

## RESEARCH ARTICLE

# A longitudinal study of thyroid markers during pregnancy and the risk of gestational diabetes mellitus and post-partum glucose metabolism

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**Funding information**

Youth Fund of the National Natural Science Foundation of China, Grant/Award Number: 81600644; The 345 Talent Project of Shengjing Hospital

**Abstract**

**Aims:** To determine the relationship between thyroid markers during pregnancy and gestational diabetes mellitus (GDM) or post-partum glucose metabolism.

**Materials and Methods:** Based on pregnancy 75-g oral glucose tolerance test (OGTT) results, 1467 subjects were grouped into normal glucose tolerance (NGTp;  $n = 768$ ) and GDM ( $n = 699$ ) groups. Furthermore, based on post-partum 75-g OGTT results, 286 GDM subjects, screened for glucose metabolism after delivery, were grouped into NGTd ( $n = 241$ ) and abnormal glucose tolerance (AGT;  $n = 45$ ) groups.

**Results:** Maternal age, family history of diabetes, acanthosis nigricans, previous adverse pregnancy outcomes and caesarean section incidence, and thyroid positive antibody rates were higher in the GDM group than in the NGTp group. In the first trimester, free triiodothyronine (FT3), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) levels were higher in the GDM group than in the NGTp group. In the second trimester, free thyroxine (FT4) levels were lower and TPOAb and TgAb levels were higher in the GDM group than in the NGTp group. After adjusting for confounding factors, FT3, TPOAb and TgAb (first trimester), and FT4, TPOAb and TgAb (second trimester) were risk factors for GDM. TPOAb and TgAb levels were higher in the AGT group than in the NGTd group and were potential predictors of abnormal post-partum glucose tolerance.

**Conclusions:** GDM risk significantly increased with increased FT3 (first trimester), TPOAb and TgAb (first and second trimesters) or with decreased FT4 (second trimester). Presence of thyroid antibodies predicted post-partum glucose abnormalities in subjects with GDM.

**KEYWORDS**

gestational diabetes mellitus, post-partum glucose metabolism, thyroid markers

## 1 | INTRODUCTION

Gestational diabetes mellitus (GDM), characterised by glucose intolerance with onset or first recognition during pregnancy, is the most common type of hyperglycaemia in pregnant women, and its prevalence is increasing annually in China.<sup>1</sup> Several clinical studies have demonstrated that hyperglycaemia during pregnancy can result in short- and long-term adverse outcomes for both the foetus and mother; however, the aetiology remains unclear.<sup>2,3</sup> Thyroid hormones regulate hepatic gluconeogenesis, intestinal glucose absorption and glucose uptake in peripheral tissues<sup>4</sup> and also regulate mRNA and protein expression levels of glucose transporters, promote pathways that accelerate glycogen decomposition, and alter circulating insulin levels.<sup>5,6</sup> Thyroid autoantibodies (including thyroid peroxidase antibodies [TPOAb] and thyroglobulin antibodies [TgAb]), which are serological autoimmune thyroid disease markers, are found in approximately 5%–15% of pregnant women.<sup>7</sup> A previous study<sup>8</sup> revealed that pregnant women with a family history of diabetes and thyroid disease are high-risk groups for positive thyroid antibodies and that 8%–16% of patients of this population will develop GDM.<sup>9,10</sup>

Based on the significant role of thyroid hormones in glucose metabolism and homeostasis, thyroid dysfunction may be closely related to GDM. However, the existing evidence remains controversial,<sup>11–14</sup> particularly because of the lack of longitudinal data during pregnancy and the lack of existing studies regarding the effect of thyroid markers on post-partum glucose metabolism. Therefore, this study aimed to explore the relationship between thyroid markers during pregnancy and GDM or post-partum glucose metabolism by examining longitudinal changes in thyroid markers during different trimesters of pregnancy in China.

## 2 | MATERIALS AND METHODS

### 2.1 | Study subjects

Between June 2015 and October 2018, pregnant women who presented to the endocrinology outpatient clinic of Shengjing Hospital of China Medical University with no adverse outcomes and with close post-partum follow-up were recruited. All subjects had a natural conception and singleton pregnancies, with gestational weeks calculated according to the last menstruation cycle and the first ultrasound during pregnancy. Exclusion criteria were multiple pregnancies; abnormal glucose metabolism before pregnancy; other diseases affecting blood glucose levels, including Cushing syndrome and pancreatitis; history of thyroid disease; visible or palpable thyroid goitres; medication affecting thyroid function such as hormonal drugs; history of thyroid-related surgery; other autoimmune diseases; and severe heart, liver or kidney disease.

