

Maternal Subclinical Hypothyroidism in the first trimester is not Associated with Gestational Diabetes Mellitus

Ping Li

Third Affiliated Hospital of Sun Yat-Sen University <https://orcid.org/0000-0003-2297-7739>

Xinjuan Chen

third affiliated hospital of Sun Yat-sen University

Jinhui Cui

third affiliated hospital of Sun Yat-sen University

Zhaoran Meng

Third Affiliated Hospital of Sun Yat-Sen University

Jianhui Fan

third affiliated hospital of Sun Yat-sen University

Shuo Lin (✉ gzlinshuo@hotmail.com)

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Abstract

Background: To explore the association between subclinical hypothyroidism (SCH) during the first trimester and gestational diabetes mellitus (GDM) that was happened later on in our cohort.

Methods: A total of 6530 pregnant women who first visited before 13 +6 gestational weeks and accepted routinely prenatal services in the third affiliated hospital of Sun Yat-Sen University from January 2015 to September 2018 were finally met the inclusion criteria and recruited. Thyroid functions (TSH, free T4 (FT4) and TPOAb) were performed at the first visit and a 2h 75-g oral glucose tolerance test was performed between 24-28 weeks. Chi-square test and multivariate logistic regression were used to evaluate the association between SCH and GDM.

Results: Though SCH group was divided into subgroups according TPOAb status and TSH levels, the incidence of GDM was no change when compared with the normal group (all $P > 0.05$). No matter adjusting or not for maternal age, maternal pregestational body mass index, parity and educational level, the results showed elevated TSH was not associated GDM (all $P > 0.05$). TPOAb status also had no effect on the incidence of GDM either before or after adjustment ($P > 0.05$).

Conclusion: Maternal SCH in the first trimester was not associated with GDM, regardless of the TPOAb status or the TSH levels.

Background

Thyroid disease is the second most frequent endocrine disorder among reproductive-aged women^[1]. As the increased serum human chorionic gonadotropin (HCG) concentration and synthesis of thyroxine-binding globulin (TBG), serum thyroid stimulating hormone (TSH) concentrations during pregnancy are not the same as those observed in nonpregnant women^[2], and at the same time makes the thyroid disorder being more likely to occur during pregnancy^[3]. Subclinical hypothyroidism (SCH) is one of the common thyroid disorder during pregnancy and is characterized by an elevated TSH level and a normal free thyroxine (fT4) level^[4]. According the American Thyroid Association (ATA) guideline (2011), SCH is estimated to affect up to 15% of pregnant women in the United States and 28% of pregnant women in China^[5, 6]. As the high incidence, increasing studies began to reassessed whether SCH, the less severe form of thyroid disease, was linked to adverse pregnancy outcomes. However, results were still conflicting^[7-10].

Thyroid disease and diabetes mellitus are two closely associated disorders in non-pregnant populations^[11]. Lack of thyroid hormone is associated with insulin resistance and glucose intolerance^[12]. Gestational diabetes mellitus (GDM) which is defined as “any degree of glucose intolerance with the onset or first recognition during pregnancy” is another common endocrine disorder during pregnancy^[13]. GDM is usually the result of β -cell dysfunction on a background of chronic insulin resistance during pregnancy and thus both β -cell impairment and tissue insulin resistance represent critical components of

the pathophysiology of GDM^[14]. Whether SCH during pregnancy has the effect on insulin resistance and glucose intolerance and then leads to GDM, several studies have evaluated the relationship, but the result remains controversial. Because of this, we designed to evaluate the association between SCH during the first trimester and GDM that was happened later on in our cohort.

Materials And Methods

Subjects

The study was conducted in the third affiliated hospital of Sun Yat-Sen University from January 2015 to September 2018 and approved by the Human Research Ethics Committee of the hospital. The characteristics of the study population were shown in Figure 1. A total of 8872 pregnant women who first visited before 13⁺⁶ gestational weeks and accepted routinely prenatal services were collected. The following pregnant women were excluded: 124 women with personal or family history of thyroid diseases, 68 cases of multiple pregnancy, 46 women with pregestational diabetes mellitus, 74 women using drugs that may influence thyroid function and 230 women lack of the oral glucose tolerance test (OGTT) results.

