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Original Article

Exploring the Impact of Maternal Subclinical Hypothyroidism on First-trimester Screening Results

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ABSTRACT

Objective: Subclinical hypothyroidism is the most frequent thyroid dysfunction in pregnancy with an incidence of 2–5% which can easily be overlooked due to the absence of clinical symptoms. Studies have shown that thyroid hormones could alter the level of free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) released from the placenta during early pregnancy. Since these two serum markers are the two of the parameters used in the first-trimester combined screening, we hypothesized that distorted risk calculation results could be obtained from pregnant women with subclinical hypothyroidism.

Methods: We conducted a prospective and cohort study at a tertiary university hospital in northwest Turkey between February 2018 and June 2018, involving 250 pregnant women in their first trimester who were seeking care at the obstetrics outpatient clinic. After evaluation of thyroid functions, first-trimester screening was performed in all 250 singleton pregnancies with fetuses at 11+0 to 13+6 gestational weeks. Thyroid-stimulating hormone (TSH) values above 2,5 mIU/L were considered high. The correlation between the results and parameters of the first-trimester combined screening and thyroid hormone values was examined.

Results: Among the participants, after analyzing the fT4 values, all 35 pregnant women with high TSH values were diagnosed with subclinical hypothyroidism. We observed a statistically weak negative correlation between TSH and β-HCG, which was expected given the similarities in their alpha subunits. There was no statistically significant correlation between TSH and PAPP-A values, combined risk scores, and age risk scores of first-trimester screening. As a matter of course, combined risk scores of first-trimester screening were found to be statistically lower in younger mothers.

Conclusion: Pregnant women with normal thyroid functions and subclinical hypothyroidism were investigated for alterations in first-trimester screening parameters and risk scores. As a result, no statistically significant correlation was found between subclinical hypothyroidism and first-trimester screening.

INTRODUCTION

Prenatal testing has been developed over the years to evaluate the patient's risk of carrying a fetus with a chromosomal abnormality. Previously, only maternal age was taken into account in predicting fetal aneuploidy. In the early 90s, reduced levels of free beta hCG subunits in serum sampled from pregnant in the first trimester were found to related with cases of trisomy 21.[1,2] In addition, pregnancy-associated plasma protein A (PAPP-A) was found to be reduced in cases of fetal trisomy 21 in maternal serum starting from 6 to 9 weeks of gestation.[3,4] Together with the investigations into first trimester biomarkers, Nicolaides et al.[5] described nuchal translucency (NT) as a well-defined fluid-filled area on the neck of the fetus. A NT greater than 3 mm was considered significant for fetal chromosomal anomalies. The rate of detecting Down syndrome by measuring the NT alone is approximately 70% and the false positive rate is 5%.[6] In the early 2000s, with the addition of biochemical markers beta-human chorionic gonadotropin (β-hCG and PAPP-A) to NT measurement, the rate of detecting Down syndrome increased up to 90%, while the false positivity rate was approximately 3–5%.[7-10] Thus, first-trimester screening that we routinely apply to all pregnant women today has emerged. Since invasive prenatal diagnostic tests are applied more effectively, the guide-

lines in recent years are aimed at recommending screening tests to every pregnant woman regardless of age.[11,12]

However, studies on the effect of maternal thyroid functions on first-trimester combined screening are insufficient in the literature. Although fetal thyroid gland begins to synthesize thyroid hormones from 12th gestational week,[13,14] functional maturation of the fetal pituitary-thyroid axis is formed starting from the second half of pregnancy;[15,16] therefore, fetus is dependent on maternal thyroxine. Maternal thyroxine (T4) hormone is converted to triiodothyronine (T3) and used by the fetal intracellular environment after passing through the placenta. Effects of T4 and T3 on the trophoblast function were investigated by Maruo et al.[17] It has been shown that optimal thyroid hormone concentration is needed for maximum stimulating effect on trophoblast endocrine function in the secretion of progesterone, estradiol-17-β, β-HCG, and human placental lactogen (hPL) by cultured early placental tissues. Unlike early placental tissues, endocrine activity of cultured term placental tissues did not react to the addition of T3 and T4.

In addition, Näntö-Salonen et al.[18] observed that thyroid hormones can affect insulin-like growth factor-1 (IGF-1) levels. According to this study, in the hypothyroidism environment, the serum levels of IGFBP-3 and IGFBP-4 are reduced. Considering that PAPP-A is an IGF-dependent IGFBP-4 protease, it is predicted that the level of maternal thyroid hormones can change the levels of PAPP-A.

