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The Relationship Between Subclinical Hypothyroidism and Gestational Diabetes Mellitus

Subklinik Hipotiroidizm ile Gestasyonel Diabetes Mellitus Arasındaki İlişki

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Abstract

Aim: The most common metabolic disorder during pregnancy is gestational diabetes mellitus (GDM). GDM can occur in anywhere between 1.7 and 11.6 percent of people. In hypothyroidism, the rates of glucose oxidation and glycogen synthesis are reduced, and the peripheral tissues' consumption of glucose is also delayed. Patients with subclinical and overt hypothyroidism develop insulin resistance because insulin is unable to adequately maintain the muscles' use of glucose. According to the literature, hypothyroidism is linked to 6–15 percent of GDM pregnancies. Additionally, the chance of having GDM is 4.3 times higher in pregnant women who have hypothyroidism. This study aimed to reveal the relationship between first-trimester thyroid function tests and GDM.

Material and Method: This retrospective cohort study was conducted between May 2021 and May 2022. 100 pregnant patients diagnosed with GDM and 500 healthy controls were included in the study. Using a 75 g glucose challenge test, GDM was identified. The trimester-specific recognized normal limits were used to evaluate the TSH and fT4 readings.

Results: There was a statistically significant difference in terms of SCH between patients with and without GDM (p=0.04). TSH's performance in predicting GDM was evaluated using AUC and ROC (AUC=0.586 and p=0.006). To forecast GDM, the TSH level cut-off value was discovered to be 1.58. The AUC was found to be 0.586 (0.521-0.652). Furthermore, the selectivity is 58% and the sensitivity is 41%

Conclusion: There are many studies in the literature investigating thyroid functions and the development of gestational diabetes mellitus. Our study also found a correlation between the diagnosis of subclinical hypothyroidism in the first trimester and GDM. The study adds to the literature the importance of being cautious and vigilant in terms of the development of gestational diabetes mellitus based on the results of the thyroid function test in the first trimester.

Keywords: Gestational Diabetes mellitus, hypothyroidism, pregnancy

Öz

Amaç: Gebelikte en sık görülen metabolik bozukluk gestasyonel diyabetes mellitustur (GDM). GDM prevalansı yüzde 1,7 ile yüzde 11,6 arasında değişmektedir. Hipotiroidizmde glukoz oksidasyonu ve glikojen sentezi hızları azalır ve periferik dokularda glukoz kullanımı yavaşlar. Subklinik ve aşikar hipotiroidili hastalarda insülin direnci gelişir çünkü insülin kasların glikoz kullanımını yeterince sürdüremez. Literatüre göre, hipotiroidizm GDM gebeliklerinin yüzde 6-15'i ile bağlantılıdır. Ayrıca hipotiroidisi olan gebelerde GDM olma olasılığı 4,3 kat daha fazladır. Bu çalışma birinci trimester tiroid fonksiyon testleri ile GDM arasındaki ilişkiyi ortaya koymayı amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif kohort çalışma Mayıs 2021 ile Mayıs 2022 tarihleri arasında yapıldı. Çalışmaya GDM tanısı konan 100 gebe hasta ve 500 sağlıklı kontrol dahil edildi. GDM, 75 g glikoz yükleme testi kullanılarak teşhis edildi. TSH ve sT4 değerleri trimestere göre kabul edilen normal sınırlara göre değerlendirildi.

Bulgular: GDM olan ve olmayan hastalar arasında SKH açısından istatistiksel olarak anlamlı fark vardı (p=0.04). AUC ve ROC, TSH'nin GDM'yi öngörme performansını değerlendirmek için kullanıldı (AUC=0.586 ve p=0.006). GDM'yi öngörmek için TSH düzeyi cut-off değeri 1.58 olarak belirlendi. AUC'nin 0,586 (0,521-0,652) olduğu bulundu. Ayrıca seçicilik %58 ve duyarlılık %41'dir.

