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Vitamin D Level, Thyroid Function, and Maternal Depression in Late Pregnancy

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Abstract

Background: Based on a possible association between thyroid function or serum 25-hydroxyvitamin D concentration and perinatal psychological symptoms, this study examined the potential link between antenatal depression and thyroid function or vitamin D level in the population of Shiraz city.
Methods: This cross-sectional study was conducted on mothers, who were under prenatal care at a teaching hospital in Shiraz, during year 2015. Evaluation of depression was performed by the Edinburgh postnatal depression scale (EPDS). Eligible pregnant females aged $\geq$ 18 and at 26 to 28 weeks of gestation were passed to the laboratory to offer a blood sample to determine serum 25-hydroxyvitamin D, TSH, FT4, and TPOAb. Finally, data from 184 pregnant females was analyzed.
Results: The mean depression score was 9.19 $\pm$ 4.44, with a median value of 9.50, and mode value of 13. Overall, 52 mothers (28.3%) had depression (depression score > 12). The mothers with and without depression were not different in relation to 25-hydroxyvitamin D, TSH, FT4, and TPOAb levels. No association was established between thyroid function and antenatal depression with a binary logistic regression analysis. Also, vitamin D deficient mothers did not have more chance of being depressed. No correlation was detected between thyroid function and vitamin D levels.
Conclusions: Based on the current findings, no association was observed between antenatal depression and thyroid function or vitamin D deficiency.

Keywords: Antenatal Depression, Perinatal Depression, 25-Hydroxyvitamin D, Thyroid Function, TPOAb

1. Background

Antenatal depression (AND) is a frequent disorder during pregnancy. Previous studies have shown a prevalence rate of 11% to 50% for this disorder. The third trimester is a time with more likely occurrence of antenatal depression rather than the first and second trimesters. It seems that antenatal depression leads to experience of postnatal depression (PND) by numerous mothers (1, 2). A study showed that the prevalence rates of PND vary between 0.5% and 60.8% across different countries (3).

There is an increased risk of obstetric complications, such as preeclampsia, pre-term birth, and low birth weight in mothers with AND. Recent studies demonstrated that maternal hypothalamic-pituitary-adrenal axis dysfunction accompanied by AND can influence the developing fetal brain, leading to a possible mental health disorder later in life (4).

A relationship between the thyroid hormones imbalance and mood disorders has been hypothesized for many years. Both hyper and hypo activity of the thyroid glands can affect mood well-being (5, 6). In addition, mood disturbances can be accompanied by subclinical hypothyroidism (7). Several studies have been conducted on the effectiveness of thyroid hormones augmentation in antidepressant resistance patients. Some of them showed increasing in response rates (8, 9). On the other hand, numerous studies attempted to find a link between perinatal depression and thyroid dysfunction. Some suggested an association between these factors (10). However, opposite results were reported by other studies (11).

Vitamin D has long been considered the main nutrient for calcium metabolism and bone health. The existence of vitamin D receptor in the majority of human's tissues and cells, such as the reproductive and endocrine system, mus-

cles, brain, skin, and liver signifies that it probably acts like a steroid hormone in the human body (12, 13). A possible association between 25-hydroxyvitamin D level and mental symptoms, such as nervousness, depression, and cognitive function has been shown by numerous studies (14). In a clinical trial, high prescribed amounts of vitamin D were helpful for individuals, who were depressed (15). In addition, researchers explored the relationship between low vitamin D and pregnancy-related depression. Murphy et al. showed a link between maternal low serum concentrations of 25-hydroxyvitamin D and elevated depression scores after birth (16). In a study by Brandenburg et al., a reverse link was found between 25-hydroxyvitamin D concentration and maternal depression score at 16 weeks of gestation (17).

On the other hand, a relationship between serum level of vitamin D and thyroid function was found in previous studies. In a study by Zhang et al., thyroid-stimulating hormone (TSH) concentrations were linked with vitamin D concentrations in an inverse manner, independently of thyroid hormone levels (18). However, other studies did not show a firm relationship between serum level of vitamin D and thyroid function (19). The purpose of the present study was to assess the potential link between antenatal depression and thyroid function or vitamin D level in the population of Shiraz city.

2. Methods

2.1. Design and Data Collection

This cross-sectional study was done from January 2015 to early December 2015 on pregnant females, both nulliparous and multiparous, who were under antenatal care at an educational hospital in Shiraz, Iran. The eligibility criteria were age of $\geq$ 18 years old, no history of psychological and physical illness, not using narcotic drugs or having alcohol dependence, without any pregnancy complications, such as preeclampsia, gestational diabetes, a singleton live fetus, and gestational age of 26 to 28 weeks by ultrasound findings. Exclusion criteria were unwillingness to provide a blood sample for the study lab tests. Initially, eligible mothers were selected by the convenience sampling method. Next, the aims of the study were made clear and if the cases were willing, a written informed consent was obtained.