Based on this information, it can be hypothesized that a thyroid dysfunction such as subclinical hypothyroidism that is not screened routinely may affect the results of first-trimester combined screening by causing these two serum markers, β-HCG and PAPP-A, to alter. To investigate this, in our study, the correlation between first-trimester combined screening parameters (β-HCG, PAPP-A) and risk calculation results and thyroid-stimulating hormone (TSH) and T4 levels taken from the participants who have no known thyroid disease was examined.

MATERIALS AND METHODS

Two hundred and seventy-eight pregnant women who applied to the obstetrics outpatient clinic of a tertiary center in North-west Turkey between February 2018 and June 2018 were included in the present study. Women with a singleton pregnancy in the first trimester were screened for TSH levels. Twenty-eight women who had multiple pregnancies, a known systemic disease, participants with pre-existing thyroid disease or thyroid medication usage, recent bleeding, or who were smokers were excluded from the study. Two hundred and fifty women's blood samples were obtained to analyze TSH levels. Serum concentrations of TSH were analyzed spectrophotometrically (Roche Diagnostic Gmbh, D-68298, Mannheim/Germany) with the Beckman Coulter Coulter DX1 800 (California/US) Immun Chemiluminescence method original kit.

First-trimester combined screening was performed to the patients between 11 and 14. gestational weeks (45–85 mm according to crown-rump length in ultrasound) as recommended in routine pregnancy follow-up. Then, according to combined risk scores, these patients were divided into three subgroups as low risk (<1: 1000), medium risk (from 1: 251 to 1: 999), and high risk (>1: 250). The correlation of TSH values with all these risk groups was examined.

Statistical Analysis

Statistical analyses were carried out with SPSS 15.0 software (SPSS Institute, Chicago, IL, USA). Median and interquartile range (25–75 percentile) values were used while presenting descriptive analyses. The conformity of the variables to normal distribution was examined by histogram graphics and the Kolmogorov–Smirnov test. Variables that did not show a normal distribution (non-parametric) were evaluated between groups and compared with the Mann–Whitney U test. In comparing categorical data, Chi-square and Fisher tests were used in appropriate places. The relationship between the measurement data with each other was examined using Spearman's correlation test. Cases where $p<0.05$ were considered as statistically significant results.

RESULTS

Serum TSH and fT4 concentrations of all participants were measured. When the fT4 values were examined, it appeared that all of these 35 participants had subclinical hypothyroidism (fT4 values were in the normal range). This may be because we did not include patients with obvious hypothyroidism in our study group. We divided the elevation of TSH into groups to see how high TSH affects the outcome among these patients. We determined the significant increase in TSH level as 4–10 mIU/L, we found that six out of 35 women had a significant TSH elevation. In remaining, 29 women TSH values were in the range of 2.5–4 mIU/L.

The total number of pregnant women included in this study was 250. The median age of the women participating was 29.0 (26.0–34.0). The median TSH value was 1.4 (0.8–2.1) mIU/L. While 115 of the patients had normal TSH values (<2.5 mIU/L), 35 of them had high TSH val-

Table 1. Evaluation of the age and clinical data of the pregnant women participating in the study

	Median	IQR
Age (years)	29.0	(26.0–34.0)
TSH (mIU/L)	1.4	(0.8–2.1)
T4	0.8	(0.6–0.9)
T3	3.3	(2.9–3.7)
Gravidity	2.0	(1.0–3.0)
Parity	1.0	(0.0–2.0)
Abortus	1.0	(1.0–2.0)

IQR: Interquartile range.

Table 2. Comparison of first-trimester screening parameters according to TSH values

	TSH				p-value
	Normal		High		
	Median	IQR	Median	IQR	
PAPP-A (MoM)	0.8	(0.7–1.2)	0.8	(0.7–1.0)	0.358
B-HCG (IU/ml)	1.0	(0.8–1.4)	1.0	(0.9–1.5)	0.876
NT (MoM)	1.1	(0.9–1.2)	1.1	(1.0–1.2)	0.390

*Mann–Whitney u test; IQR: Interquartile range.

Table 3. Comparison of TSH values and first-trimester screening combined risk result

	TSH				p-value
	Normal		High		
	n	(%)	n	(%)	
Combined risk					
Low risk	182	(85.8)	30	(14.2)	0.701[a]
Moderate risk	26	(89.7)	3	(10.3)	
High risk	9	(100.0)	0	(0.0)	

[a]Fisher test; [b]Chi-square test.