Sonuç: Literatürde tiroid fonksiyonlarını ve gestasyonel diabetes mellitus gelişimini araştıran birçok çalışma bulunmaktadır. Bizim çalışmamızda da birinci trimesterde subklinik hipotiroidi tanısı ile GDM arasında ilişki bulundu. Çalışma, birinci trimester tiroid fonksiyon testi sonuçlarına dayanarak, gestasyonel diyabetes mellitus gelişimi açısından dikkatli ve uyanık olmanın önemini literatüre katmaktadır.

Anahtar Kelimeler: Gestasyonel Diabetes mellitus, hipotiroidizm, gebelik

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INTRODUCTION

The most common metabolic disorder during pregnancy is gestational diabetes mellitus (GDM), which is defined by the World Health Organization as "impaired glucose tolerance" that begins during pregnancy.[1] GDM can occur in anywhere between 1.7 and 11.6 percent of people.[2] While GDM increases some risks for the fetus, such as macrosomia, it also poses a risk for the mother in the future for conditions such as metabolic syndrome, obesity, and dyslipidemia.[3,4] Low fT4 levels associated with GDM during the first trimester of pregnancy. Isolated maternal hypothyroxinemia was observed in 5% of women with GDM. Low fT4 was observed in 70% of patients with GDM pregnancy.[5,6] Therefore, GDM may be linked to maternal hypothyroxinemia.

Hypothyroidism presents with impaired gastrointestinal glucose absorption, delayed peripheral glucose uptake, decreased hepatic glucose output, and decreased liver and muscle gluconeogenesis.[6] Skeletal muscles of hypothyroid rats are less responsive to insulin due to reduced glucose transport in myocytes. In hypothyroidism, glucose utilization in peripheral tissues slows down as glucose oxidation and glycogen synthesis decrease. As a result of insulin's inability to appropriately maintain muscle glucose use, insulin resistance develops in patients with subclinical and overt hypothyroidism.

It is well established that maternal thyroid hormones are essential for healthy fetal growth and development during childhood.[8-10] This is certainly relevant during the first trimester when the fetus is dependent on the flow of maternal thyroid hormones over the placenta.[11,12] Maternal thyroid hormones cross the placenta via thyroid hormone transporters, where they are metabolized by deiodinases to regulate fetal thyroid hormone levels. The metabolism of thyroid hormones in GDM placentas is currently unknown. Placentas from GDM mothers have higher Deiodinase 3 expression and activity, but lower Deiodinase 2 than Normal Glucose Tolerance mothers.[13]

According to the literature, hypothyroidism is linked to 6–15 percent of GDM pregnancies.[5,14,15] Additionally, the chance of having GDM is 4.3 times higher in pregnant women who have hypothyroidism.[16]

This study aimed to reveal the relationship between first-trimester thyroid function tests and GDM.

MATERIAL AND METHOD

This retrospective cohort study was conducted between May 2021 and May 2022. The study was approved by the Ethical Committee of Gazi University (13.07.2022 / 2022-890). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Single pregnancies that were healthy at the first antenatal controls were included. Those with previous thyroid diseases, other metabolic diseases and poor obstetric history were excluded in the study. One thousand pregnant women were included in the study. Four hundred pregnant women were excluded from the study according to exclusion criteria. It was learned from the file records that 100 patients had GDM. A study group was formed from patients with a diagnosis of GDM. Five hundred non-GDM pregnant women were considered as the control group. The files of the pregnant women were scanned retrospectively. Age, gravida, parity, body mass index (BMI), Thyroid-stimulating hormone (TSH) and free T4 (fT4) values were checked from the first visit files.

The diagnosis of GDM was made with a 75gr oral glucose tolerance test. Fasting blood glucose cut-off value was 92mg/dl, 1st hour cut-off value was 180 mg/dl, 2nd hour cut-off value was 153mg/dl. If any of these values are high, gestational diabetes mellitus was diagnosed.

