Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(9): 192
https://doi.org/10.31083/j.ceog5009192

Original Research

Association Analysis of Free Thyroid Hormones, Subclinical Hypothyroidism, and Thyroid Peroxidase Antibody in the First Trimester with Gestational Diabetes Mellitus

Yi Zhou[1], Yang Dong[1,*]

[1]Department of Obstetrics, Jinhua People's Hospital, 321000 Jinhua, Zhejiang, China
*Correspondence: yangdong_VIPVIP@163.com (Yang Dong)
Academic Editor: Michael H. Dahan
Submitted: 29 December 2022 Revised: 12 May 2023 Accepted: 9 June 2023 Published: 20 September 2023

Abstract

Background: We aimed to investigate the association of free thyroxin (FT4), free triiodothyronine (FT3), subclinical hypothyroidism (SCH), and thyroid peroxidase antibody (TPOab) in the first trimester with gestational diabetes mellitus (GDM). **Methods**: We recruited 110 pregnant women with GDM and 100 pregnant women without GDM who had normal 75 g oral glucose tolerance test (OGTT) results between June 2019 and June 2021. We collected basic data from all participants and compared serum FT3 and FT4 levels, SCH, and TPOab (+) incidences in the first trimester between the two groups. We used logistic regression to identify factors that influence the development of GDM. **Results**: Serum FT3 levels were 4.58 $\pm$ 0.78 and 4.61 $\pm$ 1.42 pmol/L in the GDM group and Control group, while FT4 levels were 9.32 $\pm$ 2.54 and 10.24 $\pm$ 2.77 pmol/L. The incidence of SCH were 25.5% and 14.0%, while TPO (+) were 20.0% and 10.0%. The GDM group's FT4 levels were significantly lower than the control group's, whereas the GDM group's age, incidence of SCH, and TPOab (+) were significantly higher ($p < 0.05$). Logistic regression analysis demonstrated that age, SCH and TPO (+) were risk factors for GDM ($p < 0.05$), the regression equation: logit p = –3.484 + 0.105 (age) + 1.128 (SCH) + 1.294 (TPOab (+)). **Conclusions**: Our findings suggest that monitoring the changes in FT4 levels, SCH, and TPOab (+) incidence in the first trimester may be useful in predicting the occurrence and development of GDM.

Keywords: gestational diabetes mellitus; free hormones; subclinical hypothyroidism; thyroid peroxidase antibody

1. Introduction

The levels of thyroid hormone (TH) play a crucial role in fetal growth and development, especially in the nervous system [1]. During the first 24 weeks of gestation, the fetal hypothalamus-pituitary-thyroxine axis is not yet fully developed, and the fetus relies on maternal TH to support its development and growth [2]. As pregnancy progresses, the demand for TH in the mother increases [3]. Various mechanisms, including thyroid-binding globulin (TBG), human chorionic gonadotropin (hCG), and the fetal thyroid gland, work together to regulate maternal TH levels and increase them when necessary [4]. However, TH also reduces the body's sensitivity to insulin and increases the level of insulin breakdown substances, leading to decreased insulin sensitivity and the development of gestational diabetes mellitus (GDM) in pregnant women [5].

Subclinical hypothyroidism (SCH) during pregnancy is defined as serum thyroid-stimulating hormone (TSH) levels above the upper limit of the pregnancy-specific reference range in pregnant women, while free thyroxin (FT4) levels are within the pregnancy-specific reference range [6]. In 2017, the American Thyroid Association (ATA) recommended a serum TSH level greater than 4.0 mIU/L and FT4 within the normal range as a diagnostic criterion for hypothyroidism during pregnancy [7]. Thyroid peroxidase antibody (TPOab) is a thyroid-specific antibody [8]. Positive TPOab can cause damage to thyroid follicles, which indirectly inhibits the synthesis of thyroxine and is the main mechanism leading to hypothyroidism [9]. There have been only a limited number of studies [10,11] investigating the relationship between FT4 levels during the first trimester (up to 13 + 6 weeks of gestation) and GDM. Few studies have investigated the association of free triiodothyronine (FT3), SCH, TPOab in the first trimester with GDM. The purpose of this study is to compare the levels of FT4, FT3, SCH, TPOab (+) levels in the first trimester between pregnant women with or without GDM, and to examine the relationship between these factors and the incidence of GDM. The findings of this study may provide useful insights for GDM assessment and monitoring.

