Obstetrics; *Maternal Fetal Medicine and Perinatology*

Assessment of Thyroid Function Disorders and C-Peptide, CA 19-9, CA-125 Levels in Patients with Gestational Diabetes Mellitus

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ABSTRACT

OBJECTIVES: We aimed to evaluate thyroid function disorders and determine C-peptide, CA 19-9, and CA-125 levels in pregnant women diagnosed with gestational diabetes mellitus.

STUDY DESIGN: Data were collected from 80 women aged 18-45 years who were admitted to the Perinatology outpatient clinic of Trakya University Faculty of Medicine at 24-28 weeks of gestation. Sociodemographic characteristics, general health information, pre-pregnancy weight, and current weight were obtained. All participants underwent a 75 g oral glucose tolerance test. Based on the test results, the participants were divided into two groups: those with (n=40) and without gestational diabetes mellitus (GDM) (n=40). Thyroid function tests were assessed by measuring thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (anti-TPO) levels. Additionally, amniotic fluid index, complete blood count parameters, blood C-peptide, CA 19-9, and CA-125 values were evaluated.

RESULTS: Fasting blood glucose, 1-hour and 2-hour OGTT values, and HbA1c values were higher in pregnant women with GDM. There was no significant difference in mean amniotic fluid index values or in thyroid function test results between pregnant women with GDM and those without. While CA 19-9 values were higher in the GDM group, there was no significant difference in C-peptide and CA-125 levels. Also, higher mean corpuscular volume (MCV) and erythrocyte distribution width (RDW) values were observed in the GDM group.

CONCLUSION: Women with GDM have higher CA 19-9 levels than healthy pregnant women. The clinical significance of this finding should be expressed with long-term follow-up studies.

Keywords: C-peptide; CA 19-9; CA-125; Gestational diabetes mellitus; Tumor markers; Thyroid function.

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Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance disorder that begins or is first diagnosed during pregnancy (1). As maternal glucose levels increase, birth weight, C-peptide levels, the risk of preterm birth, birth trauma, and the need for neonatal intensive care increase (2). Although GDM is detected in approximately 5-6% of pregnant women in the United States (3), the prevalence is higher in Southeast Asia, at around 25% (4), and has been reported to be as high as 22% in Turkey (5). GDM not only affects fetal development but also the physiology and metabolism of the mother, predisposing both to disease later in life (3).

Pregnancy-induced changes can significantly affect the thyroid gland's function. During the first 12 weeks, human chorionic gonadotropin (hCG) secreted by the placenta plays a crucial role, as its alpha subunit is the same as that of thyroid-stimulating hormone (TSH). As a result of the increase in hCG, free thyroxine (fT4) increases, and TSH decreases in a healthy pregnancy (6). In some countries where pregnant women have sufficient iodine stores, the thyroid gland increases in size by 10%. In contrast, in some other regions

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where iodine deficiency is prevalent among pregnant women, the increase can range from 20% to 40% (7). The physiological changes during pregnancy can be summarized as an increase in thyroxine-binding globulin, type 3 deiodinase activity, thyroid volume, and renal iodine excretion, and in serum total triiodothyronine (T3) and T4 levels, with a decrease in TSH and thyroglobulin (Tg) levels and reduced hormone production in cases of iodine deficiency (7). Thus, thyroid hormones should be evaluated within the established trimester-specific ranges. Due to pregnancy-related changes, hypothyroidism can become evident in women with iodine deficiency or low thyroid reserves (8).

C-peptide and insulin are secreted simultaneously from the pancreas. C-peptide, or connecting peptide, is a 31-amino acid peptide released during the conversion of proinsulin to insulin. It facilitates the formation of disulfide bonds between the proinsulin A and B chains, and about 95% of it eventually converts into insulin (9). CA 19-9 is elevated in benign and malignant ovarian tumors, as well as ovarian malignancies (10). It is commonly detected in gastrointestinal cancers, including adenocarcinomas, and plays a vital role in the diagnosis and monitoring of colon, pancreas, bile duct, gastric, and lung adenocarcinomas (11). CA 19-9 levels increase during pregnancy but generally do not exceed 37 kU/L (12). CA 19-9 is present in decidual and amniotic cells, but was not detected in the placenta or chorionic cells (13). CA-125 has been observed in patients with serous ovarian carcinoma with ascites and has been used for the monitoring of non-mucinous ovarian cancers (14). During pregnancy, CA-125 levels tend to increase in the first trimester, especially between the 5th and the 8th weeks. Subsequently, decreases and is typically measured as <35 IU/mL before childbirth (15). CA-125 has also been found in the amniotic fluid and is secreted by some fetal structures (16).