Normal TSH levels varied between 0.38-5.33 mU/l and fT4 between 0.58-1.38 ng/dL. In the study, the American Thyroid Association (ATA) 2011 criteria for TSH were taken into account. Accordingly, the first trimester TSH cut-off value was determined as 2.5 mIU/mL. Subclinical hypothyroidism diagnosis was made in those with high TSH value and normal fT4 level.

The statistical analysis was performed using SPSS version 22. Data were evaluated using descriptive statistical techniques (mean SD). To assess if the variables were normally distributed, they were subjected to visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov test) evaluation. The Student's t-test was used to compare parametric data that was normally distributed. For the purpose of comparing non-normally distributed metric data, the Mann-Whitney U test was used. The analysis of the distinction between category data was performed using the Chi-square test or Fischer's exact test. The effectiveness of TSH to predict GDM was assessed using the area under the ROC curve (AUC), and the best cut-off point was determined. P-value was considered significant at <0.05.

RESULTS

One thousand pregnant women were included in the study. Four hundred pregnant women were excluded from the study according to exclusion criteria. A study group was formed from 100 patients with a diagnosis of GDM. Five hundred non-GDM pregnant women were considered as the control group.

There was a statistical difference between the groups in terms of age and BMI. When their gravida was examined, there was no difference between the groups. While TSH levels were significantly higher in the GDM group, st4 levels were significantly lower (**Table 1**).

Table 1: Comparison of demographic features and laboratory values of the GDM group with control group

	Control Group	GDM Group	p value
Age*	30.3±5.8	32.5±5.5	0.001
BMI*	22±1.4	23.3±2.1	0.000
Gravida ¶	2 (1-5)	2 (1-5)	0.09
TSH¶ (mIU/L)	1.36(0.01-10.7)	1.86(0.15-6.67)	0.003
fT4* (ng/dL)	1.1±0.2	1.0±0.4	0.000

* Data are given as mean±SD ¶ Data is given as median (minimum-maximum), GDM: Gestational Diabetes Mellitus, BMI: Body mass index, TSH: Thyroid-stimulating hormone, fT4: free T4. (p <0.05 was considered significant.)

There were 105 pregnant women diagnosed with subclinical hypothyroidism (SCH) in the study. This was 17.5% of the population. There was no statistical difference between the group diagnosed with SCH and the euthyroid group in terms of age, BMI and gravida.

When patients with GDM were evaluated with thyroid function tests performed in the first trimester, the relationship between subclinical hypothyroidism and GDM was discussed, and the rate of GDM was found to be 23.8% in patients with SCH. In the non-SCH group, the rate of GDM was 15.2%. There was a statistically significant difference in terms of SCH between patients with and without GDM (p=0.04) (**Table 2**).

Table 2: Presence of SCH according to gestational diabetes groups.

	Control Group	GDM Group	p value
SCH (-)	420 (84%)	75 (75%)	0.04 ¶
SCH (+)	80 (16%)	25 (25%)	

¶ Chi-square test :p<0,05, SCH: Subclinical hypothyroidism, GDM: Gestational Diabetes Mellitus.

TSH's performance in predicting GDM was evaluated using AUC and ROC (AUC=0.586 and p=0.006). To forecast GDM, the TSH level cut-off value was discovered to be 1.58. The AUC was found to be 0.586 (0.521-0.652). Furthermore, the selectivity is 58% and the sensitivity is 41% (**Figure 1**).

