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Association between maternal thyroid function in early pregnancy and gestational diabetes

Dr Aradhana Arvind Deshmukh[1], Dr Shekhar panditrao Shiradhonkar[2]

[1]Assistant professor government medical college chh Sambhaji nagar
[2]consultant nephrologist Seth Nandlal Dhoot Hospital chh Sambhaji nagar

Corresponding Author
Dr Aradhana Arvind Deshmukh,
Assistant professor government medical college chh Sambhaji nagar

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ABSTRACT

Background Previous studies on the relationship between thyroid gland function and the development of gestational diabetes mellitus (GDM) have reported different results, leading to the need for a cohort study design with a large sample size.

Objective: We aimed to investigate the relationship between thyroid function in early pregnancy and GDM.

Methods: This was a prospective cohort from February 2018 to December 2020. The study took place at a tertiary maternal and child health hospital. A total of 36 142 pregnant women were successfully recruited The main outcome measure was GDM.

Results: This study consisted of 26 650 pregnant women who met the inclusion criteria, of whom 3982 (14.90%) were diagnosed with GDM, and the women with GDM were older than their healthy counterparts (33.26 ± 4.01 vs 31.51 ± 3.76 years, $P < .001$). After removing potential influencing variables, we found that increased thyroid-stimulating hormone (TSH) (adjusted odds ratio [aOR] 1.030, 95% CI 1.007, 1.054, $P = .012$) and subclinical hypothyroidism (aOR 1.211, 95% CI 1.010, 1.451, $P = .039$), but not free thyroxine or thyroid peroxidase antibody, were associated with the occurrence of GDM. Further analysis indicated a nonlinear relationship between TSH and GDM ($P < .05$): when TSH ≤ 1.24 mIU/L, the occurrence of GDM was elevated with increasing TSH, but when TSH > 1.24 mIU/L, this trend was not obvious.

Conclusion: High TSH might be associated with increased risk of GDM.

Key Words: thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibody, subclinical hypothyroidism, gestational diabetes mellitus.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common endocrine disease that occurs during pregnancy and results in glucose in- tolerance. The proportion of pregnant women with GDM has continued to rise in recent decades, resulting in a substantial impact on public health (1, 2). GDM raises the danger of peri- natal maternal diseases and poor pregnancy outcomes such as hypertension related to pregnancy, preterm labor injury, pre- eclampsia, newborn respiratory distress syndrome, and car- diac hypertrophy in infants (3-5). Additionally, an increase in the lifetime danger of maternal type 2 diabetes has been linked to a diagnosis of GDM (6-8).Thyroid function and metabolism of thyroid hormones undergo significant changes during pregnancy. Placental human chorionic gonadotropin is structurally similar tothyroid-stimulating hormone (TSH) and stimulates the thy- roid gland directly through TSH receptors, so TSH secretion is briefly suppressed in the first trimester, while serum free thy- roxine (FT4) and free triiodothyronine concentrations are ele- vated in the first trimester (9). The thyroid gland's hormones are essential regulators of metabolic systems such as glucose, protein, and lipid metabolism (10, 11), and type 2 diabetes in adults and thyroid disorders have been reported to be re- lated (12, 13). Hypothyroidism in adults is associated with re- sistance to insulin, altered glucose metabolism, and being overweight, which each possibly contribute to the develop- ment of diabetes type 2 (13). Although the association be- tween GDM and thyroid diseases and thyroid markers

during pregnancy has been widely studied, findings are notconsistent, and the specific mechanisms of the associations re- main unclear. Several studies have found correlations between thyroid disease during pregnancy and GDM. For instance, Fatima et al discovered significant positive connections be- tween TSH and glucose levels during pregnancy and suggested that subclinical hypothyroidism (SCH) may affect glucose me- tabolism in pregnant women with diabetes (14). GDM risks are also raised by low early-gestational hormone levels of the thyroid (15). Li et al reported that thyroid peroxidase anti- body (TPOAb) positivity increased the occurrence of GDM (16), and a meta-analysis of 10 cohorts of research indicated that when TSH > 4.0 mIU/L, GDM incidence increased inde- pendent of thyroid antibody status, whereas GDM incidence depended on thyroid antibody status for TSH < 4.0 mIU/(17). Another meta-analysis by Luo et al found that thyroid function impairment and thyroid antibody positivity were linked to the incidence of GDM (18). However, the results of other studies do not support these correlations (19-21).As part of the present study's prospective cohort research, we investigated the correlations between hormone levels of the thy- roid at 6-13+6 weeks of gestation and the incidence of GDM, with a view to identifying women who are at a higher risk of suf- fering from GDM early and providing behavioral and/or thera- peutic approaches that can prevent GDM from occurring.