Since pregnancy is a state of significant endocrine changes, and several endocrine conditions frequently coexist, this study aimed to evaluate thyroid function disorders in patients with GDM and to determine C-peptide levels. While CA 19-9 is elevated in diabetes, its association with GDM has not been sufficiently explored. Considering that CA 19-9 is a marker not only of gastrointestinal malignancies but also of pancreatic damage, we have also measured CA 19-9. Additionally, we have calculated CA-125 levels to assess possible peritoneal irritation. This study aimed to investigate the association between CA 19-9, thyroid dysfunction, and GDM during the second trimester.

Material and Method

This prospective cohort study was conducted in 80 pregnant women aged 18-45 years and in the 24th-28th weeks of gestation, who were admitted to the Perinatology outpatient clinic of Trakya University, Faculty of Medicine, between January 2021 and December 2022. Individuals under 18 years of age, multiple pregnancies, those diagnosed with chronic liver or chronic kidney diseases, cancer, those with a diagnosis of pre-pregnancy type 1 or type 2 diabetes, or those who did not agree to participate in the study were omitted. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Trakya University Faculty of Medicine (date 9/2021), and informed consent was obtained from all the participants.

The participants' sociodemographic characteristics, general health status, pre-pregnancy body weight, height, and current body weight were obtained. A 75 g oral glucose tolerance test (OGTT) was performed in all pregnant women. For GDM diagnosis, a one-step approach was used instead of a two-step test. Pregnant women were asked to have a continuous diet for at least three days before the OGTT (with at least 150 g of carbohydrates per day). Fasting blood glucose levels were measured after at least 8 hours of fasting, then 75 g of oral glucose was ingested. Blood glucose measurements were then obtained at 1 and 2 hours. Physical activity was restricted during the test. A total of 40 pregnant women who were diagnosed with GDM based on the criteria recommended by the International Association of Diabetes and Pregnancy Study Group (IADPSG), and now accepted as standard, were included in the study group (17). An additional 40 randomly selected pregnant women with OGTT results within normal limits formed the control group. According to the criteria of the above-mentioned associations, individuals with a single high value among the three OGTT parameters were diagnosed with GDM. Those values were fasting blood glucose 92 mg/dL, 1st-hour 180 mg/dL, and 2nd-hour 153 mg/dL, as recommended.

TSH reference values change and decrease to lower levels in pregnancy; normal respective lower and upper limits for TSH levels were 0.1 to 2.5 μIU/ml, 0.2 to 3 μIU/ml, and 0.3 to 3 μIU/ml in the first, second, and third trimester of pregnancy (18). Thyroid function tests (TSH, fT3, fT4), anti-thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (anti-TPO), C-peptide, CA-125, and CA 19-9 levels were examined by the Cobas e801 module of Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany), an automated immunoassay system based on streptavidin-biotin interactions. We measured TSH, fT3, fT4, Anti-TPO, TgAb, C-peptide, CA-125, and CA 19-9 levels using the Elecsys T3, Elecsys FT4 III, and Elecsys TSH kits (Cobas, Roche Diagnostics, Mannheim, Germany), respectively. (Cobas, Roche Diagnostics, Mannheim, Germany). Additionally, hemoglobin, hematocrit, platelet, mean platelet volume (MPV), leukocyte (WBC), mean erythrocyte volume (MCV), and erythrocyte distribution width (RDW) values were obtained. Amniotic fluid was evaluated for each participant by a single operator (B.B.), with Voluson E6 (GE Electrical Systems, Zipf, Austria). Data were recorded and analyzed using the Statistical Package for the Social Sciences (SPSS).