Table 4. Investigation of the correlation between PAPP-A, β-HCG, NT, and TSH values and age, clinical features, and pregnancy outcomes

	PAPP-A		β-HCG		NT		TSH	
	rho	p	rho	p	rho	p	rho	p
TSH	−0.027	0.674	−0.190	0.003	0.014	0.821	1	.
Yaş	−0.108	0.089	−0.023	0.716	0.064	0.316	−0.029	0.647
T4	0.022	0.826	0.050	0.616	−0.214	0.031	−0.187	0.061
T3	−0.156	0.196	−0.277	0.020	0.068	0.576	0.082	0.500
Age risk	0.108	0.089	0.032	0.615	−0.062	0.325	0.035	0.577
Gravida	−0.082	0.248	−0.008	0.909	0.001	0.994	−0.133	0.059
Parity	−0.093	0.188	−0.018	0.796	0.049	0.486	−0.185	0.008
Abortus	−0.239	0.066	−0.091	0.488	−0.169	0.197	0.105	0.426

*Spearman correlation analysis

ues (>2.5 mIU/L). The median T4 value was 0.8 (0.6–0.9), the median T3 value was 3.3 (2.9–3.7), the median gravida number was 2.0 (1.0–3.0), the median parity number was 1.0 (0.0–2.0), and the median abortus number was 1.0 (1.0–2.0) (Table 1)

First-trimester screening parameters were compared according to TSH values, and no significant difference was found (p>0.05) (Table 2).

TSH values and the combined risk scores of Down syndrome in the first trimester were compared, and no significant difference was found (p>0.05) (Table 3).

Correlations between PAPP-A, β-HCG, NT, and TSH values and age and clinical features were investigated. Between TSH and β-HCG, there is a statistically poor negative correlation (rho: −0.190, p:0.003), as expected, as alpha subunits are similar.[19] There is a moderately a significant negative correlation between B-HCG and fT3 (rho: −0.277, p:0.020). There is a weakly significant negative correlation between NT and T4 (rho:−0.214, p:0.031). There is a weakly significant negative correlation between TSH and parity. (rho:−0.185, p:0.008) (Table 4). These relations did not reach a statistically significant result.

DISCUSSION

Besides the metabolism regulation functions, thyroid hormones have effects on the endocrine activities of trophoblasts. Thyroid hormones were shown to alter the level of β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) released from the placenta during early pregnancy.[17,18] Since these two serum markers are the two parameters used in the first-trimester combined screening, we hypothesized that aberration in risk scores could be obtained from pregnant with thyroid dysfunctions like subclinical hypothyroidism which is the most frequent, besides often overlooked due to no clinical symptoms. To investigate this, in our study, the correlation of first-trimester combined screening parameters and results with thyroid functions of the participants was examined.

Ashoor et al.[20] investigated the relation between maternal serum levels of TSH and free β-hCG in aneuploid and euploid pregnancies at 11–13 weeks to find out the probable significance of adding TSH in the first-trimester screening. In this study, it was observed that in pregnancies with trisomy 21, β-hCG was higher and TSH was lower than in unaffected pregnancies. Despite serum TSH was changed in pregnancies with fetal trisomy 21, this analysis did not develop the performance of screening for Down syndrome provided by NT, free β-hCG, and PAPP-A. Finding an inverse association between free β-hCG MoM and TSH MoM was consistent with the known thyrotropic characteristics of hCG.[21] In accordance with this, in our study a weakly significant negative correlation was observed between TSH and β-HCG (rho:−0.190, p:0.003). For the rest, no statistically significant correlation between TSH values above the 95th percentile and first-trimester screening parameters (β-hCG and PAPP-A) was found. Nevertheless, there was no statistically significant correlation between TSH values and the combined risk of first-trimester screening for Down syndrome (p:0.701).

In the study conducted by Aytan et al.[22] on 375 pregnant women, between 11 and 14th. gestational weeks, maternal thyroid function tests, and the parameters used in the first-trimester screening (β-HCG and PAPP-A values) were examined and no statistical significant correlation was found between them. Accordingly, in our study, it was concluded that maternal thyroid function tests in the first trimester did not have a statistically significant relationship with β-HCG (p:0.876) and PAPP-A (p: 0.358) in the first-trimester screening.