2.2. AND Assessment Instrument

In the present study, the Edinburgh postnatal depression scale (EPDS) was used with view to assess depression intensity. The EPDS consists of ten multiple choice questions, the smallest possible score is 0 and the greatest possible score is 30. The EPDS focuses on emotional signs of depression rather than the physical signs. At first, the EPDS was developed for assessment of postpartum depression, however, numerous studies have validated its use for antepartum depression assessment (20). In western population, it was revealed that the EPDS has good reliability and validity (21). In Iran, the EPDS was used in the study by Mazhari and Nakhaee, with a validity and reliability of 0.76 and 0.83, respectively (22). Cut-off points with values larger than 9, 12, 13, and 14 were developed in earlier studies to conclude perinatal depression (23, 24). This study used the cut-off point of > 12 as a greater chance of being depressed, according to Mazhari and Nakhaee's study in Iranian people (22). Thus, the mothers were subdivided to two groups; depressed mothers (EDPS score > 12) and non- depressed mothers (EDPS score of 0 to 12).

2.3. Lab Tests

The eligible participants were referred to the laboratory of endocrine and metabolism research center in order to offer blood samples to measure serum 25-hydroxyvitamin D (25(OH)D), thyroid stimulating hormone (TSH), free thyroxin (FT4), anti-thyroid peroxidase antibody (TPOAb). The serum was separated within one hour of sampling by centrifugation. The coded serum samples were frozen at -70°C and stored in the lab until the closing stages of the sampling.

Maternal serum 25(OH)D was assessed by the chemiluminescence immunoassay (CLIA) technique. Furthermore, TSH and FT4 were assessed by Electrochemiluminescence (CobasE411, Japan). Thyroid Stimulating Hormone was reported as mIU/L and FT4 as pmol/L. The TPOAb levels were calculated by the radioimmunoassay method (anti-hTPO (125I) RIA KIT, ref: RK-36CT, Izotop Co. Budapest). Furthermore, TPO was reported in IU/mL. Anti-thyroid peroxidase antibody of more than 35 IU/mL was considered as positive and the reference range for the third trimester TSH and FT4 was 0.3 to 3 mIU/L and 11.84 $\pm$ 3.86 pmol/L, respectively. Clinical hypothyroidism was defined as an elevated TSH (> 3 mIU/L) in conjunction with a low FT4. Females with TSH $\geq$ 10 mIU/L, irrespective of their FT4 level, were also considered as having clinical hypothyroidism. Subclinical hypothyroidism was defined as serum TSH of between 3 and 10 mIU/L with a normal FT4 concentration (25).

2.4. Sample Size and Statistical Analysis

The sample size was determined based on an approximate method in statistics for minimum sample size in the regression model as 10 to 20 participants per variable.

Statistical analysis was conducted with the SPSS statistical software (version 18). In addition, P values of < 0.05 reflected a statistically significant result. Quantitative

variables were compared between mothers with and without depression, using independent two samples T-test and Mann-Whitney U test in its proper manner (for normally and non-normally distributed variables, respectively). The Chi-square test or Fisher's exact test was utilized for categorical variables. A binary logistic regression model was made for variables, such as FT4, TSH, TPOAb, vitamin D, and for two demographic variables (age and parity) with AND in the single variable analysis to judge their relationship with AND. In addition, a multivariate regression model (enter method) was made to assess the relationship between the above-mentioned variables and AND. The spearman's coefficient test was used to investigate the correlation between the study variables.

The present study was approved by the ethics committee of Shiraz University of Medical Sciences with ethics code of IR. SUMS.REC.1394.87.

3. Results

In this cross-sectional study, 200 mothers were interviewed. Six mothers were not eligible to enter the study and 10 mothers did not provide a blood sample for the tests. Therefore, data from 184 mothers was analyzed.

The current participants were 26.29 ± 4.58 years old on average. The minimum and maximum of age were 18 and 39 years old, respectively. Most participants, 178 (96.7%), were housewives. Furthermore, 84 (45.7%) had high school diplomas. Overall, 112 (60.9%) participants were nulliparous and 72 (39.1%) were multiparous mothers. All mothers were married and living with their husbands.