Based on the 75-g oral glucose tolerance test (OGTT) results during pregnancy, 1467 enrolled subjects with complete data were

grouped into normal glucose tolerance during pregnancy (NGTp;  $n = 768$ ) and GDM ( $n = 699$ ) groups. Furthermore, based on the 75-g OGTT results after delivery in our hospital, 286 GDM subjects who were screened for glucose metabolism were further divided into the NGT after delivery (NGTd;  $n = 241$ ) and abnormal glucose tolerance (AGT;  $n = 45$ ) groups.

The protocol for this retrospective study was approved by the ethics committee of Shengjing Hospital of China Medical University. All study participants provided informed consent.

### 2.2 | Diagnostic criteria

In this study, GDM was defined according to the International Association of Diabetes and Pregnancy Study Groups.<sup>15</sup> GDM was diagnosed based on one or more of the following 75-g OGTT results: a fasting plasma glucose (FPG) level  $\geq 5.1$  mmol/L, 1-h plasma glucose level  $\geq 10.0$  mmol/L and 2-h plasma glucose level  $\geq 8.5$  mmol/L.

Post-partum glucose metabolism was assessed according to the World Health Organization criteria<sup>16</sup> as follows. Impaired fasting glucose (IFG) was defined as an FPG level  $\geq 6.1$  to  $< 7.0$  mmol/L and 2-h plasma glucose level  $< 7.8$  mmol/L. Impaired glucose tolerance (IGT) was defined as an FPG level  $< 6.1$  mmol/L and 2-h plasma glucose level  $\geq 7.8$  to  $< 11.1$  mmol/L. Subjects with IFG and IGT were considered prediabetic. Subjects with typical diabetes symptoms and either a random blood glucose level  $\geq 11.1$  mmol/L, FPG level  $\geq 7.0$  mmol/L or 2-h plasma glucose level  $\geq 11.1$  mmol/L were diagnosed with type 2 diabetes mellitus (T2DM). Subjects without typical diabetes symptoms but with the same test results on two consecutive days were also diagnosed with T2DM.

Guidelines for the diagnosis and management of thyroid disease during pregnancy and post-partum<sup>17</sup> recommended a trimester-specific reference range for all pregnant women. According to the National Academy of Clinical Biochemistry criteria,<sup>18</sup> our laboratory developed our hospital's reference range of trimester-specific thyroid markers<sup>19</sup> using the Abbott kit (Abbott) in July 2013 (Table S1). Additionally, antibody positivity was defined when the antibody level exceeded the reference upper limit for the Abbott kit.

### 2.3 | Data collection

Clinical data related to maternal age, height, pre-gestational weight, pre-gestational body mass index (BMI), history of menstruation, family history of diabetes and autoimmune thyroid disease, acanthosis nigricans, parity, number and causes of previous adverse pregnancy outcomes, obstetric complications, delivery time and methods, and birth weight, gender and feeding methods of new-borns were obtained. BMI was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>).

## 2.4 | Observation indicators

Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), TPOAb and TgAb levels were measured using a chemiluminescent microparticle immunoassay (Abbott).

After an overnight fast of at least 10 h, venous blood samples were collected from all subjects in the morning. FPG levels were detected using the glucose oxidase method (OLYMPUS AU5800), and fasting plasma insulin (FINS) levels were detected using a chemiluminescent microparticle immunoassay (ARCHITECT i2000). Simultaneously, glycated albumin levels were detected using an enzymatic method (OLYMPUS AU5400), and haemoglobin A1c (HbA1c) levels were detected using high-performance liquid chromatography (VARIANT II). Similarly, venous blood samples were collected 1 and 2 h after consuming 200–300 ml of a glucose solution (containing 75-g glucose powder). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as  $[\text{FINS } (\mu\text{U/ml}) \times \text{FPG (mmol/L)}] / 22.5$ .<sup>20</sup> The homeostasis model assessment of  $\beta$  cells (HOMA- $\beta$ ) was calculated as  $20 \times \text{FINS } (\mu\text{U/ml}) / [\text{FPG (mmol/L)} - 3.5]$ .<sup>20</sup>

## 2.5 | Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of variables, with normally distributed variables expressed as mean  $\pm$  standard deviation and variables with a skewed distribution expressed as median (interquartile range). For continuous variables, differences between groups were analysed using the Student's *t*-test or Mann–Whitney *U* test in case of skewed distribution. Categorical variables were compared using the Chi-square test. Logistic regression models were developed to assess the relationship between thyroid markers during pregnancy and GDM or post-partum glucose metabolism. Logistic regression analysis was performed using a stepwise adjustment for confounding factors with significant differences such as maternal age, pre-gestational BMI, family history of diabetes and autoimmune thyroid disease, acanthosis nigricans, previous adverse pregnancy outcomes, examining gestational weeks, and thyroid markers.  $p < 0.05$  was considered statistically significant. All data processing and statistical analyses were performed using SPSS 22.0 software (IBM Inc.).

