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Original Article

Association between Thyroid Hormones and the Risk Level of Screening Tests in the First Trimester of Pregnancy in Hypothyroid Women

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Abstract

Background: Endocrine disorders, such as hypothyroidism, can impact fetal growth and development. The significance and necessity of fetal screening before birth are critical for the prevention of congenital disabilities. The present study aimed to evaluate the association between thyroid hormones, specifically T3, T4, FT3, FT4, TSH, Anti TPO, Free BhCG, B-MOM, P-MOM, and NT-MOM, and the risk of screening tests conducted during the first trimester of pregnancy in women diagnosed with hypothyroidism.

Methods: This retrospective, case-control study included 82 pregnant women in their first trimester who were referred for fetal screening tests between 2022 and 2023 at Imam Reza and Motazadi hospitals in Kermanshah, Iran. The case group consisted of 41 pregnant women diagnosed with hypothyroidism and treated with levothyroxine, and the control group comprised 41 pregnant women with normal thyroid function. The assessment of serum levels of T3, free T3, T4, free T4, TSH, and Anti TPO was carried out using the ELISA method, while the first-stage fetal screening tests, including Free BhCG, B-MOM, P-MOM, and NT-MOM, were conducted using the Electro-chemiluminescent (ECL) method. Subsequently, data analysis was conducted using SPSS.

Results: In the case group, the average levels of TSH (P=0.001), TPO (P=0.006), trisomy 21 (P=0.001), and trisomy 13/18 (P=0.001) were significantly higher as compared with the control group. Conversely, in the case group, PAPP-A was significantly lower (P=0.001). However, there was no statistically significant difference between the two groups in terms of mean levels of beta-hCG (P=0.297), B-MoM (P=0.202), and NT-MoM (P=0.221). Furthermore, in the case group treated with levothyroxine, mean serum TSH level was significantly higher in the screen positive and medium risk groups of Down syndrome (DS) as compared with the negative screen group (P=0.014).

Conclusion: Our results indicated that it is important to promptly identify pregnant women with hypothyroidism and ensure that timely screening tests for fetal health are carried out as a mandatory practice.

Keywords: Gestation, Thyroxine T4, Triiodothyronine T3, Thyroid-stimulating hormone, TSH, free T4, FT4, First Trimester of Pregnancy

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1. Introduction

Hypothyroidism is a thyroid function disorder that affects 2-3% of pregnant women. Since the fetal thyroid gland does not produce significant amounts of hormones until the second trimester, the mother's thyroid hormones (TH) during pregnancy play a crucial role in the growth and development of the fetus, particularly in neurogenesis (1-3). For example, thyroxine (T4) and the biologically active hormone iodothyronine (T3) influence neurotransmission, differentiation, myelination, and synaptogenesis.

Pregnant women with overt hypothyroidism face an increased risk of adverse pregnancy outcomes, including spontaneous abortion, preeclampsia, preterm birth, placental abruption, postpartum hemorrhage, low birth weight, fetal or neonatal hyperthyroidism, neurocognitive developmental

disorders in the fetus, intrauterine growth restriction, reduced IQ in children, elevated bilirubin levels in newborns, and increased perinatal mortality (4-8). Moreover, maternal hypothyroidism, especially in the first trimester, is linked to delayed neural development in the child (1), and fetuses of hypothyroid women have a 10-20% higher likelihood of congenital abnormalities (4). Furthermore, every pregnant woman, regardless of her medical history, has a potential risk of having a child with chromosomal disorders and congenital abnormalities. Although fetal health screening tests cannot guarantee specific outcomes, they play a vital role in evaluating the likelihood of potential health issues (9). In developed countries, pregnancy screening tests are routinely conducted to detect chromosomal disorders, and in Iran, efforts are underway to expand such testing programs (10-12). The fetal health status can be comprehensively evaluated by performing early pregnancy screening tests, including double, triple, or quadruple tests, and ultrasound scans during the first and second trimesters (13).