The mean depression score of 184 participants was 9.19 ± 4.44. Also, a minimum and maximum value of 0 and 24, median 9.50, and mode 13 were detected. Fifty-two (28.3%) were depressed (depression score > 12) and 132 (71.7%) were not depressed. In all mothers, the mean 25(OH)D concentration was 12.35 ± 6.54 ng/mL with a minimum and maximum value of 4 and 49.30 ng/mL, respectively. This variable had a median value of 12.35 and mode value of 12.35. Of total, 165 (89.7%) were vitamin D deficient. The mean TSH, FT4, and TPO were 2.69 ± 2.26 mIU/L, 10.18 ± 2.08 pmol/L, and 35.84 ± 99.26 IU/mL, respectively. Of 184 mothers, 145 (78.8%) were euthyroid, 20 (10.9%) were subclinical hypothyroidism, 14 (7.6%) were clinical hypothyroidism, and 5 (2.7%) were subclinical hyperthyroidism. The mothers with depression were compared to those without depression in relation to the above mentioned variables. No significant difference was observed (Table 1). No relationship was found between thyroid function and AND, according to a binary logistic regression analysis. Also, nulliparous and vitamin D deficient mothers did not have more chance of being depressed (Table 2). The multivariate logistic regression analysis did not alter the results absolutely (Table 2).

Table 1. Maternal Characteristics, Vitamin D Level, and Thyroid Function in Mothers with and Without Depression

Variables	Depressed	Non-Depressed	P Value
Number	52 (28.3)	132 (71.7)	
Age, y	27.01 ± 4.80	26.00 ± 4.48	0.17
Educational level			0.81
Under diploma	18 (34.6)	40 (30.3)	
High school diploma	22 (42.3)	62 (47)	
Educated	12 (23.1)	30 (22.7)	
Job			> 0.99
Housewife	51 (98.1)	127 (96.2)	
Employed	1 (1.9)	5 (3.8)	
Marital status			
Living with her husband	52 (100)	132 (100)	
Divorced or widow	0 (0)	0 (0)	
Parity			0.22
Nulliparous	28 (53.8)	84 (63.6)	
Multiparous	24 (46.2)	48 (36.4)	
Thyroid function tests			
TSH, mIU/L	2.47 ± 1.50	3.25 ± 3.48	0.23[b]
FT4, pmol/L	10.31 (2.22)	10.10 (2.07)	0.69
TPOAb, IU/mL	48.16 (144.24)	30.98 (74.70)	0.84
Subclinical hypothyroidism	5 (9.6)	15 (11.4)	0.73
Hypothyroidism	4 (7.7)	10 (7.6)	> 0.99, 0.59
Subclinical hyperthyroidism	1 (0.5)	4 (3)	1.00, 0.56
Hyperthyroidism	0 (0)	0 (0)	
Vitamin D	12.54 ± 7.43	12.28 ±6.18	0.93[b]
Vitamin D			0.15
< 20, ng/dL	44 (84.6)	121 (91.7)	
> 20, ng/dL	8 (15.4)	11 (8.3)	

[a] Values are expressed as No. (%) or mean ± SD.
[b] Mann- Whitney U test was used.

The correlation between thyroid function and vitamin D levels was investigated by Spearman's coefficient. No correlation was detected between thyroid function and vitamin D levels: TSH (rho = 0.03, P = 0.65); FT4 (rho = -0.07, P = 0.31); TPO (rho = -0.08, P = 0.56). However, a correlation between TPOAb and TSH levels was detected; logistic

Table 2. Regression Models to Define the Relationship Between Antenatal Depression and Thyroid Function or Vitamin D Level

Regression Model	Variables in the Equation	B	Wald Statistic	P Value	OR (95% CI)
Univariate Logistic	TSH	0.14	3.56	0.05	1.15 (0.99 - 1.34)
	FT4	0.04	0.26	0.60	1.04 (0.89 - 1.21)
	TPO	0.00	1.03	0.30	1.00 (0.99 - 1.00)
	Vitamin D[a]	-.69	1.94	0.16	0.50(0.18 - 1.32)
	Parity[b]	-0.40	1.49	0.22	0.66 (0.34 - 1.27)
	Age	0.04	1.80	0.17	1.05 (0.97 - 1.12)
Multivariable logistic	TSH	0.18	3.03	0.08	1.16 (0.98 - 1.37)
	FT4	0.10	1.59	0.20	1.11 (0.94 - 1.31)
	TPO	0.00	1.80	0.18	1.00 (0.99 - 1.00)
	Vitamin D[a]	-0.48	0.80	0.36	0.61 (0.21 - 1.76)
	Parity[b]	-0.10	0.07	0.78	0.89 (0.42 - 1.91)
	Age	0.44	1.13	0.28	1.04 (0.96 - 1.13)

[a] Vitamin D: categorized as non deficient and deficient mothers.
[b] Parity: categorized as nulliparous and multiparous mothers.

regression did not show any relationship between TPOAb measures and having subclinical hypothyroidism.

