Comparison of Thyroid Function Tests in Pregnant Women with and without Gestational Diabetes

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ABSTRACT

Aim: The aim of this study was to determine whether there were abnormalities in thyroid hormone levels and anti-thyroid peroxidase antibodies in pregnant women with and without gestational diabetes mellitus.

Material and Methods: We analyzed the medical records of 107 pregnant women. Clinical data related to maternal age, gestational week, body mass index, thyroid function tests, and anti-thyroid peroxidase antibodies, fasting blood glucose tests and HbA1c levels were obtained. The Pearson chi-square test, the Mann-Whitney U test, independent samples t-test, the Spearman correlation coefficient and Logistic regression model were performed.

Results: Gestational diabetes mellitus group was significantly older (p=0.001). Body mass index was statistically different between the two groups (p=0.002). There were statistically significant differences in fasting blood glucose and HbA1c between the two groups (p<0.001 and p=0.004, respectively). The frequency of anti-thyroid peroxidase antibodies was higher in pregnant women with gestational diabetes mellitus, but the result was not statistically significant (p=0.716). Euthyroidism (57.9%) was more prevalent in all patients. While cases of subclinical hypothyroidism were statistically significantly different between gestational diabetes mellitus and non-gestational diabetes mellitus groups (p<0.001), euthyroidism and isolated hypothyroxinemia had no significant differences (p=0.093 and p=0.220, respectively). Our results suggest that pregnant women with subclinical hypothyroidism are 5.5 times more likely to be gestational diabetes mellitus.

Conclusion: Subclinical hypothyroidism during pregnancy was detected more frequently in women with gestational diabetes mellitus than in women without gestational diabetes mellitus. Taken together, women with GDM should be performed thyroid tests and anti TPO routinely.

Keywords: Gestational diabetes mellitus, Hypothyroidism, Anti-thyroid peroxidase antibodies

Gestasyonel Diyabetli ve Gestasyonel Diyabet Olmayan Gebelerde Tiroid Fonksiyon Testlerinin Karşılaştırılması

ÖZ

Amaç: Bu çalışmanın amacı, gestasyonel diyabeti olan ve olmayan gebelerde tiroid hormon düzeylerinde ve anti-tiroid peroksidaz antikorlarında farklılık olup olmadığını belirlemektir.

Gereç ve Yöntemler: 107 gebe kadının tıbbi kayıtlarını incelendi. Anne yaşı, gebelik haftası, vücut kütle indeksi, tiroid fonksiyon testleri ve antitiroid peroksidaz antikorları, açlık kan şekeri testleri ve HbA1c düzeyleri ile ilgili klinik veriler elde edildi. Pearson ki-kare testi, Mann-Whitney U testi ve bağımsız örnekler t testi, Spearman korelasyon katsayısı ve lojistik regresyon modeli uygulandı.

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Bulgular: Gestasyonel diyabet grubu anlamlı olarak daha yaşlıydı (p=0,001). Vücut kütle indeksi iki grup arasında istatistiksel olarak farklıydı (p=0,002). İki grup arasında açlık kan şekeri ve HbA1c açısından istatistiksel olarak anlamlı farklılıklar vardı (sırasıyla p<0,001 ve p=0,004). Gestasyonel diyabetli gebelerde anti-tiroid peroksidaz antikorları sıklığı daha yüksekti, ancak istatistiksel olarak anlamlı farklılık yoktu (p=0,716). Ötiroidizm (%57,9) tüm hastalarda daha yaygındı. Subklinik hipotiroidi olguları GDM'li olan ve olmayan gruplar arasında istatistiksel olarak anlamlı farklılık gösterirken (p<0,001), ötiroidizm ve izole hipotiroksinemi arasında anlamlı fark bulunmadı (sırasıyla p=0,093 ve p=0,220). Sonuçlarımız subklinik hipotiroidizmi olan gebelerin gestasyonel diyabet olma olasılığının 5,5 kat daha fazla olduğunu göstermektedir.

Sonuç: Gestasyonel diyabetli kadınlarda gebelikteki subklinik hipotiroidizm gestasyonel diyabetli olmayan kadınlardan daha sık saptanmıştır. Gestasyonel diyabetli kadınlara rutin olarak tiroid testleri yapılmalı ve anti-tiroid peroksidaz antikorlarına bakılmalıdır.

Anahtar Sözcükler: *Gestasyonel diabetes mellitus, Hipotiroidizm, Anti tiroid peroksidaz antikorları*

INTRODUCTION

Gestational diabetes mellitus (GDM) is a kind of glucose intolerance which is (first) diagnosed during pregnancy and usually reveals itself in the second or third trimester.