Methods

Thyroid function was performed at the first visit during the first trimester. Serum samples were obtained in the morning after at least 8-hour fasting for all study participants. Serum TSH, free thyroxine (FT4) and thyroid peroxidase antibody (TPOAb) were measured at the clinical analysis laboratory by an automated two step chemiluminescent immunoassay on an ARCHITECT analyzer (Abbott Diagnostics). The normal range of TSH in the first trimester was adopted from the 2011 ATA guidelines (0.1- 2.5 mIU/L)^[15]. The reference ranges for TPOAb (<5.61 IU/mL) and FT4 (9.01 – 19.05 pmol/L) were provided by the manufacturer. Base on the TSH and TPOAb level, the following pregnant women were excluded: TSH < 0.1 mIU/L (n=681), TSH > 10 mIU/L (n=7), or TSH normal but TPOAb positive (n=1114). Ultimately, we divided the pregnant women into two groups: the normal group (TSH normal and TPOAb negative) (n=5957) and the SCH group (TSH > 2.5 mIU/L) (n=573).

A 2h 75-g OGTT was performed between 24-28 weeks in the morning after at least 8-hour fasting. Blood glucose level was measured using the glucose oxidase method (Roche Diagnostics). The diagnosis criteria for GDM was based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (i.e., one or more plasma venous glucose values \geq 0 h, 5.1 mmol/L; 1 h, 10.0 mmol/L; or 2 h, 8.5 mmol/L)^[16].

Patients' baseline characteristics were recorded at the first visit, including age, pregestational body mass index (BMI, BMI=weight (kg) / height (m²)), parity, family or personal history diseases (thyroid disease, hypertension, pregestational diabetes mellitus and systemic lupus erythematosus) and education level.

Statistical analysis

Data were presented as median (interquartile range) for non-normally distributed data and frequency (percentage) for categorical variables. Chi-square test was used to test for differences in variables between groups. Multivariate logistic regression was used to evaluate the association between SCH and GDM. The results are represented as odds ratios (ORs) and 95% confidence intervals (95% CIs). $P < 0.05$ was considered statistically significant. SPSS19.0 software (SPSS, Inc., Chicago, IL) was used for analysis.

Results

In this study, 573 pregnant women were diagnosed as SCH and the incidence of SCH was 6.69% (573/8562). A total of 6530 pregnant women were ultimately met the inclusion criteria, including 573 SCH women and 5957 normal women (TSH normal and TPOAb negative). The characteristics of participants were shown in Table 1. The average level of TSH in SCH group and normal group was 3.02(2.70–3.64) mIU/L and 0.94(0.56–1.40) mIU/L respectively. The three times of blood glucose on 75 g-OGTT were not significantly different between SCH group and normal group [0 hour: 4.17 mmol/L (3.99–4.38) vs 4.16 mmol/L (3.97–4.39), $P = 0.730$; 1 hour: 7.61 mmol/L (6.64–8.66) vs 7.68 mmol/L (6.64 – 8.75), $P = 0.449$; 2 hour: 6.66 mmol/L (5.85–7.68) vs 6.75 mmol/L (5.93–7.74), $P = 0.142$]. The age, preBMI and education levels were also not significantly different between the two groups (all $P > 0.05$). However, there was more nullipara in SCH group than in normal group (58.30% vs 50.70%, $P = 0.000$).