The Shapiro-Wilk test was applied to assess the normality of the sample data. For quantitative variables that did not follow a normal distribution, the Mann-Whitney U test was used for group comparisons. For quantitative variables that were normally distributed, Student's t-tests were used for group comparisons. Relationships between qualitative variables were investigated using the Pearson chi-square and Fisher's exact tests. For descriptive statistics, minimum and maximum values were reported for quantitative variables, along with the mean and standard deviation for variables that followed a normal distribution, and the median with the 25th and 75th percentiles for variables that did not follow a normal distribution. For qualitative variables, the number and percentage were given. The significance level (p) was set at 0.05.

Results

The study group consisted of 40 women with GDM, while 40 others served as the controls. Patients' characteristics and OGTT and blood count values are shown in table I.

In women diagnosed as GDM, BMI before or observed at the 24 to 28 weeks of pregnancy was significantly higher compared to the controls. As expected, fasting blood glucose levels, OGTT values at the 1st and 2nd hours, and HbA1c levels in GDM patients were significantly higher than those in controls. However, all blood count values, except MPV and RDW, were similar between the groups (p>0.05).

Amniotic fluid index or deepest amniotic vertical pocket measurements were similar in the groups. There was also no significant difference in thyroid function tests or in terms of C-peptide and CA-125 values between the two groups (p>0.05). On the other hand, CA 19-9 values were significantly higher in pregnant women with GDM (Table II).

Discussion

We found significantly higher BMI values in the pre-pregnancy and at 24-28 weeks, as well as elevated MPV, RDW, and CA 19-9 values, but similar thyroid function test results in

Table I: *General characteristics, blood glucose parameters, and complete blood count values of the study and control groups (mean±SD).*

	Gestational diabetes mellitus (n=40)	Controls (n=40)	p
Age (years)	31.58±7.11	29.23±4.94	0.087
BMI (pre-pregnancy, kg/m^2)	31.23±7.82	26.53±6.13	0.011
BMI (between 24-28 weeks of gestation, kg/m^2)	34.12±7.43	29.38±5.87	**0.008**
Fasting blood glucose (mg/dL)	96.28±12.23	79.95±7.75	**0.001**
OGTT - 1st hour (mg/dL)	183.60±12.19	162.65±10.52	**0.001**
OGTT - 2nd hour (mg/dL)	156.05±18.39	138.15±7.91	**0.001**
HbA1c (%)	5.92±0.43	5.65±0.57	0.002
Hemoglobin (g/dl)	11.13±1.54	10.93±1.57	0.603
Hematocrit (%)	34.76±4.46	33.19±4.07	0.098
Platelet count (103/uL)	226.88±50.34	234.32±79.16	0.916
MPV [femtoliters (fL)]	10.90±0.95	10.31±1.18	**0.009**
WBC (103/uL)	11.85±4.14	11.37±3.45	0.504
MCV [femtoliters (fL)]	86.40±4.32	84.07±7.27	0.142
RDW (%)	15.13±5.16	13.71±1.69	**0.049**

BMI: Body mass index, HbA1c: Glycated hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, OGTT: Oral glucose tolerance test, RDW: Red cell distribution width, WBC: White blood cells.

Table II: *Amniotic fluid values, thyroid function tests, and serum marker values (mean±SD).*

	Gestational diabetes mellitus (n=40)	Controls (n=40)	p
Amniotic fluid, deepest vertical pocket (cm)	4.92±1.99	4.90±1.75	0.647
Amniotic fluid index (cm)	13.75±5.75	13.38±3.81	0.317
TSH (µIU/ml)	2.08±0.97	2.19±1.27	0.946
Free T3 (pg/ml)	2.73±0.47	2.75±0.63	0.899
Free T4 (ng/dL)	0.94±0.18	1.04±0.19	0.057
TgAb (IU/ml)	22.14±6.21	26.86±38.47	0.212
Anti-TPO (IU/ml)	15.75±26.53	44.13±135.49	0.665
C-Peptide (ng/mL)	4.66±2.97	4.56±4.70	0.184
CA-125 (IU/mL)	22.33±15.68	25.08±22.07	0.838
CA 19-9 (IU/mL)	14.0±8.67	10.41±8.95	**0.009**

Anti-TPO: Thyroid peroxidase antibody, TgAb: Anti-thyroglobulin antibody, TSH: Thyroid stimulating hormone.

women with GDM in our study. The incidence of GDM has increased significantly in recent years, making it a significant public health issue worldwide. In pregnancies complicated by GDM, both maternal and fetal risks are significantly elevated (19), but early detection and appropriate management can reduce maternal and fetal risks and prevent complications (20).

