (25) OH in pregnant women (36). Zhao et al. showed that there was no significant relationship between serum vitamin D levels and thyroid parameters (37). Nizar et al investigate that there was no significant correlation between vitamin D levels and thyroid function of pregnant women in Oman and Jordan but there was a relationship between higher concentrations (> 30 ng / ml) of vitamin D and lower TSH (38). However, Mackawy et al. showed that vitamin D deficient hypothyroid patient's vitamin D and serum calcium levels are significantly associated with hypothyroidism severity (39). While in our study the severity and the course of the disease was not taken to account.

Studies in North China have shown a high prevalence of vitamin D deficiency in pregnant women who have not used supplements. Pregnant women should take more than 800 units per day of vitamin D before pregnancy and during pregnancy. According to these studies, there is no clear relationship between levels of vitamin D and thyroid parameters (37)(40).

There was no significant difference between the mean vitamin D levels among patients undergoing cesarean section and natural delivery in our study. As like as the study of Asadi et al, the relationship between vitamin D and type of delivery was investigated (41). In the study of Savvidou et al., There was no relationship between vitamin D deficiency in the first trimester of pregnancy and cesarean section (42). In the study of Brunvand et al., There was no relationship between vitamin D deficiency at delivery and type of delivery (43).

Despite our study and previous similar finding which observed, no significant difference in the serum levels of vitamin D among women based on delivery types; cesarean section and normal vaginal delivery;

Scholl et al. reported that vitamin D deficiency at 13 weeks of gestation was associated with an increase in cesarean delivery that was due to prolonged labor (44).

Regarding the relationship between vitamin D status and newborns outcomes such as height, weight, head circumference, bilirubin, agar score, and gestational age, there were no significant differences in neonatal outcomes based on maternal vitamin D status during pregnancy; in comparison with our study neonatal jaundice as the most common neonatal problems was correlated with maternal vitamin d deficiency (45).

Limitations and strengths:

In this study, two major endocrine aspects of pregnancy :thyroid and vitamin D status were investigated ,for better evaluation, trimester specific view ,maternal and neonatal outcomes were observed that clearly helpful for clinical managements. These study participants were all from the same area in the south-west of Iran with same race, hijabs and climates, however, it's better to define clear sun exposure hours and nutritional status in future studies.

Conclusion

Pearson correlation showed that vitamin D levels did not have a significant relationship with maternal age. Only in the third trimester, there was a significant difference in maternal age based on their vitamin D status. The mean age of patients with a sufficient level of vitamin D (29.29 ± 3.87) was higher than the mean vitamin D deficiency (23.4 ± 1.51). There was no significant difference between the trimesters of pregnancy and vitamin D status. Also, there was no significant difference between serum levels of vitamin D in each trimester. The serum level of vitamin D had no particular effect on the outcome of pregnancy and the thyroid gland function.

Declarations

Ethics approval and consent to participate: this study was approved by Research Ethical Committee of Jahrom University of medical sciences (with registration code of IR.JUMS.REC.1396.036). All experimental protocols, proposal, methods were carried out in accordance with relevant guidelines were approved by the Research Ethical Committee of Jahrom University of Medical sciences.

Availability of data and materials: There isn't any additional data. All data generated or analyzed during this study are included in this published article and raw datasets used and/or analyzed during the current study, are available from the corresponding author on reasonable request.

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Author's contribution:

Design and planning, physical exams follow ups writing discussion and review: S. Ahi

Physical exams, follow ups and medical analysis of statistical data: I.Fereydouni

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Figures

Figure 1

Age of participants based on the Vitamin D status