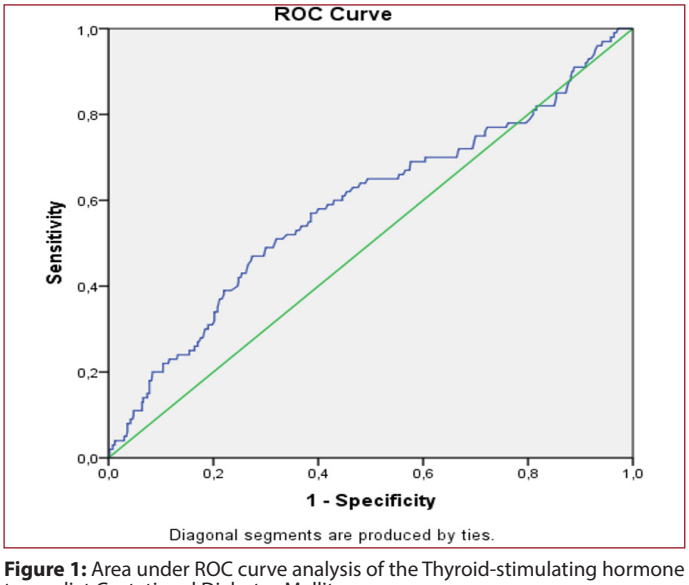

Figure 1: Area under ROC curve analysis of the Thyroid-stimulating hormone to predict Gestational Diabetes Mellitus..

DISCUSSION

In this study, we evaluated the relationship between thyroid function tests and GDM. We aimed to reveal the relationship between GDM by identifying patients with SCH. The relationship between thyroid function tests and diabetes mellitus has been previously discussed in the literature. In addition to having an impact on diabetes mellitus and insulin resistance, thyroid hormones also have an impact on these conditions.[17]

Pregnancy weight and fT4 have been shown to be inversely correlated in studies, with low fT4 in the second trimester being associated with obesity in euthyroid women.[18-20] High maternal weight and low fT4 were both linked to an increased risk of GDM, according to a FaSTER study.[21] According to a review by Biondi et al, hypothyroidism is linked to a reduction in hepatic glucose uptake and glucose absorption.[22] In our study, a significant relationship was found between GDM and high TSH - low fT4 in the first trimester. The rate of GDM was found to be 23.8% in patients with SCH. When SCH patients were compared with the control group, the rate of GDM was shown to be significantly higher (p<0.05). Our results are compatible with the literature. According to a meta-analysis of six cohort studies, individuals with SCH had a 1.35-fold greater incidence of GDM than patients in the control group. The risk of gestational diabetes increases, even in SCH women with TSH levels that are within the normal reference range.[23] A prospective study was conducted on 6031 Chinese pregnant women. In pregnancy, low FT4 levels have been shown to be risk factors for GDM and preeclampsia.[24] In the Yang et al. study, GDM women had lower levels of free T4 (FT4) in the early stages of pregnancy than non-GDM women. Increasing fT4 during the first trimester of pregnancy was linked to a statistically significant decline in the incidence of GDM, as was once again shown in this study.[25]

In a study, Safian et al. found a significant difference in the incidence of subclinical hypothyroidism between pregnant women with GDM and the control group (38.49% and 14.06%, respectively) (p =0.016).[26] A moderately significant correlation between overt hypothyroidism identified in the first trimester and the risk of GDM was found in a study by Wang et al.[27] Low fT4 levels were strongly correlated with GDM both in the first and second trimesters of pregnancy in a meta-analysis that included 44 trials. The same meta-analysis found a substantial relationship between GDM risk and hypothyroxinemia, overt and subclinical hypothyroidism, overt hyperthyroidism, and positive thyroid autoantibodies. Subclinical hyperthyroidism during pregnancy decreased the risk of GDM.[28]

The 80 (26.6%) women with GDM and the 221 (73.4%) women without GDM did not show any statistically significant differences regarding any of the thyroid function tests, according to Agarwal et al.[29] In another recent study, the risk of GDM was not significantly correlated with the TSH level, thyroid function subtypes, or TPO Ab positivity, despite a negative correlation being seen for the highest FT4 concentration tertile.[30]

CONCLUSION

There are many studies in the literature investigating thyroid functions and the development of gestational diabetes mellitus. Our study also found a correlation between the diagnosis of subclinical hypothyroidism in the first trimester and GDM. The study adds to the literature the importance of being cautious and vigilant in terms of the development of gestational diabetes mellitus based on the results of the thyroid function test in the first trimester. The study's retrospective design is its limiting factor. Prospective studies with larger samples will shed more light on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Gazi University (13.07.2022 / 2022-890).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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