Some other studies conducted in our region found women with GDM had a higher average age compared to healthy controls (21). The average age of GDM patients in our study was 31.5 years, while it was 29.2 years in the controls. Also, consistent with our findings, Chinese and Taiwanese studies observed significant relationships between pre-pregnancy BMI and GDM (22,23). In our research, the pre-pregnancy BMI was higher in GDM patients than in normoglycemic pregnant women (31.23±7.82 vs 26.53±6.13 kg/m^2). Likewise, in a survey held in Türkiye on 1042 pregnant women, the average pre-pregnancy BMI of women having GDM was higher than that of healthy women without GDM (28.1 vs 26.3 kg/m^2) (24). Moreover, all our patients were overweight before and during 24-28 weeks (34.12±7.43 vs 29.38±5.87 kg/m^2, respectively, for BMI in GDM and controls). GDM was also reported to be associated with higher body weight and BMI at the beginning of pregnancy (25). Higher-than-normal HbA1c levels in the GDM and control groups reflect poor glycemic control in our study population. The recommended weight gain during pregnancy for overweight (BMI 25.0–29.9 kg/m^2) and obese women is 0.28 (0.23–0.33) and 0.22 (0.17–0.27) kg/week, respectively (26). Although our patients gained weight within these suggested levels, and the control women had all their glucose measurements within normal limits, high pre-pregnancy BMI values may also help explain the higher-than-normal HbA1c levels. HbA1c is considered an essential marker among diabetes markers and for determining diabetes status (27). but has also been shown to be effective in detecting the complications associated with GDM. A significant relationship between HbA1c and AFI values was observed in pregestational diabetic women (28). HbA1c levels were also reported to be more closely associated with the frequency of polyhydramnios in patients with GDM compared to healthy pregnant women (29). As in another study (30), we found higher HbA1c levels in GDM patients, but similar AFI values in women with GDM and controls.

The average C-peptide values were similar in our GDM patients and controls. In line with our results, Dikmen (31) found no difference in C-peptide levels between GDM patients and non-GDM women. On the contrary, significantly higher C-peptide levels were observed in GDM patients than in healthy pregnant women (30). Early pregnancy C-peptide levels served as a marker for the development of GDM (32). It has been thought that C-peptide during 24-30 weeks of pregnancy, at a cut-off of 2.9 ng/ml, can be used to predict some adverse pregnancy outcomes (33). Thus, limited sample sizes in studies can yield different results, and measuring C-peptide in the second trimester may have little impact on the diagnosis and management of GDM.

Diabetes and thyroid disorders often coexist and are thought to be closely related, but the relationship between thyroid function and GDM is not clear in the literature. Glucose homeostasis and metabolism can be affected by thyroid hormones through their impact on pancreatic β-cell development and on the pancreas, liver, adipose tissue, and skeletal muscle (34). Insulin and insulin-like growth factor-1 (IGF-1) can affect the differentiation and proliferation of thyroid cells and the regulation of thyroid genes. TSH can promote the differentiation of pre-adipocytes into mature adipocytes. Besides, TSH has mitogenic properties in the presence of insulin (35). The thyroid function test results or antibody levels did not differ significantly between the GDM and control women in our study. Another study yielded results similar to ours, indicating no significant relationship between thyroid function and GDM (36). However, others found higher TSH, thyroxine, and anti-TPO values in GDM patients (37). Also, women having TSH levels above 4.0 mIU/L have an increased risk of GDM regardless of thyroid antibody status (38). However, a very recent study found that isolated hypothyroxinemia, but not abnormalities in TSH or thyroid antibodies, was associated with GDM. These findings challenge the long-standing idea that subclinical hypothyroidism or thyroid autoimmunity are risk factors for GDM (39). Although our study design did not allow us to comment on the relationship between thyroid function and GDM, we found no differences in thyroid hormone or antibody levels between GDM and controls. The differences between our study and the others may be attributable to the studies conducted in different centers or patient groups, which have different characteristics.

