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Is subclinical hypothyroidism a risk factor for gestational diabetes mellitus?

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ABSTRACT

Objective: Gestational diabetes mellitus is characterized by increased blood sugar that first appears during pregnancy. Multiple articles have described a relationship between hypothyroidism/subclinical hypothyroidism (SCH) and a rise in the risk of concomitant pregnancy complications, including gestational diabetes mellitus (GDM), but the effect of SCH on pregnancy is uncertain in the literature. We clarified the contribution of SCH to GDM development.

Patients and Methods: We conducted a retrospective study. From the patient records, the first 250 pregnant women who applied to our hospital for screening at 20-24 weeks and had glucose tolerance tests were included in our study. Retrospectively, all these pregnant women's first-trimester thyroid-stimulating hormone (TSH) levels were recorded. We created two groups according to the oral glucose tolerance test (OGTT) results: a case group diagnosed with GDM and a control group with average blood glucose. Their first-trimester TSH levels were compared between the two groups and defined whether they had euthyroid, subclinical hypothyroidism (TSH=2.5-5.5mIU/L) or overt hypothyroidism (TSH >5.5).

Results: We diagnosed 37 of 191 patients (19.4%) with GDM. When we checked the case and control groups, the mean TSH of the GDM group was 1.8 mIU/L, and the control group was 1.7 mIU/L, but the difference was not statistically significant (p=0.121). 24.32% (n=9) of 37 pregnant women with GDM were diagnosed with subclinical hypothyroidism/hypothyroidism; this rate was as low as 14.93% (n=28) in the non-GDM group, but no statistical difference was found (p=0.21).

Conclusion: It can be predicted that other accompanying factors may be the primary determinant in the development of GDM rather than subclinical hypothyroidism. Risk scales that include the first trimester TSH level should be established for the development of GDM.

Keywords: Gestational diabetes mellitus, Subclinical hypothyroidism, Thyroid Stimulating Hormone, Pregnancy complications

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is characterized by increased blood sugar that first appears during pregnancy [1]. Furthermore, it is the most common nonsurgical disease accompanying pregnancy and has severe implications for both mother and baby [2].

Several risk factors are defined, such as older mothers, GDM history, large for gestational age (LGA) baby, race/ethnicity, smoking, and excess body mass index [3]. On the other hand, multiple articles have described a relationship between hypothyroidism/subclinical hypothyroidism (SCH) and a rise in the risk of concomitant pregnancy complications, which include gestational diabetes, but the effect of SCH on pregnancy is uncertain [4-6].

As we know, hypothyroidism is an insufficiency of thyroid hormones; If this condition is associated with decreased thyroxine (T4) hormone (with average, high, or less TSH level), it is defined as overt hypothyroidism (OH); If the increased TSH level can keep T4 at normal ranges, it is called subclinical hypothyroidism (SCH). In fact, subclinical hypothyroidism is a compensated version of thyroid dysfunction, so its effects are limited.

Oppositely, the studies defined the relationship between SCH and GDM; some studies declared that SCH is not related to develop GDM [7,8].

Our study aims to identify how subclinical hypothyroidism contributes to the development of GDM.

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2. PATIENTS and METHODS

We conducted a retrospective study after the Ethics Committee of Izmir Katip Celebi University Atatürk Training and Research Hospital granted ethical approval for our study (No. 676). We retrospectively scanned patient records between November 1st, 2022, and January 30th, 2022 250 pregnant women who applied to our hospital for screening at 20-24 weeks and had glucose tolerance tests were included in our study.

Retrospectively, all these pregnant women's first-trimester thyroid-stimulating hormone (TSH) levels were recorded for those who had been treated according to their TSH levels.

We could not reach the TSH level records of the first trimester for 38 pregnancies, we saw that 21 patients did not come for the follow-up to our hospital after the 20-24th week of screening. Therefore, 59 patients were not included.

We evaluated 75 g oral glucose tolerance test (OGTT) results of patients according to American Diabetes Association (ADA) criteria. Patients with 1st-hour fasting blood glucose, and 2nd-hour fasting blood glucose results ≥92 mg/dL, ≥180 mg/dL, ≥153 mg/dL, respectively, were diagnosed as GDM [9].

We created two groups according to OGTT results: a case group diagnosed with GDM and a control group with average glucose levels. Their first-trimester TSH levels were compared and diagnosed as having euthyroid subclinical hypothyroidism (TSH=2.5-5.5mIU/L with normal T4) or overt hypothyroidism (TSH >5.5 mIU/L).

Statistical Analysis

IBM SPSS Statistics version 20 was used for statistical analysis. While evaluating the study data, descriptive statistics (mean, standard deviation, and frequency) were used. A students t test was used for the parameters that showed a normal distribution between the two groups. Results were evaluated with 95% confidence intervals, and significance was set at p <0.01.

3. RESULTS

The mean age of our patients was 29 years. The medium crown to rumps length (CRL) at which serum TFT samples were taken was 58.1 mm. The average TSH values was 1.8 ± 1.0 mIU/L (0.35-5.34 mIU/L) (Table I).