It may lead to common fetal and maternal complications, and it has a prevalence rate of 12.4-18.9 % (1, 2). GDM may cause morbidities such as fetal macrosomia, gestational hypertension-preeclampsia, postpartum metabolic disease, cardiovascular disease, fetal macrosomia, postpartum type 2 diabetes and abnormal glucose metabolism (3). These outcomes can be reversible through physical activity, dietary intervention, and if necessary taking insulin treatment (4). In addition, increased insulin requirement during pregnancy may result in further the development of GDM (5).

Similarly, thyroid diseases and GDM are common endocrine diseases detected during pregnancy and they have a prevalence rate of 16.6 % (6, 7). In addition, thyroid diseases have similar adverse outcomes in pregnancy. Thyroid hormones have a critical role in glucose homeostasis (8). Maternal thyroid hormones may affect blood sugar levels due to glucose level in the blood and this is also associated with the placental lactogen, placental insulin enzyme, estrogen, thyroid binding globulin (9).

Recent studies have stated that thyroid dysfunction and GDM have a significant relationship (2, 10, 11). A large number of changes take place in thyroid function in the period of gestation and insufficient adaptation to these changes may cause thyroid dysfunction (12). During pregnancy anti-thyroid peroxidase antibodies (anti TPO) and thyroid dysfunction may be detected together, and they may have a crucial impact on glucose metabolism (13). Furtermore, studies revealing the relationship between thyroid disease and GDM are challenging (14-16). Pregnant women with GDM may have elevated thyroid antibodies. In pregnant women, the prevalence of thyroid antibodies in pregnant women is nearly 10%-15% (17).

Our aim in this study is to define whether there were differences in the thyroid hormone levels and anti TPO in pregnant women with GDM and non-GDM.

MATERIALS and METHODS

Study Population

This study was a retrospective study in Ege University Faculty of Medicine Endocrinology and Obstetrics Departments. We obtained the medical records of 107 pregnant women in two groups; GDM (n=54) and non-GDM (n=53). All were admitted to our outpatient clinics in the period of December 2020-February 2021. All women had a natural conception, singleton pregnancies, and they were at ≥24 weeks of gestation. In GDM group, the inclusion criteria including patients with ages 18 to 40 years, history of normal thyroid function during GDM; the control group was without GDM and history of normal thyroid function. Exclusion criteria were pre-existing thyroid dysfunction, age less than 18 years or below, and 40 or above, and having diabetes before gestation (types 1 and 2).

Clinical data related to the gestational week when admitted to our outpatient clinics, body mass index (BMI), maternal age, height, and weight were obtained as well as thyroid-stimulating hormone (TSH), thyroid function tests (free thyroxine (FT4)), glycosylated hemoglobin (HbA1c), anti TPO, and fasting plasma glucose (FPG) tests.

The study protocol was approved by the Ethics Committee of Ege University Faculty of Medicine (21-3.1T/66). Informed consents were obtained from all subjects.

Diagnosis of GDM

GDM was diagnosed through a 2-hour (h), 75-g oral glucose tolerance test (OGTT) according to American Diabetes Association (ADA) and the International Federation of Gynecology and Obstetrics (FIGO) criteria (18, 19). GDM was diagnosed based on one or more of the 75-g OGTT results: 1-h plasma glucose level ≥180 mg/dL, 2-h plasma

glucose level ≥153 mg/dL, and FPG level ≥92 mg/dL on the 24-28th gestational week (20).

Thyroid Function

The laboratory references were selected as TSH (0.27-4.2 mU/L) and FT4 (0.89-1.76 ng/dL). Anti-TPO was elevated if the level was equal or more than 34 IU/mL (21). During thyroid status evaluation, the guidelines of Endocrine Society, American Thyroid Association [ATA], European Thyroid Association [ETA] were considered (22). Trimester-specific reference range of ATA for TSH, patients with GDM and without GDM were classified into four groups: euthyroid (TSH < 2.5 mIU/L); subclinical hypothyroidism (SCH) (TSH 2.5–4 mIU/L); hypothyroidism (TSH > 4 mIU/L) and isolated maternal hypothyroxinemia (IMH). IMH was defined low FT4 concentrations despite normal TSH concentrations in pregnancy and was detected in the third trimester (23). SCH could be detected in any trimester. All pregnant women having subclinical hypothyroidism initiated levothyroxine therapy.

Statistical Analysis

Since frequency tables and the Pearson chi-square test used for the analysis of categorical variables in GDM groups; descriptive statistics were calculated for the continuous variables. The Shapiro-Wilk normality test was used to check normality assumption of the continuous variables. The Mann-Whitney U test (Wilcoxon rank-sum test) and independent samples t-test were performed to determine whether the differences between the GDM groups were statistically significant. Firstly, logistic regression models were performed to evaluate the significant variables associated with GDM in single variables, and then a final model was executed with the backward stepwise method. The correlation between TSH and FT4 was examined with the Spearman correlation coefficient in all patients' data and GDM groups. A value of P < 0.05 was considered significant in all hypothesis tests. The IBM SPSS version 25.0 was used in all statistical analyses (Chicago, IL, USA).