Given that several factors can influence fetal abnormality screening and risk determination, it is expected that variations in thyroid hormone levels and their impact on fetal growth requirements in the first trimester of pregnancy may correlate with the risk of screening tests. Given the significance of fetal health and the treatment of mothers with levothyroxine, it is essential to assess thyroid hormone levels and anti-TPO levels and their association with the risk of first-trimester screening tests. Therefore, this study aimed to investigate the association between FT4-TSH and Anti-TPO hormones and the risk level of Down syndrome (DS) screening tests in hypothyroid women in Kermanshah, Iran, in 2022-2023.

2. Methods

This retrospective case-control study enrolled 82 pregnant women during their first trimester, referred to Imam Reza and Motazadi hospitals for fetal screening tests in Kermanshah, Iran. The minimum sample size of 41 samples per group was determined using the sample size formula for comparing two means with a 95% confidence level and 80% power. The required sample size was calculated based on previous study (14), which reported average PAPP-A levels in two groups as 0.9±0.43 and 1.11±0.46, respectively. Consequently, this study included 41 participants in each group, totaling 82 pregnant mothers. The case group consisted of 41 hypothyroid pregnant women treated with levothyroxine, while the control group included 41 pregnant women with normal thyroid function, who were also referred for fetal screening tests. There are no significant differences between case and control group in terms of maternal age and fetal age.

The inclusion criteria comprised pregnant women aged 18-35 years, gravid one, and carrying singleton pregnancies. The exclusion criteria were: pregnant women with diabetes, high blood pressure, endocrine disorders, smoking, drug addiction, and a history of systemic diseases or use of specific drugs. All participants provided a written informed consent, and data were collected through the electronic medical record system. The study adhered to ethical guidelines established by the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1400.213).

First, 5 ml of blood was drawn from patients in both case and control group. After centrifugation, serum samples were separated and promptly stored in a refrigerator. The serum levels of T3, FT3, T4, FT4, TSH, and TPO were assessed using the ELISA method. The first stage fetal screening tests, including Free BhCG, B-MOM, P-MOM, and NT-MOM, were measured using a quantitative luminescence method with the Cobas E411 device.

Based on the results of Down's syndrome (DS) screening test in the first trimester, patients were categorized as follows: high risk (Positive screen group) if the risk exceeded 1:250, Borderline risk (Medium risk group) if the risk fell between 1:250 and 1:500, and Low risk (Negative screen group) if the risk was less than 1:500.

Statistical analysis was performed using SPSS version 24. Categorical data were assessed using χ^2 or Fisher's exact test, while quantitative data (according to KS test for normality) were analyzed with the independent sample t-test or the non-parametric U-Mann-Whitney test. The results were summarized using two-dimensional tables and numerical indicators, such as mean and standard deviation. P value<0.05 was considered as significant difference between groups.

3. Results

The mean age of the mothers in this study

was 32.02±2.13 years. Both groups, exhibited homogeneity in terms of mean age (P=0.615). Furthermore, none of the mothers in either groups had a history of systemic illness, cigarette smoking, or substance abuse.

The average levels of T4, T3, FT3 (P=0.001) PAPP-A (P=0.001), and P-MOM (P=0.001) in the case group were found to be significantly lower than those in the control group. Also, the average levels of TSH (P=0.001) and TPO (P=0.006) in the case group treated with levothyroxine were significantly higher than in the control group. Moreover, given the mean levels of BHCG (P=0.297), B-MOM (P=0.202), and NT-MOM (P=0.221), no significant statistical difference was observed between the two groups. Finally, the incidence of trisomy 13/18 and 21 was higher in the case group as compared with the control group (P=0.001) (Table 1).

Based on the results of DS screening tests, all individuals in the control group were categorized as low risk for DS. However, 29.3 and 7.3 percent of individuals in the case group were classified as borderline and high-risk, respectively (Table 2).

In the control group, Down's syndrome screening did not yield any positive results for mothers classified as either moderate or high risk. All mothers in the control group fell into the low-risk category for Down's syndrome screening (Table 2).

Within the control group, no instance of Down syndrome was detected among, as all the mothers belonged to the low-risk category for Down's syndrome screening (Table 2).

In the group of mothers receiving levothyroxine, the mean TPO serum level showed no statistically significant difference among the three risk groups of DS screening tests (P=0.3). However, the mean serum levels of TSH and FT4 were notably higher in the positive and moderate screening groups as compared with the negative screening group (P=0.014 and P=0.001, respectively) (Table 3).

