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Original Article

Subclinical hypothyroidism in pregnant women with diabetes

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Abstract: Objective: To study whether a pregnant women is highly likely to develop subclinical hypothyroidism (SCH). Methods: In this cohort study, we recruited 62 pregnant women with diabetes mellitus (DM) (DM group) and 65 pregnant women without diabetes (control group). We divided our subjects with DM (n = 62) into two subgroups, as those with gestational DM (GDM, n = 28) and pregestational DM (pre-GDM, n = 34). From the time of the pregnant women's hospitalization, laboratory measurements of serum thyroid stimulating hormone (TSH), serum free thyroxine (FT4) were tested by electrochemiluminescence immunoassay. Between 24 and 28 weeks of gestation, blood glucose (BG) was measured by the hexokinase method, glycosylated hemoglobin (HbA1c) by HLC-723G7, and high/low density lipoprotein cholesterol (H/LDL-C) were performed by the enzyme colorimetry. Results: The prevalence of SCH in the GDM group did not differ significantly from that in the control group ($P = 0.13$), but differences existed between the pre-GDM and control groups ($P < 0.01$). BMI, systolic and diastolic blood pressure, FPG, HbA1c, BUN, total cholesterol level, and triglyceride values were higher in pregnant women of the pre-GDM group and GDM group than those of the control group. The pregnant women with SCH tended to have poorer blood glucose control and higher body mass index (BMI). The findings indicated that poor blood glucose control and higher BMI increased the possibility of occurrence of SCH in pregnant women with diabetes. Conclusion: SCH should be considered for pregnant women exhibiting weak glycemic control and obesity.

Keywords: Blood glucose control, diabetes mellitus, obesity, pregnant women, subclinical hypothyroidism

Introduction

Subclinical hypothyroidism (SCH) is defined as a condition characterized by the combination of increased serum thyroid stimulating hormone (TSH) and standard serum free thyroxine (FT4) levels [1]. Pregnancy imposes a considerable influence on the thyroid gland and its functioning. It is a well-known fact that the amount of thyroid hormone required is greatly elevated in women during pregnancy [2]. For pregnant women, the observed prevalence of overt hypothyroidism is 0.5%, while that of subclinical hypothyroidism is 2-3% [3]. Several reports have proven the close correlation of SCH to Graves' disease and neuropsychological underdevelopment in the offspring, coupled with other maternal complications such as miscarriage, preterm birth, and pre-eclampsia [4].

The risk of thyroid dysfunction after the diagnosis of type I diabetes is almost tripled during pregnancy [5]. The latest study found that subclinical hypothyroidism is found to occur more frequently in pregnant women with diabetes [6]. However, there is no clear study on the relationship between pre-pregnancy diabetes and gestational diabetes mellitus and subclinical hypothyroidism. It is very crucial that both subclinical hypothyroidism and hypothyroidism are diagnosed in a timely manner, preferably as early as possible, and treated effectively in pregnant mothers to minimize the adverse effects on pregnancy [7].

As the most common endocrine dysfunction in pregnancy, diabetes could be classified into either gestational diabetes mellitus (GDM) or pre-gestational diabetes (pre-GDM), depending on the time of diagnosis [8]. General complications for GDM are gestational hypertension-preeclampsia, fetal macrosomia, and chronic conditions such as postpartum type-II diabetes, and cardiovascular and metabolic dysfunc-

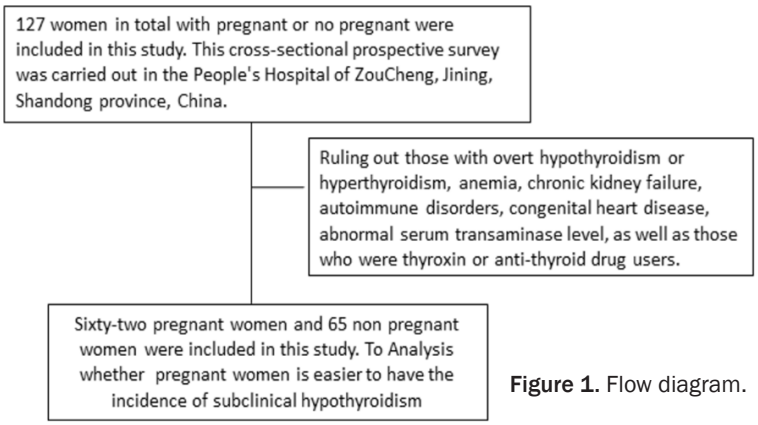

Figure 1. Flow diagram.

tions. Additionally, offspring can also acquire an abnormal glucose metabolism feature [9]. However, the situation can be controlled with the right exercise, complementary diet, and balanced insulin treatment [2, 10].

Some reports indicate that individuals with or without GDM shared similar TSH and FT4 levels, as well as thyroperoxidase antibody (TPOAb) status [11]. Moreover, other reports also suggested that there was no significant relationship between GDM and subclinical hypothyroidism [12]. So far, most literature has suggested a correlation between SCH and expectant mothers with GDM [5].

To explore this controversial issue, our study focused on investigating the association between SCH and diabetes in pregnant women. The difference in the control of blood glucose levels between expectant mothers with SCH and those without SCH has received increasing amounts of attention.