Table I. *Demographic variables and follow-up findings in pregnancy*

Variables	Days
Demographic Variables	
Age, median (IQR)	29 (8)
Gravida median (IQR)	2 (1)
Parity, median (IQR)	1 (2)
Variables of the follow-up findings in pregnancy	
First-trimester fasting blood glucose (mg/dL) median (IQR)	80.0 (13.0)
First-trimester (TSHmU/L) , median (IQR)	1.76 (1.0)
CRL, mm, median (IQR)	58.1 (12.5)

IQR: Interquartile range, GDM: Gestational diabetes mellitus, CRL: Crown to rump length, THS: Thyroid stimulating hormone

We have diagnosed 37 of 191 patients (19.4%) with GDM according to OGTT test results. (Figure 1).

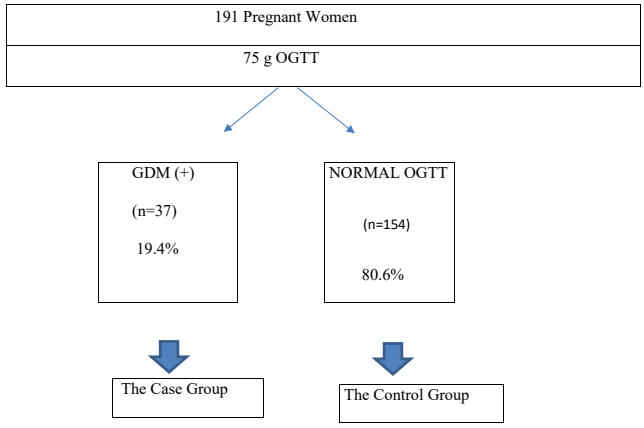

Figure 1*. Flowchart of the study*

When we compared the case and the control groups, the TSH of the GDM group was 1.8 mIU/L and that of the control group was 1.7 mIU/L, but the difference was not statistically significant. (p=0.121) (Table II). All demographic variables and follow-up findings of case and control groups are shown in Table II.

Table II. *Demographic variables and follow-up findings of case and control groups*

Variables	The non-GDM group (n=154)	The GDM group (n=37)	Univariate P value
Age. median (IQR)	27 (8)	31 (8)	0.06
Gravida median (IQR)	2 (1)	2 (1)	0.320
Parity, median (IQR)	1 (2)	1 (1)	0.257
First-trimester TSHmIU/L) , median (IQR)	1.7 (1.0)	1.8 (1.2)	0.121
CRL date, days, median (IQR)	86 (7)	86 (5)	0.902
CRL, mm, median (IQR)	59.0 (13.5)	57.0 (9.3)	0.708

IQR: Interquartile range, GDM: Gestational diabetes mellitus, CRL Crown to rump length, TSH: Thyroid stimulating hormone

Four pregnancies were diagnosed with overt hypothyroidism (TSH >5.5 mIU/L), and GDM developed in 1 (25%) of them.

Twenty-seven pregnant women were diagnosed with subclinical hypothyroidism (TSH=2.5-5.5 mIU/L), and 8 (29.62%) of them developed GDM.

One hundred sixty pregnant women were euthyroid (TSH ≤ 2.5 mIU/L) and 28 of them (17.5%) developed GDM (Table III).

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Table III. *Thyroid hormone status of the case group*

	Euthyroid TSH ≤ 2.5 mIU/L group (n=160)	Hypothyroid(SCH+OH) TSH>2.5 mIU/L group (n=31)	P value
GDM (+)	17.5% (n=28)	29.03% (n=9)	0.14

SCH: subclinical hypothyroidism, OH: overt hypothyroidism, TSH: Thyroid stimulating hormone

When all pregnant women with TSH >2.5 mIU/L and euthyroid pregnant women were compared, the lowest incidence of GDM development was in euthyroid pregnant women (29.03% vs. 17.5% p=0.14), but there was no statistically significant difference.

24.32% (n=9) of 37 pregnant with GDM were diagnosed with subclinical hypothyroidism/hypothyroidism; this rate was as low as 14.93% (n=28) in the non-GDM group, but no statistical difference was found (p=0.21) (Table IV).

Table IV. *Hypothyroidism incidence of case and control groups*

	The GDM group	The non-GDM group	P value
TSH>2.5 mIU/L	24.32% (n=9)	14.93% (n=28)	0.21

TSH: Thyroid stimulating hormone, DGM: Gestational diabetes mellitus

4. DISCUSSION

There is a consensus in the literature about the complications of overt hypothyroidism in pregnancy, but the effects of subclinical hypothyroidism are still unclear. There is much confusion about pregnancy outcomes of subclinical hypothyroidism and diagnosis of SCH in the literature.

In a study by Goldman et al. in which they evaluated 10990 pregnant women, they found that subclinical hypothyroidism in both the first and second trimesters did not increase the risk of developing gestational diabetes, on the contrary, they found a higher incidence of gestational diabetes in the euthyroid group in both trimesters [(1st trim.:3.0% vs 2.6%; OR:0.86 95% CI :0.37–1.96) and 2nd trim.:3.0% vs 1.7%; OR:0.63 95% CI:0.23–1.73)] [10].