Weinans et al.[23] evaluated the relationship between the TSH and the rate of Down syndrome on 138 pregnant women. Although maternal serum TSH levels of babies with Down syndrome were found to be slightly lower than the control group, no statistically significant difference was found. In our study, the combined risk for Down syndrome in the first-trimester screening was examined after measuring the TSH values. No statistically significant relationship was found between the maternal TSH and the first-trimester combined risk calculation results.

Although a small sample size is the major limitation, prospective cohort study design is the strength of our study.

Conclusion

It has been predicted that maternal thyroid dysfunctions would alter the parameters of the first-trimester screening (β-HCG and PAPP-A). Patients may be misled as a result of incorrect risk calculations. Since subclinical hypothyroidism is a common and unnoticed condition during pregnancy, all patients were screened in this direction. In our study, the thyroid functions and with the first-trimester combined screening parameters and results were examined, but no statistically significant correlation was observed.

Ethics Committee Approval

This study approved by the Marmara University Pendik Training and Research Hospital Clinical Research Ethics Committee (Date: 05.01.2018, Decision No: 09.2018.041).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.T.D.; Design: A.T.D.; Supervision: S.S.; Materials: K.Ç.; Data: A.T.D.; Analysis: K.Ç.; Literature search: A.T.D.; Writing: A.T.D.; Critical revision: S.S.

Conflict of Interest

None declared.

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Maternal Subklinik Hipotiroidizmin Birinci Trimester Tarama Sonuçları Üzerindeki Etkisinin Araştırılması

Amaç: Subklinik hipotiroidizm %2-5 insidans ile gebelikte en sık görülen tiroid fonksiyon bozukluğudur ve klinik semptom olmaması nedeniyle kolaylıkla gözden kaçabilir. Çalışmalar, tiroid hormonlarının, gebeliğin erken döneminde plasentadan salınan insan koryonik gonadotropin (β-hCG) ve gebelikle ilişkili plazma protein-A (PAPP-A) düzeyini değiştirebileceğini göstermiştir. Bu iki serum belirteci, birinci trimester kombine taramasında kullanılan parametrelerden ikisi olduğu için, bu çalışmada subklinik hipotiroidizmi olan gebelerde hatalı risk hesaplama sonuçlarının elde edilebileceği varsayılmıştır.

Gereç ve Yöntem: Şubat 2018 ile Haziran 2018 tarihleri arasında Türkiye'nin kuzeybatısındaki bir üçüncü basamak üniversite hastanesinde kadın doğum polikliniğinde tedavi görmek isteyen ilk üç aylık dönemindeki 250 gebeyi içeren prospektif bir kohort çalışması yürüttük. 11+0 ile 13+6 gebelik haftaları arasındaki fetüsleri olan 250 tekil gebenin tamamına tiroid fonksiyonları değerlendirildikten sonra birinci trimester taraması yapıldı. 2.5 mIU/L'nin üzerindeki TSH değerleri yüksek kabul edildi. Birinci trimester kombine tarama ve tiroid hormon değerlerinin parametreleri ile sonuçları arasındaki korelasyon incelendi.

Bulgular: Katılımcılar arasında fT4 değerleri analiz edildikten sonra TSH değerleri yüksek olan 35 gebe kadının tamamına subklinik hipotiroidizm teşhisi konuldu. TSH ve β-HCG arasında, alfa alt birimlerindeki benzerlikler göz önüne alındığında beklenen, istatistiksel olarak zayıf bir negatif korelasyon gözlemledik. TSH ve PAPP-A değerleri, kombine risk skorları ve birinci trimester tarama yaş risk skorları arasında istatistiksel olarak anlamlı bir ilişki yoktu. Doğal olarak, genç annelerde birinci trimester taramasının kombine risk skorları istatistiksel olarak daha düşük bulunmuştur.

Sonuç: Normal tiroid fonksiyonları ve subklinik hipotiroidisi olan gebeler ilk trimester tarama parametreleri ve risk skorlarındaki değişiklikler açısından araştırıldı. Sonuç olarak, subklinik hipotiroidizm ile birinci trimester taraması arasında istatistiksel olarak anlamlı bir ilişki bulunmadı.

Anahtar Sözcükler: İlk trimester kombine tarama testi; koryonik gonadotropik hormon; gebelikle ilişkili plazma proteini-A; subklinik hipotiroidizm; prenatal tanı.