MATERIALS AND METHODS

Participants and study design

This prospective cohort study All the enrolled pregnant women received regular prenatal care during the first trimester at the hospital from February 2018 to December, 2021. A total of 36 25 pregnant women were initially enrolled inclusion criteria (22). Patients were then excluded for the following reasons: (1) withdrawal from the CBCS after recruitment (n = 513); (2) nonsingleton preg- nancy confirmed by ultrasound in the first trimester (n = 1094); (3) prepregnancy thyroid disease (including prepreg-

nancy thyroid dysfunction, thyroid tumor, thyroid surgery, thy- roiditis, or thyroid cysts; n = 2091); (4) diabetes before conception or fasting venous blood glucose level greater than or equal to 7.0 mmol/L in the first prenatal visit (n = 144); (5) taking medication affecting thyroid function, glucose, or lipids before pregnancy (including L-T4, prednisone, methylpredniso- lone, dexamethasone, budesonide, lipid-lowering medicine, la- betalol, or propylthiouracil; n = 165); (6) thyroid gland function values not being accessible before week 14 of preg- nancy (n = 2010); or (7) lacking oral glucose tolerance test (OGTT) results (n = 3497). Ultimately, 26 742 pregnant wom- en were enrolled in our study (Fig. 1).

DATA COLLECTION

The following demographic characteristics were obtained us- ing the CBCS-based enrollment questionnaire: date of birth, height, prepregnancy weight, medication use, prepregnancy thyroid disease, smoking, alcohol consumption, and mode of pregnancy (classified as either natural pregnancy or withassisted reproductive technology). The enrolled pregnant women were placed into 2 groups depending on their age (≥35 and <35 years old), and 3 groups that were defined by prepregnancy body mass index (BMI): obese, overweight, and normal (≥24.0 kg/m^2, 24.0-28.0 kg/m^2, <24.0 kg/m^2). Smoking and alcohol consumption were classified as yes or no. The presence of thyroid disease before pregnancy was de- termined using questionnaires and hospital records.

RESULTS

Clinical Features of the Enrolled Pregnant Women Clinical and demographic data for the participants are shown in Table 1. Among the 26 742 pregnant women finally en-rolled, 3985 had GDM (incidence of 14.90%). Participants who had GDM tended to be older than those in the group without it (33.26 ± 4.01 vs 31.51 ± 3.76 years, P < .001). In comparison with the group that did not have GDM, the pre- pregnancy BMI was higher in the GDM group (23.02 ± 3.49 vs 21.47 ± 3.07 kg/m^2, P < .001) as well, and the percentage of primipara pregnancies was lower in the group with GDM than in the group without GDM (48.6% vs 55.9%, P< .001). When compared with the group without GDM, the group with GDM had a greater incidence of assisted reproduc- tion (9.2% vs 5.1%, P < .001), and the group with GDM con- tained many more pregnant women who had previously smoked compared with the group without GDM (4.2% vs 2.8%, P < .001). However, there were no significant differen- ces in the proportion of women with or without GDM who consumed alcohol or in ethnicity (3.6% vs 4.0%, P = .172; 7.4% vs 7.6%, P = .334).