In our study, twenty-seven pregnant women were diagnosed with subclinical hypothyroidism and 8 (29.62%) developed GDM. One hundred sixty pregnant women were euthyroid (TSH ≤ 2.5 mIU/L) and 28 of them (17.5%) developed GDM.

Although, some studies seem to have found a relationship between GDM and SCH, it was found that there was no statistically significant relationship in risk calculations adjusted for maternal age, weight, and parity in these studies [8]. Similarly, in our study, 24.32% (n=9) of 37 pregnant women with GDM were diagnosed with subclinical hypothyroidism/hypothyroidism; this rate was as low as 14.93% (n=28) in the non-GDM group, but no statistical difference was found (p=0.21).

Moreover, the diagnosis of subclinical hypothyroidism continues to be discussed and revised with new recommendations. First of all, the 2011 American Thyroid Association (ATA) guidelines recommended 2.5 mIU/L of the first trimester TSH upper limit during pregnancy [11]. Then, they increased the upper limit to 4 mIU/L in 2017 [12]. Otherwise, many studies indicate that if we accept the reference limit in this way, we will miss the diagnosis of many subclinical hypothyroidism [13-16]. In our study, we accepted the first trimester TSH upper reference limit as 2.5 mIU/L and defined subclinical hypothyroidism according to this. We found the incidence of GDM in the subclinical hypothyroidism group more than in the euthyroid group, however, it was not statistically significant. If we had accepted the upper limit of TSH as 4 mIU/L, we could have obtained statistically significant results.

On the other hand, many studies have shown that subclinical hypothyroidism may be associated with diabetes mellitus, and that thyroid hormones are effective in insulin resistance [17]. Increased insulin resistance in a normal pregnancy may be complicated by the additional effect of SCH [18].

When we retrospectively studied 1. trimester TSH values of the patients diagnosed with GDM, we found that the non-GDM group had similar TSH values. [1.8 mIU/L vs 1.7 mIU/L, (p=0.121)]. Similarly, in the study of Mukesh et al., no statistically significant difference was found between 80 (26.6%) women with GDM and 221 (73.4%) women without GDM for any of the thyroid function tests [19].

Additionally, Shahbaziant et al., studied thyroid functions of 61 diabetic pregnant women and compared the results with that of 35 healthy pregnant women. Higher thyroid dysfunction was detected in the GDM group, but the difference was not statistically significant [18% vs. 8.6% (P = 0.2)], also, thyroid dysfunction in GDM and the pregestational group did not have a significant difference with the control group (p =0.99, 0.054 respectively) [20].

Our study revealed that although there was no statistically significant difference, the mean TSH value was generally higher in the GDM groups. Similarly, a prospective study in which Ying et al., examined 7084 pregnant women found that subclinical hypothyroidism in early pregnancy was related to a raised risk of GDM [21].

If we classified the patients according to their TSH levels into two groups, euthyroid and subclinical hypothyroidism/hypothyroidism, the lowest incidence of GDM development was in euthyroid pregnant women (29.03% vs. 17.5% p=0.14). Although, we could not find any statistical differences in our work, similar to our study, the review of Li-Li Gong et al., reported that the relative risk of gestational diabetes was also increased in subclinical hypothyroidism with an OR of 1.558 (95% CI 1.292-1.877, p < 0.001) [22].

Furthermore, Yang et al., underlined that thyroid hormone insufficiency in the first trimester raises the risk of GDM development; for that reason, they advised that thyroid hormone levels should be defined in the early months [23]. Li-Li Gong et al., stated that hypothyroidism induces insulin resistance, disrupts glucose metabolism and increases the risk of gestational diabetes [22].

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In a recently published review, Lee et al., stated that the effects of maternal subclinical hypothyroidism on obstetric outcomes have still been debated [24]. In another review, Gietka-Czernel et al., highlighted the controversies in the diagnosis and treatment of TSH in pregnant women [25].

We scanned the patient records retrospectively for their first trimester TSH values, this could be a limitation. On the other hand, since our study group was small, the number of patients diagnosed with overt hypothyroidism was low. All of these are our limitations for making a final generalizable judgment.

Conclusion

Considering these results, although hypothyroidism is a risk parameter for the development of GDM, it can be predicted that other accompanying factors such as maternal age, weight, and parity and previous/family history may be the primary determinants in the development of GDM.

In conclusion, risk scales should be established for the development of GDM, and the first trimester TSH level should be included as an essential factor in the scale.

On the other hand, thyroid hormone-level status must be determined unconditionally in the first trimester as part of pregnancy follow-up. If there is overt or subclinical hypothyroidism in the first-trimester screening, it should be treated, and these patients should be followed closely for developing GDM.

Compliance with Ethical Standards

Ethical Approval: The Ethics Committee of Izmir Katip Celebi University Atatürk Training and Research Hospital granted ethical approval for this study (No. 676). Informed consent was obtained from all patients.

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