## 3 | RESULTS

### 3.1 | Subject characteristics

Of 1467 subjects, 768 had normal glucose tolerance test results and 699 had GDM. Maternal age, family history of diabetes, acanthosis nigricans and incidence of previous adverse pregnancy outcomes and caesarean section were higher in the GDM group than in the NGTp group (Table S2). Comparison of the 75-g OGTT and glucose metabolism indicators during pregnancy between the NGTp and GDM groups is shown in Table 1.

### 3.2 | Longitudinal changes and comparison of thyroid markers during pregnancy

Thyroid function tests during pregnancy were performed in the following gestational weeks:  $9.8 \pm 1.9$ ,  $17.0 \pm 4.0$  and  $32.0 \pm 2.8$  weeks.

The positive antibody rate was higher in the GDM group than in the NGTp group (43.5% vs. 14.8%,  $p < 0.001$ ). In the first trimester, FT3 (4.65 [4.30, 4.90] vs. 4.20 [3.81, 4.57] pmol/L,  $p < 0.001$ ), TPOAb (2.82 [0.31, 37.37] vs. 1.00 [0.00, 1.95] IU/ml,  $p < 0.001$ ) and TgAb (2.04 [0.62, 47.59] vs. 0.18 [0.00, 0.52] IU/ml,  $p < 0.001$ ) levels were higher in the GDM group than in the NGTp group. In the second trimester, FT4 levels (12.66 [11.32, 14.54] vs. 14.14 [12.54, 15.28] pmol/L,  $p = 0.012$ ) were lower and TPOAb (0.84 [0.21, 28.72] vs. 0.40 [0.00, 1.08] IU/ml,  $p = 0.008$ ) and TgAb (1.33 [0.72, 10.23] vs. 0.07 [0.00, 1.74] IU/ml,  $p < 0.001$ ) levels were higher in the GDM group than in the NGTp group. No significant differences were observed in thyroid markers between the two groups in the third trimester (Figure 1).

### 3.3 | Risk analysis of factors affecting GDM

In a logistic regression model, FT3, TPOAb and TgAb in the first trimester, and FT4, TPOAb and TgAb in the second trimester were risk factors for GDM.

Logistic regression analysis was performed using a stepwise adjustment for confounding factors with subjects at the first interquartile level as controls. The results showed a significantly increased GDM risk with increased FT3, TPOAb and TgAb levels in the first trimester (Table 2). Similarly, as FT4 levels decreased and TPOAb and TgAb levels increased in the second trimester, GDM risk significantly increased (Table 3).

### 3.4 | ROC curve for GDM

ROC curves were used to determine the cut-off values of thyroid markers to predict GDM (Figure S1).

As shown in Figure S1A, the cut-off values of FT3, TPOAb and TgAb in the first trimester were 4.61 pmol/L (sensitivity 42.9% and specificity 80.7%; area under the curve [AUC] 0.724, 95% CI: 0.697–0.752,  $p < 0.001$ ), 25.01 IU/ml (sensitivity 48.8% and specificity 85.8%; AUC 0.642, 95% CI: 0.611–0.673,  $p < 0.001$ ) and 29.60 IU/ml (sensitivity 70.0% and specificity 80.2%; AUC 0.793, 95% CI: 0.768–0.818,  $p < 0.001$ ), respectively.

As shown in Figure S1B, the cut-off values of FT4, TPOAb and TgAb in the second trimester were 14.00 pmol/L (sensitivity 52.5% and specificity 71.4%; AUC 0.626, 95% CI: 0.535–0.717,  $p = 0.012$ ), 18.51 IU/ml (sensitivity 39.5% and specificity 86.7%; AUC 0.665, 95% CI: 0.555–0.775,  $p = 0.008$ ) and 23.90 IU/ml (sensitivity 51.3% and specificity 86.2%; AUC 0.833, 95% CI: 0.746–0.921,  $p < 0.001$ ), respectively.