CORRELATION BETWEEN FIRST-TRIMESTER THYROID FUNCTION (TPOAB, TSH, AND FT4), SCH, AND GDM

the relationships between the thyroid function in early pregnancy and GDM based on binary logistic regres- sion analysis. The group with GDM had considerably higher TSH levels than the group without GDM (1.60 ± 1.28 vs 1.52 ± 1.38 mIU/L, P = .003), and this difference remained when comparing the intergroup relationship with TSH quin- tile spacing (P < .001). Additionally, the GDM group's FT4 level was considerably lower than that of the group without GDM (16.27 ± 2.34 vs 16.38 ± 2.51 pmol/L, P = .007), and

this difference remained when comparing the intergroup relationship with FT4 quintile spacing ($P = .012$). Compared with the group without GDM, the TPOAb positive rate was greater in the group with GDM (11.3% vs 12.5%, $P = .037$). Furthermore, compared with the non-GDM group, more pregnant women with SCH were in the GDM group. However, the difference was not statistically significant (3.9% vs 3.4%, $P = .063$).after controlling for maternal age, first pregnancy status, prepregnancy BMI, pregnancy mode, and smoking status, the occurrence of GDM was significantly as- sociated with TSH (aOR 1.030, 95% CI 1.007, 1.054, $P = .012$) but not with FT4 (aOR 0.998, 95% CI 0.984, 1.012, $P = .777$) or TPOAb (aOR 1.079, 95% CI 0.970, 1.200, $P = .160$). Subsequently, we classified all enrolled preg- nant women into 2 groups: the SCH group and the non-SCH group. Binary logistic regression indicated that the rates of GDM and SCH did not correlate statistically significantly (OR 1.181, 95% CI 0.991, 1.408, $P = .063$). However, after controlling for maternal age, prepregnancy BMI, first preg- nancy status, pregnancy mode, and smoking status, we found that pregnant women with SCH had a greater risk of GDM (aOR 1.211, 95% CI 1.010, 1.451, $P = .039$). Moreover, higher maternal age, higher prepregnancy BMI, assisted re- productive technology conception, and smoking were noted risk factors for GDM (Table S1 (25)). Relationships Between Early Pregnancy FT4, TSH, and TPOAb Levels and GDM RiskTo investigate the relationship between the function of the thyroid and the risk of GDM, all enrolled participants were separated into quintile groups dependent on their TSH and blood FT4 levels. The TPOAb-negative group, the lowest quintile array of TSH, and the lowest quintile array of FT4 were utilized as references for logistic regression analysis, de- pending on the correlation findings. Because statistically sig- nificant variations in first pregnancy status, pregnancy mode, prepregnancy BMI, maternal age, and smoking status were observed between groups with and without GDM, the multiple logistic regression analysis was adjusted for the above-mentioned influencing factors, and the results are shown in Table 4. There were significant variations in the rate of GDM among the various TSH quintile groups (P for trend = .013). Furthermore, a greater level of TSH was related to a higher GDM risk (OR_{Q3} 1.174, 95% CI 1.055, 1.308, $P = .003$; OR_{Q4} 1.160, 95% CI 1.042, 1.293, $P = .007$; OR_{Q5} 1.191, 95% CI 1.070, 1.325, $P = .001$), and this asso- ciation remained after controlling for first pregnancy status, maternal age, prepregnancy BMI, pregnancy mode, and smoking status (OR_{Q3} 1.124, 95% CI 1.006, 1.256, $P = .039$; OR_{Q5} 1.124, 95% CI, 1.006, 1.256, $P = .038$).
However, there were no discernible differences in the inci- dence rate of GDM between the FT4 quintile groups (P for trend = .934). In Q1, a slight statistical difference was ob- served (OR_{Q1} 1.144, 95% CI 1.029, 1.272, $P = .013$), but it disappeared after controlling for first pregnancy status, mater- nal age, smoking status, prepregnancy BMI, and pregnancy mode (aOR_{Q1} 0.996, 95% CI 0.892, 1.111, $P = .937$)
Moreover, there was no connection between TPOAb status and the occurrence of GDM.
In restricted cubic splines were used to model and visualize the association of TSH and FT4 with the risk of GDM. Notably, we found a significant nonlinear relationship between TSH and GDM ($P < .05$) but not FT4 ($P > .05$). shows that TSH was positively correlated with the incidence of GDM, and the incidence of GDM when TSH ≤ 1.24 mIU/L increased rapidly with an increase in TSH. In con- trast, when TSH > 1.24 mIU/L the increase in GDM was rela- tively stable with an increase in TSH.
Sensitivity analysis showed that the significance and direc- tion of our results were robust and consistent when partici- pants with assisted reproduction were excluded, when current or former alcohol drinkers were excluded, and when current or former smokers were excluded (Table S2 (25)).