4. Discussion

In the current cross-sectional study, the incidence of AND, vitamin D deficiency, and thyroid dysfunction was 28.3%, 89.7%, and 21.2%, respectively. Numerous studies have assessed the prevalence of antenatal depression with various tools and cut-off points. In a cohort research, 11.8% of mothers at 18 weeks and 13.5% at 32 weeks were depressed based on a threshold score of $\geq$ 13 (26). In Brazil, at a private center, the occurrence of depression throughout pregnancy was 19.6% with the Beck tool (27). In Oslo, prevalence of depression was 13% at 28 weeks. Nevertheless, depression was observed at a greater prevalence in ethnic minorities, such as Middle Eastern and South Asian mothers (19.5% and 17.5%, respectively) with a threshold of $\geq$ 10 (28).

Vitamin D deficiency is a prevalent problem around the world, which can be found even in countries with enough sunlight (29). Previous studies have shown that the prevalence of vitamin D deficiency is frequent in Iran. In a study by Kazemi et al., 86 % of females with a term pregnancy in winter, and 46% in the summer had vitamin D concentrations of < 25 ng/mL (30). Pregnancy related physiologic changes result in an increased accessibility of thyroid hormones by 50% to provide the demands of both the mother and fetus throughout pregnancy. The main factor that alters thyroid function in pregnancy is a rise of human chorionic gonadotropin (HCG), which stimulates the TSH receptor. Human chorionic gonadotropin-induced changes in thyroid function can result in gestational hyperthyroidism and hyperemesis gravidarum. The principal transient decrease in serum TSH can be observe in the first trimester, which is seemingly linked to high HCG levels (31, 32). In the current study, 10.9% of the total participants had subclinical hypothyroidism based on the American thyroid association guidelines (25). This result was in line with that of another study conducted on an Iranian population with 11.3% rate of subclinical hypothyroidism (33). However, in a study by Casey et al. in the US, 2.3% of pregnant females had subclinical hypothyroidism (34) and in a study conducted in India, 6.47% had subclinical hypothyroidism (35). Iran is one of the countries where consumption of iodine has been corrected (36), yet iodine deficiency can be considered as an important factor that causes higher incidence of subclinical hypothyroidism compared to other countries (37). The current found that clinical hypothyroidism was about three folds more than a previous study conducted in Shiraz (33). Furthermore, TPOAb positivity was 9.25% in the present study. Evidence has shown that 10% to 20% of pregnant mothers can be TPO and Tg antibody positive, yet in euthyroid status (25). In a study by Saki et al., 12.8% of Iranian pregnant female were positive for TPOAb (38).

This study did not find any relationship between AND and thyroid function measures, vitamin D deficiency, age, and parity in late pregnancy. However, several studies have been conducted on thyroid function and postpartum depression, and the current researchers found a few studies reporting a relationship between AND and thyroid function. A recent prior publication by Kuijpens et al. reported

an association between TPOAb positivity and mood disturbance during pregnancy (39). In line with the current study, in studies by Koleva et al., Bunevicius et al., and Leigh and Milgrom age and parity did not have an association with AND (40, 41). In contrast, Rich-Edwards et al. observed that younger mothers had a two-fold greater chance of AND (42).

On the other hand, studies exploring the association between thyroid function and postpartum depression (PPD) have shown inconsistent results. For example, thyroid function (hormones and ATPOAb) at 48 hours after birth could not predict PPD in a study from Spain (11); in a study by Kuijpens et al., TPOAb positive mothers during pregnancy were at risk for depression at four and 12 weeks postpartum (39). In Greek females, no connection was found between thyroid antibody levels and depression scores. However, within normal limits, poorer levels of FT3 and FT4 were linked with occurrence of psychological disorders in the first week after childbirth (10).

In the current study, AND did not have a relationship with 25-hydroxyvitamin D concentration. However, in several past studies, a reverse relationship was detected between maternal 25-hydroxyvitamin D level and AND (17, 43). It is worth mentioning that most of the current participants had vitamin D deficiency. Therefore, the current researchers did not detect any relationship between AND and 25-hydroxyvitamin D level.

On the other hand, the current researchers did not observe any correlation between 25-hydroxyvitamin D measures and thyroid function. In contrast to the current study, one study demonstrated that high vitamin D concentration in young non-pregnant individuals is linked with low circulating TSH (44). Also, a study conducted by Shin et al. established a negative association between 25-hydroxyvitamin D and TPOAb levels amongst non-pregnant individuals. In addition, it was revealed that low 25-hydroxyvitamin D level was a potential risk factor of TPOAb positivity (45).

4.1. Limitation

The present study was conducted in one prenatal clinic affiliated to Shiraz University of Medical Sciences. Therefore, whether or not the study findings can be generalized to the entire population is doubtful. Also, the sampling method was non-random sampling.

4.2. Conclusion

Based on the findings of the current study, no association was observed between antenatal depression and thyroid function or vitamin D deficiency. Mental disorders are multifactorial health problems. There is a possibility that some other factors, such as social support, major life events, and low income (41) could affect mental condition more than other medical conditions. Further multicenter studies with random sampling are recommended to obtain better results regarding associated factors for antenatal depression.

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Footnote

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