2. Methods

2.1 General Data

The subjects of this study were pregnant women who attended routine antenatal clinics at Jinhua People's Hospital between June 2019 and June 2021. The GDM group comprised 110 pregnant women diagnosed with GDM, while the control group consisted of 100 pregnant women with normal results on oral glucose tolerance test (OGTT) during the same time period. General information about the

patients, including body mass index (BMI) at enrollment, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), gravidity, parity, history, and timing of glucose tolerance testing, were collected from the prenatal examination records between 11 to 13 + 6 weeks of gestation. Past medical history was assessed, including a history of thyroid or endocrine. Family history was evaluated to rule out significant genetic predisposition or thyroid disease. The ethics committee of Jinhua People's Hospital approved this study (IRB-2021033-R). All the patients signed informed consent. The sample size calculation was based on the assumption that the incidence of SCH in pregnant women is about 5%, and the incidence of GDM in pregnant women without SCH is about 10%. To detect a statistically significant difference in the incidence of GDM between the SCH group and the non-SCH group, with a power of 80% and a significance level of 0.05, a sample size of 100 pregnant women in each group was required. Therefore, we enrolled 110 pregnant women with GDM and 100 pregnant women with normal OGTT results as the control group in this study.

The inclusion criteria were as follows: GDM group: (1) adhere to the GDM definition [12]: patient met on of the following indicators in the results of the 75 g OGTT during 24 to 28 weeks of pregnancy: fasting blood glucose (FPG) over 5.1 mmol/L, one-hour postprandial blood glucose (1 hPG) over 10.0 mmol/ L, or two hours postprandial blood glucose (2 hPG) over 8.5 mmol/L; (2) pregnant women without previous hypertension, diabetes, abnormal renal function, familial genetic diseases or abnormal hepatic lipid metabolism; (3) age $\leq$40 years old; (4) normal cognitive function; (5) signed informed consent. Control group: (1) all inspection results were within the normal range; (2) no history of GDM; (3) singleton pregnancy; (4) signed informed consent.

Patients were excluded if they met one or more of the following criteria: (1) patients with pre-pregnancy confirmed diabetes or first trimester diagnosed diabetes (blood tests for FPG $\geq$7.0 mmol/L); (2) patients with polycystic ovary syndrome (PCOS); (3) patients with personal or familial thyroid disease; (4) patients with macroscopic or palpable thyroid nodules; (5) patients taking drugs affecting thyroid function, such as thyroid hormone replacement therapy, antihyperthyroid drugs, or hormones before or during pregnancy; (6) patients with autoimmune diseases and multiple pregnancies.

2.2 Indicators and Methods of Detection

Instrument Information: automated electrochemiluminescence immunoassay analyzer (Cobas602, Roche Diagnostics GmbH, Mannheim, Germany), automated radioimmunoassay analyzer (Beijing North Institute of Biotechnology Co., Ltd., Beijing, China), automatic biochemical analyzer (Cobas8000 c702 Chemistry System, Roche Diagnostics GmbH, Mannheim, Germany), centrifuge (Xiangtan Xiangyi Instrument Co., Ltd., Xiangtan, Hunan, China) and pipette (Thermo Fisher Scientific, Waltham, MA, USA). Reagent Information: FT3, FT4, and TSH kits (Roche Diagnostics GmbH, Mannheim, Germany).

Three milliliters of blood were collected via cubital venipuncture from each participant during their first trimester visit. The blood was collected in a coagulation tube and allowed to stand at room temperature for 10 minutes before being centrifuged at 3800 r/min for 8 minutes to extract the serum for future testing.