The Association Between TSH and GDM stratified by Age and Prepregnancy BMI
the association between TSH and GDM found by multiple logistic regression in different age and prepreg- nancy BMI subgroups. In unadjusted models, there was a sig- nificant linear trend between TSH and GDM for the maternal age <35 years subgroup as well as for the prepregnancy and BMI subgroups (P for trend < .05). After adjusting for con- founding factors, this relationship disappeared in the subgroup<35 years of age. However, there was a stable and significantpositive association between TSH and the occurrence of GMD in subgroups with prepregnancy BMI (P for trend < .05). After adjusting for confounding factors, TSH levels in the highest quintile of the prepregnancy BMI ≥ 24 kg/m^2 subgroup were found to be associated with increased risk for GDM compared with the lowest quintile, and in the interaction analysis of age and prepregnancy BMI on GDM, there were no statistically sig- nificant interaction between groups before or after adjusting for confounding factors (P for interaction > .05). After adjusting for confounding factors, we observed that this relationship disap- peared in the subgroup <35 years of age, but there was a stable and significantly positive association between TSH and the oc- currence of GMD in subgroups with prepregnancy BMI (P for trend < .05). After adjusting for confounding factors, TSH levels in the highest quintile of prepregnancy BMI ≥ 24 kg/m^2 subgroup were associated with increased risk for GDM compared with the lowest quintile. In the interaction ana- lysis of age and prepregnancy BMI on GDM, we found no inter- action between groups either before or after adjusting for

confounding factors (*P* for interaction > .05).