4. Discussion

The present study aimed to investigate the association between Thyroid hormones and the risk level of screening tests in the first trimester of pregnancy in hypothyroid women. According to our results, the average levels of TSH (Thyroid-Stimulating Hormone), TPO (Thyroid Peroxidase Antibodies), T21, and T13/18 in the case group

Table 1: Comparison of Mean (Standard Deviation) of Investigated Variables between the two Groups

Variable	Case	Control	P value
T3	1.31 (0.24)	1.50 (0.14)	0.001
T4 (µg/mL)	8.95 (1.66)	9.77 (1.44)	0.021
TSH (*mIU/mL)*	2.76 (1.31)	1.65 (0.75)	0.001
TPO (IU/ml)	62.40 (12.34)	5.09 (2.85)	0.006
FT3 (ng/ml)	2.43 (0.35)	3.03 (0.29)	0.001
FT4 (µg/ml)	1.13 (0.31)	1.32 (0.24)	0.001
PAPPA (mg/L)	2060.04 (1533.5)	4978.12 (4556.5)	0.001
PMOM	0.91 (0.65)	1.62 (0.82)	0.001
BHCG (ng/mL)	128.64 (51.38)	40.53 (40.25)	0.297
B-MOM	1.81 (1.73)	1.46 (1.40)	0.202
NT-MOM	1.33 (0.24)	1.27 (0.24)	0.221
T21	0.004 (0.0028)	0.0002 (0.00018)	0.001
T13/18	0.0008 (0.004)	0.0000	0.001

TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase; FT3: Free triiodothyronine; FT4: Free thyroxine; PAPP-A: Pregnancy – associated plasma protein A; PMOM: population multiple of the median; BHCG: Beta-Human Chorionic Gonadotropin; B-MOM: B-multiple of the median; NT-MOM: Nuchal translucency – multiple of the median

Table 2: Comparison of frequency and percent of risk results of Down syndrome screening tests in two case and control groups

Patient Risk	Case	Control	Total
Low Risk	21 (63.4 %)	41 (100)	62 (80.5%)
Borderline Risk	12 (29.3 %)	0	12 (15.6%)
High Risk	3 (7.3 %)	0	3 (3.9%)
Total	36 (100.0%)	41 (100.0%)	77 (100.0%)

Table 3: Comparison of the serum level of thyroid hormones (TSH, FT4, TPO) with the results of risk screening tests in the case group

Patient risk	TSH	FT4	TPO
Low risk	2/37 (1/09)	1/27 (0/3)	40/31 (81/81)
Borderline risk	3/19 (1/36)	0/91 (0/1)	122/52 (199/62)
High risk	4/38 (1/58)	0/84 (0/17)	13/45 (1/35)
P value	0.014	0.001	0.3

TSH: Thyroid stimulating hormone; FT4: Free thyroxine; TPO: Thyroid peroxidase

were significantly higher than in the control group. Also, there was no statistically significant difference between the case and control groups in the mean levels of BHCG (Beta-Human Chorionic Gonadotropin), B-MOM (Beta-MOM), and NT-MOM (Nuchal Translucency-MOM). Furthermore, the mean level of PAPP-A (Pregnancy-Associated Plasma Protein-A) was significantly lower in the case group than in mothers with normal thyroid function.

In 2020, Fallatah and colleagues investigated the adverse outcomes and consequences of pregnancy in obese pregnant women with hypothyroidism. They demonstrated that hypothyroidism during pregnancy leads to adverse maternal and fetal outcomes, including miscarriage, intrauterine growth retardation, premature birth, and cognitive impairment in the accompanying children. Therefore, screening for thyroid function tests in the prenatal and antenatal periods is crucial to prevent the occurrence of potential adverse outcomes (15). Moreover, Villanger and co-workers examined TSH level and its association with attention-deficit/hyperactivity disorder in infants. Their results showed that the risk of attention-deficit/hyperactivity disorder among infants with low TSH levels, such as those with hyperthyroidism, was 1.5 times higher than that in the control group (16).