Pregnant women with FT3  $> 4.61$  pmol/L, TPOAb  $> 25.01$  IU/ml or TgAb  $> 29.60$  IU/ml in the first trimester had a greater risk of

TABLE 1 Comparison of 75-g OGTT and glucose metabolism indicators at GDM diagnosis

	NGTp (n = 768)	GDM (n = 699)	p
Fasting plasma glucose (mmol/L)	4.7 (4.4, 4.9)	5.5 (5.2, 5.8)*	<0.001
1-h plasma glucose (mmol/L)	7.5 (6.7, 8.3)	9.8 (8.6, 10.9)*	<0.001
2-h plasma glucose (mmol/L)	6.5 (5.7, 7.5)	8.2 (6.9, 9.3)*	<0.001
Fasting plasma insulin ( $\mu$ U/ml)	8.7 (7.1, 10.9)	11.6 (7.8, 16.6)*	0.023
1-h plasma insulin ( $\mu$ U/ml)	63.4 (39.1, 85.7)	72.9 (48.4, 109.2)	0.207
2-h plasma insulin ( $\mu$ U/ml)	51.9 (33.6, 76.1)	70.2 (50.5, 116.8)*	0.043
GA (%)	12.2 (11.1, 13.5)	12.2 (10.7, 13.4)	0.968
HbA1c (%)	5.0 (4.8, 5.1)	5.3 (5.0, 5.7)*	<0.001
HOMA-IR	1.9 (1.5, 2.4)	2.8 (1.9, 4.0)*	0.001
HOMA- $\beta$	151.3 (122.5, 174.0)	117.6 (85.6, 171.4)*	0.046

Note: Data are presented as the median (interquartile range).

Abbreviations: GA, glycated albumin; GDM, gestational diabetes mellitus; HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cells; NGTp, normal glucose tolerance during pregnancy; OGTT, oral glucose tolerance test.

\* $p < 0.05$  versus the NGTp group.

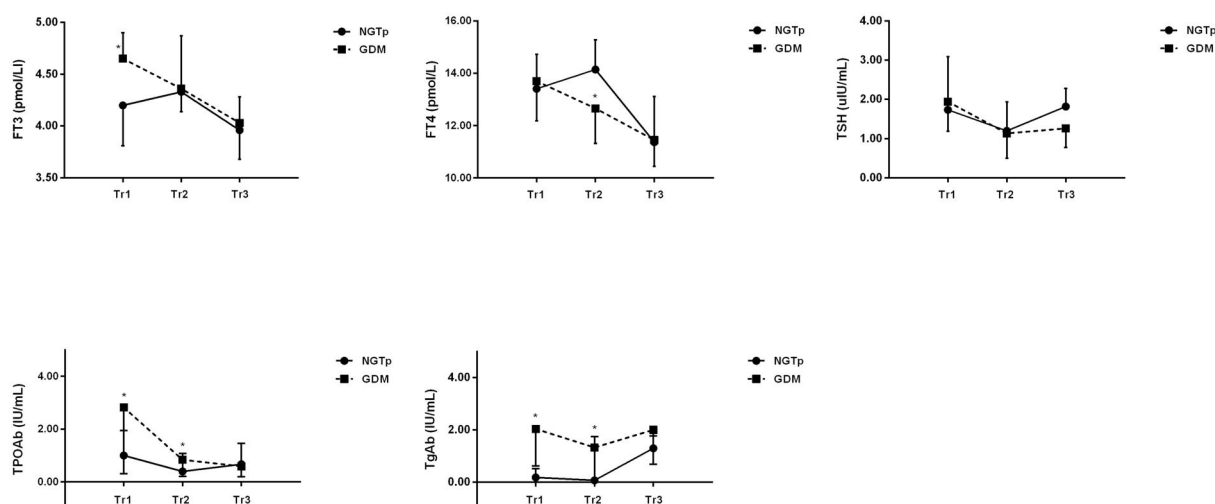


FIGURE 1 Longitudinal changes and comparison among thyroid markers during pregnancy. FT3, free triiodothyronine; FT4, free thyroxine; GDM, gestational diabetes mellitus; NGTp, normal glucose tolerance during pregnancy; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; Tr, Trimester; TSH, thyroid-stimulating hormone. \* $p < 0.05$  versus the NGTp group

GDM. Meanwhile, pregnant women with FT4 <14.00 pmol/L, TPOAb >18.51 IU/ml or TgAb >23.90 IU/ml in the second trimester had a greater risk of GDM.

### 3.5 | Analysis of thyroid markers during pregnancy affecting post-partum glucose metabolism

Of 286 GDM subjects who underwent post-partum OGTT, 241 had normal results and 45 (15.7%) had abnormal glucose tolerance test results (35 had prediabetes and 10 had T2DM). The mean interval from delivery to post-partum OGTT was  $12.0 \pm 7.5$  weeks, and the screening rate was 40.9%. Comparison of post-partum glucose

metabolism between the NGTd and AGT groups is shown in Table 4.