Serum TSH levels were measured using an automated electrochemiluminescence immunoassay analyzer (Cobas602, Roche Diagnostics GmbH, Mannheim, Germany) with a normal reference range of 0.35 to 4.94 mU/L. FT3 and FT4 levels were also measured using the same analyzer, with normal reference ranges of 2.65 to 5.7 pmol/L and 9.0 to 19 pmol/L, respectively.

TPOab levels were measured using an automated radioimmunoassay analyzer (Beijing North Institute of Biotechnology Co., Ltd., Beijing, China) with a normal reference range of 0 to 15%. The automatic biochemical analyzer (Cobas8000 c702 Chemistry System, Roche Diagnostics GmbH, Mannheim, Germany) was used to measure blood glucose levels.

SCH was defined as having a serum TSH level higher than the upper limit of the reference range, while FT4 levels remained within the reference range. The pipette used in this study was from Thermo Fisher Scientific, Waltham, MA, USA.

The lipid profile including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured using enzymatic colorimetric methods. Uric acid was measured using the uricase-phenol amino acid oxidase method.

75 g OGTT test [13]: 75 g OGTT method: Pregnant women fast for more than eight hours before the OGTT test and take 300 mL of liquid containing 75 g glucose orally in 5 minutes. Cubital venous blood was drawn during fasting and at one hour and two hours after glucose administration, followed by injection into a test tube containing sodium fluoride. Plasma glucose was measured using the glucose oxidase method [14].

2.3 Statistical Analysis

For all statistical studies, the SPSS Statistics software (version 26.0; IBM corp, Chicago, IL, USA) was utilized. Continuous variable data that followed the normal distribution were expressed as mean $\pm$ standard deviation. Enumeration data were compared using the Chi-square test. To analyze statistical differences between the two sample means of continuous variables, the *t*-test (if the variance is homogeneous) or corrected *t*-test (if the variance is not homogeneous) was conducted. In multivariate regression analysis, logistic regression was first used for the primary screening of risk factors. To avoid the omission of factors,

Table 1. Comparison of general clinical data between the two groups (mean ± SD).

Variables	GDM group (n = 110)	Control group (n = 100)	*p*-value
Age, years	31.74 ± 5.19	29.84 ± 4.52	0.003
Gestational weeks at the time of glucose tolerance screening, weeks	25.22 ± 2.25	25.58 ± 2.27	0.125
BMI, kg/m^2	22.32 ± 3.21	22.64 ± 3.43	0.242
SBP, mmHg	121.90 ± 10.24	120.23 ± 9.61	0.112
DBP, mmHg	75.73 ± 7.08	74.21 ± 7.35	0.065
Number of Gravidity	2.34 ± 0.38	2.41 ± 0.35	0.084
Number of Parity	0.72 ± 0.13	0.74 ± 0.14	0.142
Glucose (GLU)	5.45 ± 0.24	5.43 ± 0.05	0.093
1H GLU	10.81 ± 0.08	10.77 ± 0.23	0.193
2H GLU	9.20 ± 0.13	9.51 ± 0.31	0.304

GDM, gestational diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, Glucose; SD, standard deviation.

$\alpha = 0.15$ was set for univariate analysis. The factors with $p < 0.15$ in univariate analysis were included in logistic regression to analyze the correlation between free thyroid hormone and GDM. The results were reported as odds ratio (OR) with 95% confidence intervals (CI). A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1 General Clinical Data

This study included a total of 210 patients. General data, including body mass index (BMI) at enrollment, age, SBP, DBP, gravidity and parity were compared. The age of the GDM group was significantly higher than that of the control group ($p = 0.003$). There was no statistical difference between the two groups in terms of gravidity, parity, basal SBP and DBP, BMI, and the time of glucose tolerance testing ($p > 0.05$). The general clinical data of the patients are presented in Table 1.