DISCUSSION

In the above results we observed an increase in the incidence of GDM with increasing maternal age, and the incidence of GDM also increased with an increase in prepregnancy BMI. When the prepregnancy BMI ≥ 24 kg/m^2, the being in the highest quintile of TSH level increased the risk of GDM com- pared with the lowest quintile. Moreover, the incidence ofGDM in pregnant women with assisted reproduction was higher than in natural pregnancy. The incidence of GDM was also higher in pregnant women who were previous or cur- rent smokers than in those who had never smoked. Furthermore, the participants in the GDM group had elevated first-trimester TSH levels compared with the corresponding participants without GDM. With rising TSH, the incidence of GDM rose as well, suggesting that a low level of TSH is pro- tective against GDM. When TSH ≤ 1.24 mIU/L, GDM risk in- creased significantly with rising TSH, but this relationship was not obvious when TSH > 1.24 mIU/L. Participants with SCH had a greater incidence of GDM than those without SCH. These results indicate that high TSH level and SCH may be risk factors for GDM. In our study population, the rate of development of GDM was 14.9%, similar to a previous report (15). Wang et al re- ported that in China, diabetes prevalence increased from 10.9% in 2013 to about 12.4% in 2018 (26). In this study, the incidence of GDM exceeded those found in European and American populations, which may be because East Asians have a limited ability to secrete insulin compared with these populations. Just a slight drop in the production of insulin could result in an acute decline in the level at which this resistance to insulin becomes a risk factor for developing diabetes (27). Mikhail et al found that for the same BMI, the incidence of GDM is greater in Asia than in the United States and Europe, which may be related to the higher rate of visceral fat in Asia (28). The rise in diabetes cases in recent years em- phasizes the importance of paying attention to this issue, espe- cially in Asia. Furthermore, Bar-Zeev et al and Bianchi et al found that smoking and assisted reproductive technology were risk factors for gestational diabetes mellitus, which is consistent with the results of our study (29, 30). Based on the results of the present study, we propose that higher TSH level is a risk factor for GDM. Thyroid gland hor- mones play key roles in the metabolism of glucose, and serum TSH in subjects with normal thyroid function is positively cor- related with hyperglycemia and insulin resistance (31). Similarly, in an investigation of 7258 pregnant participants in Tianjin, China, Leng et al discovered that the levels of TSH were strongly correlated with the incidence of GDM, es- pecially in overweight or obese women (32). Our study also found that pregnant women in the SCH group had a higher percentage of GDM than those without SCH, in agreement with the results of prospective research in China and 2 meta- analyses on thyroid disease and GDM (18, 33, 34). These re- sults lend credence to the idea that GDM risk increases with increasing TSH levels. Upon further analyzing the relationship
between GDM and TSH, we found that the increase in GDM prevalence with increasing TSH levels was evident for TSH ≤
1.24 mIU/L. Some studies have found that elevated TSH levels and thyroid antibody positivity may increase the possibility of GDM (35, 36), which contrasts with the findings of our inves- tigation, where no correlation between antibodies to the thy- roid and the occurrence of GDM was observed, but the various approaches taken to gauge thyroid hormone levels and the substantial variations in sample sizes could be the underlying cause of this discrepancy. The possible mechanism by which TSH affects GDM is as follows: TSH directly decreases the capacity of pancreatic β cells to generate and release insulin, thereby increasing blood glucose levels (11). The TSH level is also thought to influence the development of resistance to insulinshowed that a level of TSH within the range of reference had a beneficial relationship with the insulin resistance index re- gardless of type 2 diabetes status, suggesting that TSH has an independent correlation with insulin resistance (37). Furthermore, TSH may directly affect the metabolic parame- ters of human adipose tissue and stimulate leptin secretion
(38). The existence of TSH receptors has been confirmed in human and animal cell tissues, and adipocytes also contain them (39). When TSH attaches to TSH receptors in adipocytes, it induces the production of interleukin-6, which regulates preadipocyte and adipocyte proliferation, differenti- ation, and leptin secretion (40, 41). Leptin is a crucial neuro-endocrine system regulator of thyroid stimulating hormone in terms of feedback control as it can either directly regulate the gene expression of thyrotropin-releasing hormone (TRH) in the nucleus of the paraventricular or indirectly control the lev- els of TRH through the action of the arcuate nucleus (11Leptin levels have also been found to be associated with TSH and are known to be elevated in patients with hypothy- roidism (38). In a recent animal experiment on mice, Garay Guerrero et al found that TRH deletion affected the expres- sion of fibroblast growth factor 21 (FGF21) in islets and that TRH regulated the expression of FGF21 in the cell line, indicating that maintaining mouse islet function may involve the TRH–FGF21 pathway (42). Leptin also plays a crucial role in glucose metabolism in the liver, where it has been found both to promote and reduce glycogen storage and promote gluconeogenesis (43).

This study has several strengths. First, this was a prospect- ive cohort study with a large sample, and all enrolled pregnant women with GDM were reliably diagnosed by clinicians based on OGTT results. Second, thyroid function was eval- uated at 6-13^{+6} weeks of pregnancy, greatly reducing the vari- ation in thyroid function due to different gestational weeks. However, even in light of these strengths several of our study's limitations warrant discussion. First, this was a single-center study, and therefore does not represent the whole population of China. Second, the study population was

mainly Han Chinese; it is unknown to what extent the findings generalize to other ethnic populations. Third, residual confounding may have occurred due to untested factors. Fourth, this study did not measure urinary iodine levels, but all pregnant women en- rolled lived in iodine adequate areas. Finally, although we found some significant statistical associations, the specific mo- lecular mechanisms have not been elucidated to underpin our conclusions.

In conclusion, our findings indicate that elevated TSH in early pregnancy is a risk factor for GDM, even when the TSH level is within the normal range, providing new evidence that thyroid function during pregnancy affects GDM. These results were further supported by the relatively high GDM rate in participants with SCH during pregnancy. Notably, higher TSH levels may increase the risk of GDM, especially when prepregnancy BMI $\geq$ 24 kg/m^2. However, because other possible confounders were not measured, the mechanisms re- main unclear and require further investigation. Moreover, our results suggest that women with BMI $\geq$ 24 kg/m^2 before preg- nancy can control their weight through diet regulation and ex- ercise to reduce the incidence of GDM. Finally, our findings also illustrate the importance of thyroid function examination during early pregnancy.

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