Table 1

Basic characteristics between subclinical hypothyroidism and normal pregnant women divided by the first-trimester TSH concentrations *

| Characteristics | Total (n = 6530) | Normal (n = 5957) | SCH (n = 573) | P |
|--|---------------------|----------------------|--------------------|-------|
| Maternal age (years) | 29(27–32) | 29(27–32) | 29(27–32) | 0.695 |
| Pregestational BMI (kg/m ²) | 20.31(18.82–22.21) | 20.31(18.82–22.21) | 20.31(18.67–22.06) | 0.393 |
| Parity | 3352(51.33) | 3018(50.70) | 334(58.30) | 0.000 |
| Nullipara (%) | 3178(48.67) | 2939(49.30) | 239(41.70) | |
| Education level | 3515(53.83) | 3199(53.70) | 316(55.10) | 0.507 |
| High school or lower Bachelor or higher | 3015(46.17) | 2758(46.30) | 257(44.90) | |
| Thyroid function at early pregnancy | 0.22(0.01–0.51) | 0.20(0.01–0.46) | 0.50(0.10–35.75) | 0.000 |
| TPOAb (IU/mL) | 13.20(12.18–14.28) | 13.27(12.26–14.35) | 12.51(11.50–13.47) | 0.000 |
| fT4 (pmol/L) | 1.02(0.60–1.58) | 0.94(0.56–1.40) | 3.02(2.70–3.64) | 0.000 |
| TSH (uIU/mL) | | | | |
| Blood glucose on 75-g OGTT | 4.17(3.97–4.39) | 4.16(3.97–4.39) | 4.17(3.99–4.38) | 0.730 |
| 0 hour (mmol/L) | 7.68(6.64–8.74) | 7.68(6.64–8.75) | 7.61(6.64–8.66) | 0.449 |
| 1 hour (mmol/L) | 6.74(5.92–7.73) | 6.75(5.93–7.74) | 6.66(5.85–7.68) | 0.142 |
| 2 hour (mmol/L) | | | | |
| * Medians (interquartile ranges) | | | | |
| TSH, thyroid stimulating hormone; BMI, body mass index; TPOAb: thyroid peroxidase antibody; fT4, free thyroxine 4; OGTT: oral glucose tolerance test | | | | |

Table 2

Comparison the incidence of gestational diabetes mellitus between subclinical hypothyroidism and normal pregnant women divided by TSH levels and TPOAb status in early pregnancy.

| | GDM (%) | χ^2 | P |
|--|-----------------|-----------|-----------|
| Normal | 16.3 (971/5957) | Reference | Reference |
| Subclinical hypothyroidism | | | |
| TSH(H) TPOAb(-/+) | 14.1(81/573) | 1.811 | 0.178 |
| TSH(H) TPOAb(-) | 13.8(53/384) | 1.662 | 0.197 |
| *TSH(H ₁) TPOAb(-) | 13.5(46/340) | 1.823 | 0.177 |
| †TSH(H ₂) TPOAb(-) | 15.9(7/44) | 0.005 | 0.944 |
| TSH(H) TPOAb(+) | 14.8(28/189) | 0.297 | 0.586 |
| *TSH(H ₁) TPOAb(+) | 12.9(18/140) | 1.193 | 0.275 |
| †TSH(H ₂) TPOAb(+) | 20.4(10/49) | 0.600 | 0.439 |
| GDM, gestational diabetes mellitus; TSH, thyroid stimulating hormone; TPOAb: thyroid peroxidase antibody | | | |
| *TSH(H ₁): > 2.5 uIU/mL, < 4.0 uIU/mL; †TSH(H ₂): ≥ 4.0 uIU/mL. | | | |