3.2 Comparison of Free Triiodothyronine, Free Thyroxin, Thyroid-Stimulating Hormone, Cholesterol, and Uric Acid

The comparison of FT3, FT4, TSH, cholesterol, and uric acid between the two groups showed that the mean values of TSH, FT3, FT4, cholesterol, and uric acid were different between the two groups. The FT3 levels were 4.58 ± 0.78 and 4.61 ± 1.42 pmol/L in the GDM group and control group, respectively, while FT4 levels were 9.32 ± 2.54 and 10.24 ± 2.77 pmol/L, and TSH levels were 1.42 ± 1.31 and 1.43 ± 1.29 mIU/L in the two groups. However, there was no statistically significant difference in FT3, TSH, cholesterol, and uric acid between the two groups ($p > 0.05$) (Table 2). The comparison of FT4 between the two groups showed a significant difference ($p = 0.006$), with the mean value of FT4 in the GDM group being lower than that in the control group (Table 2).

3.3 Incidence of Subclinical Hypothyroidism and Thyroid Peroxidase Antibody (+)

The prevalence of SCH in the first trimester was 25.5% (28/110) in the GDM group and 14.76% (14/100) in the control group, and the difference was statistically significant ($p = 0.038$) (Table 3). Moreover, the prevalence of TPOab (+) in the first trimester was 20% (22/110) in the GDM group and 10% (10/100) in the control group, and the difference was statistically significant ($p = 0.044$) (Table 3).

3.4 Logistic Regression Analysis of Influencing Factors for Gestational Diabetes Mellitus

Logistic regression analysis was performed among age, SCH, TPOab (+), and the incidence of GDM. Whether GDM occurred (GDM = 1, Non-GDM = 0) has been chosen as the dependent variable. Binary logistic regression analysis was performed by including age, SCH, TPOab (+) as independent variables. The results showed that women with TPOab (+) in the first trimester had a 3.646 times higher risk of GDM than pregnant women with TPOab (–). Moreover, patients with SCH had a 3.088 times higher risk of developing GDM in early pregnancy than those with normal thyroid function. Table 4 shows that for every one-year increase in maternal age, there was a 1.111 times increase in the risk of GDM. The regression equation for the model is logit p = –3.484 + 0.105 (age) + 1.128 (SCH) + 1.294 (TPOab (+)).

4. Discussion

The main findings of our study suggest that there is a significant association between FT4 levels, SCH, and TPOab in the first trimester with the development of GDM. Our results indicate that the GDM group had significantly lower FT4 levels, as well as higher age, incidence of SCH, and TPOab (+) compared to the control group. Furthermore, logistic regression analysis identified age, SCH, and TPO (+) as significant risk factors for GDM. Our findings highlight the importance of monitoring changes in FT4 lev-

Table 2. Comparison of FT3, FT4, TSH, cholesterol, and uric acid between the two groups (mean ± SD).

Group	Cases	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mIU/L)	Cholesterol (mmol/L)	Uric acid (umol/L)
GDM	110	4.58 ± 0.78	9.32 ± 2.54	1.42 ± 1.31	4.57 ± 1.08	299.56 ± 108.66
Control	100	4.61 ± 1.42	10.24 ± 2.77	1.43 ± 1.29	4.49 ± 1.12	282.34 ± 104.59
t value		–0.192	–2.511	–0.056	0.527	1.168
p-value		0.423	0.006	0.478	0.299	0.122

GDM, gestational diabetes mellitus; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyroid-stimulating hormone.

Table 3. Comparison of the incidence of SCH ad TPOab (+) between the two groups.

Variables	GDM group (n = 110)	Control group (n = 100)	*p*-value
SCH, n (%)	28 (25.5%)	14 (14%)	0.038
TPOab (+), n (%)	22 (20%)	10 (10%)	0.044

GDM, gestational diabetes mellitus; SCH, subclinical hypothyroidism; TPOab (+), positive thyroid peroxidase antibody.

els, SCH, and TPOab (+) incidence during the first trimester to predict the occurrence and development of GDM.