Findings revealed that the average T3 (Triiodothyronine), FT4 (Free Thyroxine), TSH, and TPO levels showed significant elevation in the case group as compared with the control group. Furthermore, TSH serum levels displayed a significant increase in the screen-positive group and the borderline risk group of DS as opposed to the negative screen group. Nevertheless, in a cohort study investigating the association between first-trimester screening tests and thyroid function tests, including TSH, FT4, and thyroid antibodies, Ong and colleagues found no significant difference in FT4 levels between pregnant and non-pregnant women. They also reported that a TSH level exceeding 2.15 did not predict adverse pregnancy outcomes (8).

A low level of PAPP-A heightens the risk of complications during pregnancy. The study results also indicated that the average level of PAPP-A exhibited a significant decrease in the case group as compared with the control group. Similarly, in 2020, Tosun and colleagues reported that mean levels of PAPP-A MoM (Multiple of the Median) and Free-BhcG MoM were notably lower in levothyroxine users (17).

When examining the results of fetal DS screening tests during the first trimester of pregnancy, it was observed that in the control group, all patients were in the negative screen (low risk) group for DS, while 63.4%, 29.3%, and 7.3% of the case group patients were in a low risk, borderline risk, and high-risk groups for DS, respectively.

In other words, the risk of DS was reported to be higher in the group of hypothyroid mothers as compared with mothers with normal thyroid function. Additionally, in the levothyroxine case group, mean level of TSH was significantly higher in the screen-positive group and the medium-risk group for DS than in the negative screen group for DS. Liu and colleagues investigated the association between thyroid disorders and the prevalence of DS in Taiwanese infants. In their study, 51 babies diagnosed with DS were included, and their thyroid function was assessed. According to the results, the prevalence of thyroid disorders in Taiwanese babies with DS was significantly higher than in healthy and normal babies (18). This finding was consistent with the established importance of TH in brain development during intrauterine and early life stages (19-20).

Given that fetal abnormalities and the birth of an unhealthy baby are a big challenge. Fetal screening tests in the first trimester of pregnancy is the best diagnostic strategy in order to determine the risk of the fetus suffering from birth defects.

However, these tests are 80-95% accurate and are not a definite proof of whether the fetus is healthy or sick and new markers should be added to the set of these tests to increase the detection rate of these tests. The goal is to enhance the screening process for fetal abnormalities by concurrently measuring thyroid hormones and thyroid peroxidase levels, in addition to conducting screening tests. This approach aims to improve the overall detection rate of fetal abnormalities during screening. Also, with higher reliability of the results, it prevents psychological pressures on the couple as well as spending money, time and other adverse consequences.

4.1. Limitations

The main limitations of this study were the high cost of laboratory tests and screening. Also, some mothers did not cooperate due to their reluctance to reveal the screening results and confirm any fetal abnormalities.

5. Conclusion

The risk of Down syndrome (DS) was found to be higher among mothers with hypothyroidism compared to those with normal thyroid function. Furthermore, in the case group treated with levothyroxine, the mean serum Thyroid Stimulating Hormone (TSH) level was significantly elevated in both the screen-positive group and the medium-risk group for DS, exceeding the levels observed in the negative screen group for DS. As a result, it is crucial to assess thyroid hormone status, with a specific emphasis on TSH levels, as an integral component of the essential pre-pregnancy assessments and counseling.

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Ethics Approval

The Ethics Committee of Kermanshah University of Medical Sciences in Kermanshah, Iran approved the protocol of this study with the code of IR.KUMS.REC.1400.213. Also, written informed consent was obtained from the participants.

Authors' Contribution

Negin Rezavand: Contribution to the conception and design of the study, drafting the work. Somayeh Darvishi: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Maryam Hematti: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Mansour Rezaei: Contribution to the conception and design of the study, material preparation, data collection, and analysis, critical review of the manuscript for significant intellectual content. Houshang Nemati: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Seyed Mohammad Saleh Seyedzadeh: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Alireza Kamravamanesh: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Saydeh Saba Seyedzadeh: Contribution to the conception and design of the study, material preparation, data collection, and analysis, drafting the work. Mastaneh Kamravamanesh: Contribution to the conception and design of the study, drafting the work, critical review of the manuscript for significant intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work, such that the questions related to the accuracy or integrity of any part of the work.

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