The results showed that TPOAb (50.66 [0.47, 557.02] vs. 1.19 [0.02, 58.59] IU/ml,  $p = 0.002$ ) and TgAb (39.34 [4.70, 158.21] vs. 2.37 [1.03, 35.52] IU/ml,  $p = 0.007$ ) levels in the first trimester were significantly higher in the AGT group than in the NGTd group. However, no significant differences were noted in thyroid markers between the two groups in the second and third trimesters. After adjusting for confounding factors with significant differences, TPOAb (odds ratio = 1.611, 95% confidence interval: 1.141–2.276,  $p = 0.007$ ) and TgAb (odds ratio = 1.925, 95% confidence interval: 1.223–3.031,  $p = 0.005$ ) levels in the first trimester were potential predictors of abnormal post-partum glucose tolerance.

TABLE 2 Association of thyroid markers in the first trimester with GDM

	Interquartiles of FT3			
	1	2	3	4
FT3	3.84 (3.63, 3.96)	4.27 (4.18, 4.35)	4.58 (4.51, 4.66)	5.00 (4.89, 5.18)
Model 1	1.0 (reference)	0.847 (0.622, 1.154)	1.165 (0.860, 1.577)	1.775 (1.310, 2.404)**
Model 2	1.0 (reference)	0.841 (0.615, 1.050)	1.138 (0.836, 1.548)	1.673 (1.229, 2.279)**
Model 3	1.0 (reference)	1.023 (0.720, 1.454)	1.224 (0.863, 1.738)	1.548 (1.085, 2.208)*
Model 4	1.0 (reference)	1.007 (0.701, 1.445)	1.169 (0.815, 1.677)	1.485 (1.030, 2.141)*
	Interquartiles of TPOAb			
	1	2	3	4
TPOAb	0.00 (0.00, 0.07)	0.77 (0.57, 0.94)	1.92 (1.45, 2.71)	54.61 (18.93, 228.00)
Model 1	1.0 (reference)	3.870 (2.883, 5.197)**	5.629 (3.367, 9.412)**	5.454 (3.135, 9.516)**
Model 2	1.0 (reference)	3.296 (2.911, 5.295)**	5.416 (3.218, 9.114)**	5.818 (3.309, 10.232)**
Model 3	1.0 (reference)	5.853 (4.195, 8.166)**	6.139 (3.444, 10.945)**	9.984 (5.527, 18.033)**
Model 4	1.0 (reference)	6.729 (4.783, 9.467)**	7.074 (3.948, 12.694)**	11.534 (6.360, 20.915)**
	Interquartiles of TgAb			
	1	2	3	4
TgAb	0.00 (0.00, 0.00)	0.22 (0.16, 0.30)	1.05 (0.69, 1.70)	79.06 (26.07, 317.93)
Model 1	1.0 (reference)	2.278 (1.484, 3.497)**	13.640 (9.063, 20.529)**	20.626 (13.579, 31.329)**
Model 2	1.0 (reference)	2.228 (1.447, 3.431)**	13.158 (8.715, 19.865)**	19.956 (13.099, 30.402)**
Model 3	1.0 (reference)	2.081 (1.299, 3.333)**	6.963 (4.389, 11.048)**	15.749 (9.985, 24.842)**
Model 4	1.0 (reference)	2.046 (1.275, 3.283)**	6.844 (4.308, 10.873)**	15.625 (9.899, 24.661)**

Note: Model: logistic regression analysis. Model 1: adjusting for maternal age and pre-gestational BMI; Model 2: Model 1+family history of diabetes, acanthosis nigricans, previous adverse pregnancy outcomes; Model 3: Model 2+examining weeks of thyroid markers; Model 4: Model 3+other different thyroid markers in addition to this parameter.

Abbreviations: FT3, free triiodothyronine; GDM, gestational diabetes mellitus; TgAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody.

\* $p < 0.05$ , \*\* $p < 0.01$  versus the first interquartile.

In addition, of 286 GDM follow-up subjects, 140 had measured post-partum thyroid markers. Comparison of post-partum thyroid markers between the NGT<sub>d</sub> and AGT groups is shown in Table S3.