Both gestational hypothyroidism and GDM are common endocrine and metabolic disorders of pregnancy, and their association has been widely studied [10]. Studies [15,16] have found that the thyroid hormones play an important role in regulating the metabolism of blood lipids and blood glucose. Insufficient thyroid hormone levels can lead to abnormal metabolic indicators, including obesity and insulin resistance, which can further lead to hyperglycemia. Additionally, research has demonstrated that the thyroid gland, as a target organ of high glucose, can be damaged by chronic inflammation and high glucose levels, which can worsen thyroid deficiency in individuals with diabetes [17]. Studies [18,19] have confirmed that increasing age, physical changes, and BMI can increase gestational hypertension, GDM, and thyroid disease. With increasing age, insulin resistance increases, and the degree of affinity of insulin-related receptors to insulin decreases, ultimately leading to an increase in the incidence of GDM [20]. Shuang *et al*. [21] found that the risk of GDM increased 1.15 times for every 1-year increase in age when age was $\geq$35 years in a study of Chinese pregnant women. In our study, the results showed that the mean age of the GDM group was higher than that of the control group, and it was again demonstrated based on previous studies that age was an independent factor in the incidence of GDM.

Yang *et al*. [10] studied early low thyroxine levels and gestational diabetes in 27,513 pregnant women. The study suggested that FT4 could be used as an independent predictor of GDM disease prediction, and the incidence of GDM decreases with increasing FT4. In a study of 11,365 pregnant women [22], it was demonstrated that there is a relationship between serum thyroxine concentration in early pregnancy and the occurrence of GDM, and that hypothyroxinemia in early pregnancy is also associated with the incidence of GDM. The study also pointed out that FT4 level was deceased in patients with GDM compared to the non-GDM group. The results were consisted with our study. In this study, the FT4 levels were significantly lower in the GDM group than in the control group.

TPOab as a thyroid-specific antibody may be an independent risk factor for adverse pregnancy outcomes [23]. Positive TPOab can cause damage to thyroid follicles, indirectly inhibit the synthesis of thyroxine, which is the main mechanism leading to hypothyroidism [24]. A significantly higher incidence of GDM compared with 578 euthyroid control pregnant women in a study of 167 hypothyroid pregnant women with positive TPOab [25]. SCH is significantly associated with elevated blood glucose level and insulin level, and is also associated with an increased risk of insulin resistance [26]. Pregnant women with SCH have a 50% increased risk of GDM compared with euthyroid pregnant women [27]. A meta-analysis [28] also showed that SCH increased the risk of GDM development by 1.558 times. TPOab (+) is a specific indicator of autoimmune thyroid disease and is associated with the etiological and prognostic evaluation of SCH, while it is also an essential factor in predicting GDM [29]. In this study, the results indicated a higher incidence rate of positive TPOab in the GDM group than in the control group, and the difference was statistically significant. The incidence of SCH in the first trimester in GDM women was 22.5%, which is significantly higher than that in non-GDM women (14.0%). Logistic regression analysis showed that GDM was positively correlated with SCH and TPOab (+), respectively, and TPOab (+) women increased the risk of GDM by 3.646 times; meanwhile, SCH increased the risk of GDM by 3.08 times. In our study, we aimed to investigate the association between FT4, FT3, SCH, and TPOab in the first trimester with GDM. Our findings suggest that monitoring the changes in FT4 levels, SCH, and TPOab (+) incidence in the first trimester may be useful in predicting the occurrence and development of GDM.

There were several limitations to this study that should be acknowledged. Firstly, the study design was retrospec-

Table 4. Logistic regression analysis of influencing factors for GDM.