RESULTS

The demographics and clinical characteristics of all patients were demonstrated in Table 1. Among them 54 patients (50.5%) had GDM and 53 (49.5%) were non-diabetic pregnant women. The median age was 31.00 years in patients with GDM and 26.00 years in the control group. Compared with the non-GDM group, pregnant women in the GDM group were statistically significantly older (p=0.001). The mean BMI was 30.78±4.84 in the GDM group whereas for the control group it was 28.01±4.11, which presents a statistical difference in terms of BMI in two groups (p=0.002). Also,

there were statistically significant differences in HbA1c and FPG between GDM groups (p<0.001 and p=0.004, respectively). On the other hand, TSH levels and FT4 concentrations were not significantly different in both GDM groups (p=0.263 and p=0.265, respectively). Statistically, there was a significant negative correlation between the TSH and FT4 in the GDM group (r=-0.278; p=0.041). However, the correlation of TSH and FT4 in the non-GDM group was not significant (p=0.203). In the total patients' data set, the correlation between the TSH and FT4 was statistically significant (r=-0.248; p=0.010). The frequency of anti TPO was higher in pregnant women with GDM than that of the control group but the result was not statistically significant (p=0.716). Positive anti TPO was observed in 7.5% (4 of 54 patients) of women with GDM and 5.6% (3 of 53 patients) of healthy pregnant women. In addition, TSH levels and FT4 concentrations were not significantly different in patients having positivity of anti TPO (3 of 7 patients with GDM, 4 without GDM) (TSH 0.80 (0.41-3.83); p=1.000, FT4 0.93 (0.75-1.09); p=0.480, respectively).

In the GDM group, patients' need for thyroxin replacement treatment was higher than the control group, however the difference was not statistically significant (48.1% vs. 34.0%; p=0.136). Thyroid hormone status is displayed in Table 2 for both groups. Euthyroidism (57.9%) was more prevalent in all patients. None of our patients had hypothyroidism. While cases of subclinical hypothyroidism were statistically significantly different between GDM and non-GDM groups (p<0.001), euthyroidism and isolated hypothyroxinemia had no significant differences (p=0.093 and p=0.220, respectively).

We selected five statistically significant variables from Table 1. Binary logistic regression models for single variables and the final model to predict GDM were shown in Table 3. In the univariate logistic regression models of the GDM [non-GDM (0) and GDM (1)], all variables were statistically significant to predict GDM (p < 0.05). Subclinical hypothyroidism in pregnancy is a significant factor that increases the risk of GDM. Significant associations were detected between GDM and three variables including age, FPG and SCH in the final model (p < 0.05). Although BMI and HbA1c were statistically significant in the univariate model, they were not found significant in the final model. The odds ratio for SCH has the highest value of 5.558 (95% CI [1.450–21.297]; p=0.012). Thus, our results suggest that pregnant women with the subclinical hypothyroidism are 5.5 times more likely to be GDM. In addition to these results, odds ratios for age and FPG were 1.149 (95% CI [1.052–1.255]; p=0.002) and 1.107 (95% CI [1.044–1.173]; p=0.001), respectively.

Table 1: Demographics and clinical characteristics of enrolled patients.

Variables	Total (n=107)	GDM (n=54, 50.5%)	Non-GDM (n=53, 49.5%)	P
Age (years)[b]	29.00 (9.00)	31.00 (8.00)	26.00 (10.50)	**0.001**[e]
BMI (kg/m²)[a]	29.41 ± 4.69	30.78 ± 4.84	28.01 ± 4.11	**0.002**[d]
Weeks of gestation[b]	30.00 (7.00)	29.00 (8.25)	30.00 (6.50)	0.357[e]
Fasting plasma glucose (mg/dL)[a]	85.45 ± 9.84	89.69 ± 10.86	81.13 ± 6.30	**<0.001**[d]
HbA1c (%)[a]	5.24 ± 0.41	5.35 ± 0.44	5.12 ± 0.34	**0.004**[d]
Thyroid Function				
TSH (mIU/L)[b]	1.79 (1.29)	1.96 (1.65)	1.77 (0.97)	0.263[e]
FT4 (ng/dL)[a]	0.94 ± 0.13	0.92 ± 0.13	0.96 ± 0.14	0.265[d]
TPOAb (IU/mL)[c]				
≥34 (positive)	7 (6.5)	3 (42.9)	4 (57.1)	0.716[f]
<34 (negative)	100 (93.5)	51 (51.0)	49 (49.0)	

[a] mean ± standard deviation, [b] median (IQR), [c] n (%), [d] independent samples t-test, [e] Mann-Whitney U test, [f] chi-square test
GDM: Gestational diabetes mellitus; **BMI:** Body mass index, **TSH:** Thyroid Stimulating Hormone, **FT4:** Free Thyroxine, **TPOAb:** Thyroid Peroxidase Antibody

Table 2: Thyroid hormone status and GDM groups.