As shown in Fig. 2, the incidence of GDM was compared between the SCH and normal pregnant women. SCH group was further divided into subgroups according TSH levels and TPOAb status in the first trimester. There were 384 TPOAb negative women and 189 TPOAb positive women in SCH groups. More than 80 percent SCH women (83.77%, 480/573) had the TSH slightly elevated (between 2.5 mIU/L to 4.0 mIU/L) and just 16.23% (93/573) women had the TSH level \geq 4.0 mIU/L. Though SCH group was divided into TPOAb negative and TPOAb positive subgroups, the incidence of GDM was not different when compared with the normal group (TPOAb negative vs normal: 13.8% vs 16.3%, $\chi^2 = 1.662$, P = 0.197; TPOAb positive vs normal: 14.8% vs 16.3%, $\chi^2 = 0.297$, P = 0.586). Then we further subdivided the SCH group women according to the different elevated TSH levels (TSH (H₁): > 2.5 uIU/mL, < 4.0 uIU/mL) and high level (TSH(H₂): \geq 4.0 uIU/mL)), and then compared the incidence of GDM with the normal group. In TSH (H₁) group, we observed no difference in the incidence of GDM (TPOAb(-): 13.5% vs 16.3%, $\chi^2 = 1.823$, P = 0.177; TPOAb(+): 12.9% vs 16.3%, $\chi^2 = 1.193$, P = 0.275). In TSH (H₂) group, we got the same conclusion (TPOAb(-): 15.9% vs 16.3%, $\chi^2 = 0.005$, P = 0.944; TPOAb(+): 20.4% vs 16.3%, $\chi^2 = 0.600$, P = 0.439).

We used a multivariate logistic regression analysis to investigate whether SCH in the first trimester associated with GDM, as shown in Table 3. The results showed that no matter adjusting or not for age, pregestational body mass index (preBMI), parity and educational level, elevated TSH was not associated GDM that was happen later on (all P > 0.05). TPOAb status also had no effect on the incidence of GDM either before or after adjustment (P > 0.05).

Table 3

Multivariate logistic regression analysis for the association of SCH in the first trimester and GDM

| | Unadjusted model OR (95% CI) | P | Adjusted model ¹ OR (95% CI) | P | Adjusted model ² OR (95% CI) | P |
|-----------------------|---------------------------------|-------|--|-------|--|-------|
| TSH(N) TPOAb(-) | 1.0(Ref) | | 1.0(Ref) | | 1.0(Ref) | |
| SCH | | | | | | |
| *TSH(H ₁) | 0.772(0.587– 1.014) | 0.063 | 0.787(0.595– 1.041) | 0.093 | 0.798(0.581– 1.096) | 0.164 |
| †TSH(H ₂) | 1.215(0.724– 2.041) | 0.461 | 1.175(0.688– 2.007) | 0.555 | 1.208(0.657– 2.220) | 0.543 |

SCH, subclinical hypothyroidism; GDM, gestational diabetes mellitus; TSH, thyroid stimulating hormone; TPOAb: thyroid peroxidase antibody

Adjusted model¹: Adjustment for maternal age, maternal pregestational body mass index, parity and educational level.

Adjusted model²: Adjustment for model¹ plus TPOAb status.

*TSH(H¹): > 2.5 uIU/mL, < 4.0 uIU/mL; †TSH(H²): ≥ 4.0 uIU/mL.

"

Discussion

The purpose of the present study was to evaluate the association between SCH during the first trimester and the risk of GDM in our cohort and we also took TPOAb status and TSH level into consideration. The glucose levels of OGTT were shown no differences between SCH women and euthyroid women. The incidence of GDM was no change as the TSH level increased in either TPOAb negative or TPOAb positive SCH women. We also used the multivariate logistic regression analysis to adjust the confounders and the result did no change after adjusted for maternal age, educational levels and preBMI. Thus, our study demonstrated that maternal SCH in the first trimester was not associated with GDM that was happened later on.

Presently, the association between SCH and GDM is still conflicting. Different cutoffs that are adopted for the diagnosis of SCH, highly varied gestational ages in which thyroid functions are tested, as well as TPOAb status are the main reasons for different results. In our study, thyroid function was performed before 13⁺⁶ gestational weeks. We adopted the 2011 ATA guideline for the diagnostic cutoff and the reference intervals for TSH is 0.1–2.5 mIU/L in the first trimester. TPOAb status was also taken into account. In Ying et al.'s study, they used 0.06–3.83 mIU/L as the reference intervals for TSH in the first trimester that was established at their institution. They showed that elevated TSH combined with positive TPOAb was associated with a 3-fold increased risk for GDM compared to euthyroid women in the first trimester (RR: 3.26, 95% CI: 1.55 to 6.84)^[17]. However, in elevated TSH but TPOAb negative women, no relationship was found between SCH and GDM (RR: 0.55, 95% CI: 0.12 to 2.51). Karakosta's study showed that there was no obviously increased risk of GDM in SCH women with TPOAb negative in early pregnancy (RR: 1.4, 95% CI: 0.5 to 3.8), whereas those with an elevated TSH and autoantibodies were at a four-fold increased risk for GDM (RR: 4.3, 95% CI: 2.1 to 8.9)^[18]. Different from us, they tested the thyroid functions before 15 gestational weeks and the reference intervals of TSH were 0.05–2.53 mIU/L. Our finding was agreed with several other investigations. In