Variables	*b*-value	*p*-value	OR	Lower 95% CI	Upper 95% CI
Age, years	0.105	0.001	1.111	1.043	1.183
SCH, n	1.128	0.004	3.088	1.426	6.689
TPOab (+), n	1.294	0.004	3.646	1.497	8.879
Constant (b_0)	–3.484	0.001	-	-	-

GDM, gestational diabetes mellitus; SCH, subclinical hypothyroidism; TPOab (+), positive thyroid peroxidase antibody; OR, odds ratio; CI, confidence interval.

tive, and the information used was already existing, which may lead to information bias due to missing data. Secondly, the thyroid hormone levels were measured from blood samples taken between 11 to 13 + 6 weeks of gestation, and the mean age of the GDM group was significantly higher than that of the control group, which may potentially affect the relationship between the hypothyroidism and the development of GDM. Finally, the analysis did not consider the timing of blood sampling, which may introduce data bias.

Our study provides further evidence for the importance of early detection and management of thyroid dysfunction during pregnancy, which may reduce the risk of GDM. However, further studies are needed to validate the universal screening approach and to determine the optimal timing and criteria for screening and treatment.

5. Conclusions

The study concluded that monitoring FT4 levels, SCH, and TPOab incidence in the first trimester could be useful in predicting the occurrence and development of GDM. The study found that the incidence of SCH and TPOab (+) were significantly higher in the GDM group. Logistic regression analysis indicated that age, SCH, and TPOab (+) were risk factors for GDM, suggesting that these factors should be considered when predicting GDM development.

Availability of Data and Materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author Contributions

YZ carried out the study concepts, study design, literature research and manuscript review; YD focused on the data acquisition, data analysis and manuscript editing. Both authors have read and approved this article. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The ethics committee of Jinhua People's Hospital approved this study (IRB-2021033-R). All the patients signed informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Prezioso G, Giannini C, Chiarelli F. Effect of Thyroid Hormones on Neurons and Neurodevelopment. Hormone Research in Paediatrics. 2018; 90: 73–81.

[2] Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017; 342: 68–100.

[3] Moleti M, Trimarchi F, Vermiglio F. Thyroid physiology in pregnancy. Endocrine Practice. 2014; 20: 589–596.

[4] Alemu A, Terefe B, Abebe M, Biadgo B. Thyroid hormone dysfunction during pregnancy: A review. International Journal of Reproductive Biomedicine. 2016; 14: 677–686.

[5] Martinez B, Ortiz RM. Thyroid Hormone Regulation and Insulin Resistance: Insights from Animals Naturally Adapted to Fasting. Physiology. 2017; 32: 141–151.

[6] Castillo Lara M, Vilar Sánchez Á, Cañavate Solano C, Soto Pazos E, Iglesias Álvarez M, González Macías C, *et al*. "Hypothyroidism screening during first trimester of pregnancy". BMC Pregnancy and Childbirth. 2017; 17: 438.

[7] Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, *et al*. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017; 27: 315–389.

[8] Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A. Antithyroid peroxidase autoantibodies in thyroid diseases. Journal of Clinical Endocrinology and Metabolism. 1990; 71: 661–669.

[9] Shimizu Y, Nabeshima-Kimura Y, Kawashiri SY, Noguchi Y, Nagata Y, Maeda T, *et al*. Anti-thyroid peroxidase antibody and thyroid cysts among the general Japanese population: a cross-sectional study. Environmental Health and Preventive Medicine. 2020; 25: 7.

[10] Yang S, Shi FT, Leung PCK, Huang HF, Fan J. Low Thyroid Hormone in Early Pregnancy Is Associated with an Increased