Thyroid hormone status n (%)		GDM group (n=54, 50.5%)	Non-GDM group (n=53, 49.5%)	P
Euthyroidism	-	27 (60.0)	18 (40.0)	0.093
	+	27 (43.5)	35 (56.5)	
Subclinical hypothyroidism	-	36 (42.4)	49 (57.6)	0.001*
	+	18 (81.8)	4 (18.2)	
Isolated hypothyroxinaemia	-	45 (53.6)	39 (46.4)	0.220
	+	9 (39.1)	14 (60.9)	

*P<0.01

Table 3: Binary logistic regression models for single variables and a final model to predict GDM.

Variables	Single Variables		
	P	OR	95% C.I.
Age	0.001*	1.135	1.052-1.224
BMI	0.003*	1.152	1.049-1.265
Fasting plasma glucose (mg/dL)	<0.001*	1.122	1.061-1.187
HbA1c (%)	0.007*	4.439	1.515-13.011
Subclinical hypothyroidism	0.002*	6.125	1.909-19.650
Variables	**Final Model[a]**		
	P	OR	95% C.I.
Age	0.002*	1.149	1.052-1.255
BMI	-	-	-
Fasting plasma glucose (mg/dL)	0.001*	1.107	1.044-1.173
HbA1c (%)	-	-	-
Subclinical hypothyroidism	0.012*	5.558	1.450-21.297

*P<0.05, statistically significant; **CI:** Confidence Interval, **OR:** Odds ratio.
[a]Multiple logistic regression final model was executed on all these variables, included together in the model.

DISCUSSION

Many studies have reported that increased insulin resistance rather than decreased insulin secretion is the main reason for GDM (17, 24). Insulin resistance plays a pivotal role for the thyroid antibodies and the presence of thyroid antibodies may increase proinflammatory cytokines, inducing insulin resistance and GDM (25). Pregnant women with subclinical hypothyroidism may have an increase in insulin resistance and increased risk for gestational diabetes (11).

In our study, we found no significant difference in the positivity of anti TPO antibodies between two groups. In contrast, according to the thyroid status SCH was statistically different between GDM and non-GDM group. Recently, Safian et al. have supported our results and have demonstrated that the prevalence of SCH was higher in patients with GDM than in patients without GDM (26). Significant associations were also detected between GDM and age, FPG, SCH. Thus, our study reveals that SCH may be an important risk factor for GDM. Yang et al. reported hypothyroxinemia plays a pivotal role in developing GDM (14). There are controversial reports about the relationship between, thyroid antibodies, thyroid function abnormalities, and GDM. For instance, a previous meta-analysis demonstrated that SCH was detected higher in GDM patients (27). By contrast, in our study, thyroid status of SCH was found higher in the non-GDM group (28). In some studies, the relationship between thyroid antibodies and the risk of GDM was reported (17) but there was no significant difference in the prevalence of anti TPO antibodies between the two groups. Hornnes et al. revealed that during pregnancy, patients with thyroid autoimmunity could be susceptible to developing glucose intolerance, whereas other reports have contrasting conclusions (25, 29). Such incompatible results may occur due to small sample sizes and different study designs.

Thyroid dysfunction in pregnancy may result in many gestational and obstetrical complications and adverse pregnancy outcomes (30). Several mechanisms were reported about the relationship between the thyroid hormone levels and glucose metabolism. Thyroid hormones may decrease the half-life of insulin and may increase the expression of glucose transporter 2 in liver cell membranes so that they support hepatic glucose output (14). Furthermore, they accelerate glycogenolysis by activating β adrenergic receptors via cAMP (31). When taken together, glucose metabolism and thyroid function have common pathways so that both thyroid dysfunction and diabetes may develop in pregnant women. Moreover, in line with the results of our study, it seems reasonable to suggest that patients with GDM tend to have older maternal age than patients without GDM.

About the limitations, this was a retrospective study and did not include FT3 and anti Thyroglobulin (anti TG) levels. These parameters could not be included in the analysis because patients records were retrospectively collected. Moreover, the number of our study population was limited which can affect the reliability of making generalizations.

In conclusion, the frequency of anti TPO was higher in pregnant women with GDM, but the result was not statistically significant. Subclinical hypothyroidism during pregnancy was detected more frequently in women with GDM than in women without GDM. Although, further studies are needed for a large number of patients, women with GDM should be performed thyroid tests and anti TPO routinely.

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