## 4 | DISCUSSION

Our study determined the relationship between thyroid markers during pregnancy and GDM or post-partum glucose metabolism. TPOAb and TgAb levels in the first and second trimesters and positive antibody rates were significantly higher in the GDM group than in the NGT<sub>p</sub> group. After adjusting for confounding factors such as maternal age, pre-gestational BMI and family history of diabetes, TPOAb and TgAb levels in the first and second trimesters were risk factors for GDM. Furthermore, as TPOAb and TgAb levels increased, the risk of GDM significantly increased. Karakosta et al.<sup>12</sup> and Huang et al.<sup>21</sup> both reported that TPOAb levels in the first trimester were closely related to GDM; the higher the antibody level, the greater the risk of GDM. Another study<sup>10</sup> also drew the same conclusion of a higher incidence of GDM in individuals with

positive antibodies in the first and second trimesters than in those with negative antibodies. A newly published meta-analysis of 11 studies also found that there was no correlation between serum TSH levels and GDM; however, combined positive TPOAb increased the risk of GDM.<sup>22</sup> TPOAb destroys thyroid tissue by inhibiting thyroid peroxidase activity in vivo and a series of antibody-dependent cell-mediated cytotoxic effects.<sup>23</sup> Moreover, TgAb promotes protein hydrolysis at a certain concentration in thyroid tissue.<sup>24</sup> The presence of antibodies destroys the structure of thyroid follicular epithelial cells, resulting in abnormalities in the synthesis and release of hormones, uptake and utilisation of glucose, and metabolic disorders.<sup>25</sup>

In this study, FT3 levels in the first trimester were higher and FT4 levels in the second trimester were lower in the GDM group than in the NGT<sub>p</sub> group. GDM risk significantly increased, with increased FT3 levels in the first trimester or decreased FT4 levels in the second trimester. Our study results are consistent with those of Rawal et al.<sup>14</sup> and Oguz et al.<sup>26</sup> who showed the association between higher FT3 levels or lower FT4 levels with subsequent GDM. However, Karakosta et al.<sup>12</sup> found no correlation between FT3 and GDM. Yang

TABLE 3 Association of thyroid markers in the second trimester with GDM

	Interquartiles of FT4			
	1	2	3	4
FT4	16.22 (15.30, 17.88)	13.62 (13.31, 14.22)	12.11 (11.83, 12.57)	10.28 (9.50, 10.89)
Model 1	1.0 (reference)	1.205 (0.514, 2.828)	2.523 (0.942, 6.756)	3.684 (1.239, 10.955)*
Model 2	1.0 (reference)	1.237 (0.512, 2.988)	2.276 (0.824, 6.290)	3.238 (1.056, 9.929)*
Model 3	1.0 (reference)	1.254 (0.522, 3.013)	2.048 (0.740, 5.666)	3.507 (1.154, 10.653)*
Model 4	1.0 (reference)	1.581 (0.616, 4.061)	2.411 (0.816, 7.121)	3.673 (1.135, 11.886)*
	Interquartiles of TPOAb			
	1	2	3	4
TPOAb	0.01 (0.00, 0.10)	0.34 (0.23, 0.43)	1.19 (0.88, 1.44)	48.57 (21.61, 352.11)
Model 1	1.0 (reference)	0.816 (0.273, 2.441)	2.313 (0.694, 7.707)	16.444 (1.922, 140.701)*
Model 2	1.0 (reference)	1.146 (0.315, 4.169)	1.984 (0.473, 8.323)	26.112 (2.803, 243.281)**
Model 3	1.0 (reference)	1.620 (0.412, 6.337)	2.535 (0.553, 11.607)	34.907 (3.566, 341.650)**
Model 4	1.0 (reference)	1.205 (0.265, 5.475)	2.366 (0.441, 12.688)	39.522 (3.611, 426.694)**
	Interquartiles of TgAb			
	1	2	3	4
TgAb	0.00 (0.00, 0.07)	0.70 (0.48, 0.90)	1.69 (1.27, 2.20)	39.34 (10.20, 157.07)
Model 1	1.0 (reference)	4.746 (1.111, 20.272)*	4.917 (1.139, 21.218)*	45.156 (4.875, 418.283)**
Model 2	1.0 (reference)	5.259 (1.251, 22.113)*	5.506 (1.299, 23.331)*	50.887 (5.522, 468.964)**
Model 3	1.0 (reference)	9.900 (2.755, 35.580)**	9.900 (2.755, 35.580)**	54.000 (6.185, 471.447)**
Model 4	1.0 (reference)	9.936 (2.724, 36.250)**	10.617 (2.858, 39.434)**	56.351 (6.393, 496.734)**

Note: Model: logistic regression analysis. Model 1: adjusting for maternal age and pre-gestational BMI; Model 2: Model 1+family history of diabetes, acanthosis nigricans, previous adverse pregnancy outcomes; Model 3: Model 2+examining weeks of thyroid markers; Model 4: Model 3+other different thyroid markers in addition to this parameter.