Risk of Gestational Diabetes Mellitus. Journal of Clinical Endocrinology and Metabolism. 2016; 101: 4237–4243.
[11] Haddow JE, Craig WY, Neveux LM, Palomaki GE, Lambert-Messerlian G, Malone FD, *et al*. Free Thyroxine During Early Pregnancy and Risk for Gestational Diabetes. PLoS ONE. 2016; 11: e0149065.
[12] Association Obstetrics Group of Obstetrics and Gynecology Branch of Chinese Medical. Guidelines for diagnosis and treatment of gestational diabetes mellitus (2014). Chinese Journal of Obstetrics and Gynecology. 2014; 49: 561–569. (In Chinese)
[13] Kim SH, Park TS, Jin HY. Rethinking the accuracy of 75 g glucose used in the oral glucose tolerance test in the diagnosis and management of diabetes. Primary Care Diabetes. 2017; 11: 555–560.
[14] Dubovaia LI, Grigorenko VK. An increase of glucose in the saliva, determined by the glucose oxidase method, as a sign of psychoemotional stress in dentistry. Laboratornoe Delo. 1990; 70–71. (In Russian)
[15] Mehran L, Amouzegar A, Azizi F. Thyroid disease and the metabolic syndrome. Current Opinion in Endocrinology, Diabetes, and Obesity. 2019; 26: 256–265.
[16] Jang J, Kim Y, Shin J, Lee SA, Choi Y, Park EC. Association between thyroid hormones and the components of metabolic syndrome. BMC Endocrine Disorders. 2018; 18: 29.
[17] Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocrine Reviews. 2019; 40: 789–824.
[18] Li F, Hu Y, Zeng J, Zheng L, Ye P, Wei D, *et al*. Analysis of risk factors related to gestational diabetes mellitus. Taiwanese Journal of Obstetrics & Gynecology. 2020; 59: 718–722.
[19] Li G, Wei T, Ni W, Zhang A, Zhang J, Xing Y, *et al*. Incidence and Risk Factors of Gestational Diabetes Mellitus: A Prospective Cohort Study in Qingdao, China. Frontiers in Endocrinology. 2020; 11: 636.
[20] Muller DC, Elahi D, Tobin JD, Andres R. The effect of age on insulin resistance and secretion: a review. Seminars in Nephrology. 1996; 16: 289–298.
[21] Shuang W, Huixia Y. Analysis of the effect of risk factors at gestational diabetes mellitus. Zhonghua Fu Chan Ke Za Zhi. 2014; 49: 321–324. (In Chinese)
[22] Li C, Yu L, Li Q. Relationship of hypothyroxinemia to gestational diabetes mellitus during early pregnancy. Chinese Journal of Endocrinology Metabolism. 2017; 33: 194–197.
[23] Yuan N, Sun J, Li Z, Chai S, Zhang X, Ji L. Relationship between anti-thyroid peroxidase antibody positivity and pregnancy-related and fetal outcomes in Euthyroid women: a single-center cohort study. BMC Pregnancy and Childbirth. 2020; 20: 491.
[24] Peng X, Zhu X, Cheng F, Zhou B, Zhu X, Zhu L. Correlation between thyroid autoantibodies and the risk of thyroid papillary carcinoma. Gland Surgery. 2020; 9: 950–955.
[25] Furukawa S, Miyakawa K, Shibata J, Iwashita M. Women with Subclinical Hypothyroidism Are at Low Risk of Poor Pregnancy Outcome in Japan. Tohoku Journal of Experimental Medicine. 2017; 242: 167–172.
[26] Jia M, Wu Y, Lin B, Shi Y, Zhang Q, Lin Y, *et al*. Meta-analysis of the association between maternal subclinical hypothyroidism and gestational diabetes mellitus. International Journal of Gynaecology and Obstetrics. 2019; 144: 239–247.
[27] Vyakaranam S, Vanaparthy S, Nori S, Palarapu S, Bhongir AV. Study of Insulin Resistance in Subclinical Hypothyroidism. International Journal of Health Sciences and Research. 2014; 4: 147–153.
[28] Gong LL, Liu H, Liu LH. Relationship between hypothyroidism and the incidence of gestational diabetes: A meta-analysis. Taiwanese Journal of Obstetrics & Gynecology. 2016; 55: 171–175.
[29] He Y, He T, Wang Y, Xu Z, Xu Y, Wu Y, *et al*. Comparison of the effect of different diagnostic criteria of subclinical hypothyroidism and positive TPO-Ab on pregnancy outcomes. Zhonghua Fu Chan Ke Za Zhi. 2014; 49: 824–828. (In Chinese)