| | Unadjusted model | P | Adjusted model ¹ | P | Adjusted model ² | P |
|-----|--|---|-----------------------------|---|-----------------------------|---|
| | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
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Figures

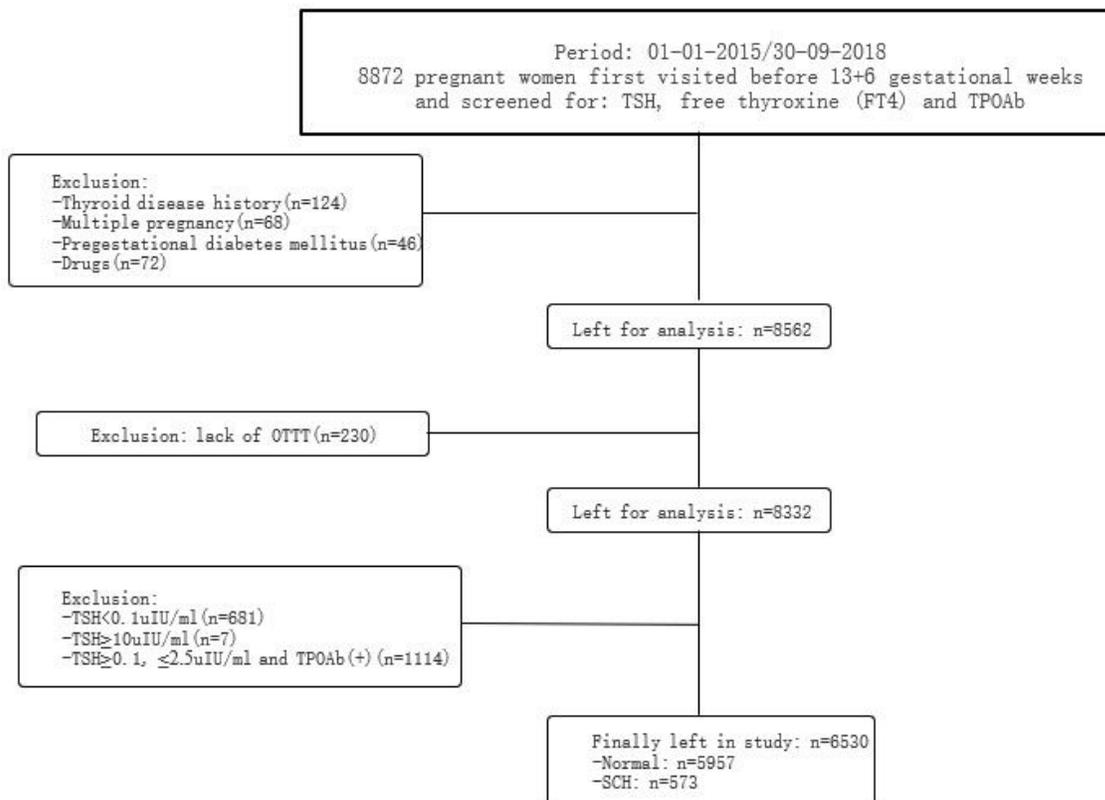


Figure 1

| Flow chart showing the selection of the finally included women in the study. | | | | | |
|--|---|-----------------------------|---|-----------------------------|---|
| Unadjusted model | P | Adjusted model ¹ | P | Adjusted model ² | P |
| OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
| | | | | | |