Abbreviations: FT4, free thyroxine; GDM, gestational diabetes mellitus; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

\* $p < 0.05$ , \*\* $p < 0.01$  versus the first interquartile.

TABLE 4 Comparison of post-partum glucose metabolism in patients with GDM

	NGTd (n = 241)	AGT (n = 45)	p
Fasting plasma glucose (mmol/L)	5.5 (5.1, 5.7)	6.3 (5.6, 6.7)*	<0.001
1-h plasma glucose (mmol/L)	8.4 (7.2, 10.2)	10.3 (9.0, 12.3)*	<0.001
2-h plasma glucose (mmol/L)	6.8 (6.4, 7.4)	8.6 (7.6, 9.1)*	<0.001
Fasting plasma insulin ( $\mu$ U/ml)	7.7 (5.0, 12.6)	10.1 (5.9, 15.2)	0.117
1-h plasma insulin ( $\mu$ U/ml)	66.6 (37.7, 131.9)	70.4 (38.9, 99.5)	0.444
2-h plasma insulin ( $\mu$ U/ml)	38.5 (26.6, 69.0)	53.6 (38.5, 86.5)*	0.018
GA (%)	11.4 (10.4, 12.8)	12.0 (10.9, 13.7)	0.053
HbA1c (%)	5.3 (5.0, 5.6)	5.7 (5.3, 6.2)*	<0.001
HOMA-IR	1.9 (1.1, 3.2)	2.7 (1.4, 4.2)*	0.020
HOMA- $\beta$	74.5 (60.1, 131.4)	80.2 (56.8, 110.7)	0.706

Note: Data are presented as median (interquartile range).

Abbreviations: AGT, abnormal glucose tolerance; GA, glycated albumin; GDM: gestational diabetes mellitus; HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cell; NGTd, normal glucose tolerance after delivery.

\* $p < 0.05$  versus the NGTd group.

et al.<sup>27</sup> also considered that lower FT4 levels in early pregnancy was a risk factor of GDM. Among thyroid hormones, triiodothyronine (T3) is the primary bioactive hormone involved in glucose metabolism, whereas thyroxine (T4) is considered a prohormone, serving as a substrate for the biologically active form of T3.<sup>28</sup> Approximately 80% of the circulating T3 is transformed peripherally by deiodinase activity and single deiodination of T4; thus, this transformation is also considered to be representative of the peripheral deiodinase activity.<sup>28,29</sup> Guzman-Gutiérrez et al.<sup>30</sup> proposed that the low FT4 level associated with GDM may be compensated by an increased placental availability of T3/T4 based on the elevated activity of thyroid hormone transporters and/or reduction in deiodinases in the fetoplacental circulation. There was no correlation between serum TSH levels and GDM in our study, which was consistent with several previous findings<sup>11,14,31</sup>; however, several studies<sup>10,12,32</sup> showed that the incidence of GDM could increase with increasing TSH levels. The reasons for this difference include differences in population characteristics (such as ethnicity), study design, sample size and inconsistent or inadequate adjustment for confounding factors. Furthermore, it could be because of the differences in glucose metabolism screening methods and diagnostic criteria for GDM in each study under different times and conditions, as well as differences in criteria for trimester-specific reference ranges, resulting in different definitions of thyroid dysfunction and positive antibodies.

Changes in thyroid hormone and antibody levels were also observed throughout pregnancy in this study. In early pregnancy, hormones such as human chorionic gonadotropin lead to fluctuations in TSH levels, with a gradual increase in TSH levels towards mid-late pregnancy. FT3 and FT4 levels showed a declining trend (slightly elevated in the NGTp group), and antibody levels simultaneously declined with increased gestation weeks, which is consistent with the findings of other studies.<sup>33,34</sup>

Our study also assessed the effect of thyroid markers during pregnancy on post-partum glucose metabolism in GDM subjects. TPOAb and TgAb levels in the first trimester were significantly higher in the AGT group than in the NGTd group. Moreover, in our study, thyroid antibody levels in the first trimester were risk factors for abnormal post-partum glucose tolerance, suggesting that both antibodies were associated with post-partum glucose metabolism in GDM subjects.