Risk of type 2 diabetes was found to be increased in subjects with high CA19-9 and low CEA levels. The risk of prediabetes was also significantly higher in subjects with high CEA and high CA19-9 levels (40). Many authors have reported elevated CA19-9 levels during hyperglycemia (41-45). Also, associations between CA19-9 elevation and insulin resistance or β-cell function have been observed (42,44,45), as well as associations between CA19-9 levels and fasting blood glucose or HbA1c values. CA19-9 levels decreased after improvement of glycemic control (43). The exact mechanism of elevated serum CA19-9 in diabetic patients remains unclear. The average CA 19-9 level in women with GDM was higher than in controls in our study. We can speculate that this situation might be a result of pancreatic dysfunction. The relationship between CA 19-9, an essential marker of pancreatic tissue damage, and diabetes has been well documented in the literature, but its association with GDM has not been adequately studied. In a study, no significant relationship was found between first-trimester CA 19-9 levels and the development of later GDM (46). CA 19-9 is a marker for the diagnosis of pancreatic cancer, but is also a marker of pancreatic tissue dam-

age that might be caused by diabetes (41). In a study examining the development of pancreatic cancer and its relationship with GDM, women with a history of GDM showed a high relative risk of developing pancreatic cancer (47).

Obesity is a cause of systemic and local chronic inflammation. Inflammatory pathways may play a role in the pathogenicity of obesity in patients with normal weight but high body fat percentage, a condition known as normal-weight obesity (48). In obese patients, white adipose tissue is infiltrated by immune cells, which may appear as chronically injured tissue and produce proinflammatory mediators (49). Chronic tissue injury, such as that occurring during adipose tissue inflammation, can generate a preneoplastic microenvironment by stimulating wound-healing mechanisms (49). Thus, obesity may play a role in elevated CA 19-9 levels. On the other hand, obesity is a significant risk factor for GDM (50). Therefore, it is an expected result that patients with GDM in our study had high BMI.

In women with GDM, MPV and RDW values were higher compared to healthy pregnant women in our study. Some studies reported lower MPV values in GDM compared to controls (21), while others found no significant relationship between GDM and MPV (51). Higher RDW values were also observed in women with GDM (52). Studies conducted at different centers have yielded conflicting results. These differences can be associated with factors such as the number of patients included in the studies, the geographic locations where the studies were conducted, and whether the studies were single-center or multi-center.

The weaknesses of our study are a small sample size, no power analysis, no iodine data, no postpartum follow-up or neonatal outcome data, and results from a single institution rather than a multicenter study. However, to the best of our knowledge, this is the first study showing that CA19-9 levels are elevated in women with GDM.

In conclusion, thyroid hormone and thyroid antibody levels were similar in women with GDM. Although its clinical significance is unclear and remains within normal limits, CA19-9 levels are higher in women with GDM. To demonstrate the clinical relevance of this, studies requiring long-term follow-up of these patients and investigation with larger patient series are needed.

Declarations

Ethics approval and consent to participate: All participants provided written informed consent before enrollment in the study. The study was reviewed and approved by the ethics committee of Trakya University Faculty of Medicine (date 9/2021). All procedures were performed in accordance with the Declaration of Helsinki.

Availability of data and materials: The data supporting this study are available through the corresponding author upon reasonable request.

Competing interests: The authors declare no competing interests in any products mentioned in the study.

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Authors' contributions: CS and BB raised the presented idea. CS, Cİ, and BB designed the study. SA participated in data analysis, interpretation, and draft revision. GBK, SA, and FV participated in data collection and interpretation of results. BB, CS, and SA developed the first draft of the manuscript. All authors contributed to the writing of the paper, and all authors read and approved the final manuscript.

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