The aetiology of GDM is still unclear; however, it is generally believed that insulin resistance (IR) and insufficient insulin secretion are the most important pathophysiological mechanisms. Insulin resistance is defined as a glucose homeostasis disorder.<sup>35</sup> Thyroid hormone is a primary regulator of body homeostasis and energy metabolism, which act on various organs in a tissue-specific manner to affect glucose metabolism.<sup>36-38</sup> It could affect glucose absorption and uptake, gluconeogenesis, glycogen metabolism, and control insulin and glucagon secretion. In addition to the negative feedback loop on hypothalamus and pituitary gland, studies revealed that thyroid hormone could also regulate glucose output and insulin sensitivity by selective hepatic sympathetic and parasympathetic denervation, and exert systemic effects through the autonomic nervous system.<sup>39,40</sup> These

effects of thyroid hormone will deteriorate glucose metabolism and lead to glucose intolerance or IR.<sup>36-38</sup> In hyperthyroidism, thyroid hormone enhances gluconeogenesis through directly altering the transcription of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase and increasing the expression of glucose transporter 2 on hepatocyte plasma membranes.<sup>5,6</sup> It also results in hyperglycaemia and the subsequent increase in glucose-stimulated insulin secretion by enhancing gastrointestinal glucose absorption.<sup>5,6</sup> In peripheral tissues, thyroid hormone stimulates lipolysis in adipose tissues to increase the concentration of free fatty acids and accelerate insulin degradation, and mediates the action of glucose transporter 4 to increase basal and insulin-mediated glucose uptake in skeletal muscles.<sup>5,6</sup> Like obesity, thyroid hormone-induced oxidative stress in target tissues alters the pro-oxidant-antioxidant balance of euthyroid tissues through increased oxidant production and may be responsible for hyperthyroidism-linked peripheral IR.<sup>41,42</sup> Furthermore, increased concentrations of IL-6 and TNF- $\alpha$ , which inhibit the expression of several factors involved in insulin signalling pathway, may promote IR in peripheral tissues.<sup>43</sup> Additionally, IR associated with hyperthyroidism may be related with changes in other hormones.<sup>44</sup> Similarly, several studies concluded that hypothyroidism causes a decrease in insulin-dependent glucose utilization.<sup>45,46</sup> Decreased gluconeogenesis and glycogen synthesis, decreased intestinal glucose absorption, impaired muscle oxidative capacity, as well as decreased blood flow in peripheral tissues were all associated with IR in hypothyroidism.<sup>5,6</sup> Normal glucose metabolism may be damaged by either an excess or a deficit of thyroid hormone; however, more researches were necessary to elaborate the pathophysiological association between IR, obesity and thyroid disorders.

This study had several strengths. First, thyroid marker levels in different trimesters throughout the whole pregnancy were examined in a longitudinal study, with a comprehensive evaluation of the relationship between thyroid markers and GDM or post-partum glucose metabolism. Second, our study used our hospital's trimester-specific reference ranges of thyroid function for all pregnant women. However, this study had limitations such as the lack of both post-partum data on thyroid function and the long-term follow-up of GDM subjects. Another limitation was that we could not provide data on dietary iodine intake and the measurement of urinary iodine clearance to assess maternal iodine status.

In conclusion, this longitudinal study showed that changes in thyroid marker levels during pregnancy were related to GDM and that the risk of GDM significantly increased with increased FT3 levels in the first trimester, increased TPOAb and TgAb levels in the first and second trimesters or decreased FT4 levels in the second trimester. Thyroid antibody levels were also associated with post-partum glucose metabolism in GDM subjects. These findings have significant clinical relevance, which can enable clinicians in identifying pregnant women at a high risk of GDM. Similarly, the findings serve as a reminder to screen for thyroid functions as soon as possible. Furthermore, even in pregnant women with normal thyroid function test results with positive antibodies, attention needs to be paid to the management of blood glucose during pregnancy and blood glucose

changes need to be dynamically monitored to ensure the safety of the foetus and mother.

## ACKNOWLEDGEMENTS

The authors wish to thank the physicians at the Department of Endocrinology, Shengjing Hospital of China Medical University. The study is supported by the Youth Fund of the National Natural Science Foundation of China (81600644) and the 345 Talent Project of Shengjing Hospital.

## CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest.

## ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Shengjing Hospital of China Medical University. Informed consents were provided by all participants.

## AUTHOR CONTRIBUTION

Lei Tang was responsible for data collection, writing this article and statistical analysis. Ping Li and Hua Zhou was responsible for data collection and statistical analysis, and Ling Li was responsible for guiding and reviewing this article. All authors have read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The raw/processed data cannot be shared at this time as the data also forms part of an ongoing study.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Tang L, Li P, Zhou H, Li L. A longitudinal study of thyroid markers during pregnancy and the risk of gestational diabetes mellitus and post-partum glucose metabolism. *Diabetes Metab Res Rev.* 2021;37:e3441. <https://doi.org/10.1002/dmrr.3441>