Materials and methods

This cohort study was carried out in the Changzhi People's Hospital. Total of 127 pregnant women, half with diabetes, were included in this study. (The GDM screening was performed in the 24th to 28th week of pregnancy. Fifty g of glucose powder is dissolved in 200 ml of water and given within 5 minutes. After 1 hour, if the blood glucose level is ≥ 7.8 mmol/L, which is positive for sugar screening. Fasting blood glucose should be checked, and if fasting blood glucose is abnormal this can be diagnosed as diabetes, and those with normal fasting blood glucose should be tested for glucose tolerance (GTT)). There are 62 pregnant women with diabetes mellitus (DM group) and 65 pregnant women without diabetes (control group). We divided our subjects with DM (n = 62) into two groups, as those with gestational DM (GDM) (those diagnosed between the last menstrual period and 13 weeks of gestation were GDM, n = 28) and pregestational DM (pre-GDM, n = 34). The study was planned and executed by the Changzhi People's Hospital, with strict adherence to the protocol of the hospital's institutional review board. Informed consent was obtained from all the subjects involved in the study, and high-level privacy protection was given to them. The flow diagram was shown in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: pregnant women with diabetes were adopted in the DM group, and the pregnant women without diabetes were adopted in the control group. All the pregnant women were between the last menstrual period and 13 weeks of gestation. Exclusion criteria: pregnant women had overt hypothyroidism or hyperthyroidism, anemia, chronic kidney failure, autoimmune disorders, congenital heart disease, abnormal serum transaminase level, as well as those who were thyroxin or anti-thyroid drug users.

Subjects were recruited at early gestational periods (between the last menstrual period and 13 weeks of gestation). The 75 g glucose test was performed and blood samples for FPG, HbA1c, HDL-C, and LDL-C measurement were collected between 24 and 28 weeks of gestation. Blood samples for thyroid function analysis were collected at the first trimester (between the last menstrual period and 13 weeks of gestation) and the second trimester of gestation (between 13 and 28 weeks of gestation).

Examination methods

We obtained blood samples from the pregnant women, isolated the serum through centrifugation, and stored the samples at -80°C for future testing. The study mainly used the electrochemiluminescence immunoassay to

test the serum TSH and FT4 concentrations. The intra-assay and inter-assay coefficients of variation were < 4.7% and < 4.3% for TSH blood concentrations, and < 2.2% and < 3.5% for FT4 blood concentrations. The reference intervals for thyroid function that were calculated by following the American Thyroid Association (ATA) and the National Academy of Clinical Biochemistry (NACB) guidelines were as follows: 0.1-3.8 mIU/L of TSH and 1.0-1.6 ng/dL of FT4 in the first trimester of pregnancy, and 0.07-4.4 mIU/L of TSH and 1.0-1.53 ng/dL of FT4 in the second trimester. Our subjects were classified into various pregnancy trimesters based on the embryonic ages of their offspring, observed from the initial sampling blood test. The TSH and FT4 sera were then grouped into the following three categories by applying the relative reference intervals: i.e. low (subjects with serum TSH and FT4 levels < the calculated reference range), normal (subjects with TSH and FT4 levels within the calculated reference range), and high (subjects with serum TSH and FT4 levels > the calculated reference range). SCH was diagnosed after observing the combined TSH (with a trimester-specific reference value) and FT4 concentrations (with a normal value range). Serum thyroid stimulating hormone (TSH) levels were slightly elevated, while serum thyroid hormone (FT4, FT3) levels were normal, patients with no hypothyroidism or only mild hypothyroidism, which could be diagnosed as SCH [13]. During the initial antenatal examination, the thyroid level was thoroughly examined, and all subjects filled out questionnaires to obtain the necessary information, including demographic information, medical history (menstrual cycle, medication usage history, and pregnancy history), living style and health habits, fetal growth parameters, and physical parameters like body height, weight, and blood pressure. Body mass index (BMI) was calculated as the weight of subjects divided by their height (kg/m^2) starting at the last menstrual period, and we compared the average BMI in the result. Blood pressure was measured in subjects in a calm state, after being giving at least 10 mins of rest beforehand. Venous blood samples were collected after at least 12 hours of overnight fasting. All data were maintained in an online database.

The hexokinase method (AU 5400 Autoanalyzer, Olympus, Tokyo, Japan) was used to measure blood glucose (BG). Glycosylated hemoglobin (HbA1c) was measured by high performance liquid chromatography (HLC-723G7, Tosoh, Tokyo, Japan). The study used enzyme colorimetry (Kyowa Medex Co. Ltd., Tokyo, Japan) to measure the cholesterol level, the glycerol elimination method for triglyceride measurement, direct enzymatic assays (Kyowa Medex Co. Ltd.) for high-density lipoprotein cholesterol (HDL-C) measurement, and followed the Friedewald's formula to measure low density lipoprotein cholesterol (LDL-C).

Statistical methods

All values in this study have been expressed in terms of mean ± SD, numbers, or percentages. SPSS 16.0 (version 20.0, IBM Co., Armonk, NY, USA) was used for data reduction and statistical analysis. The Students' *t*-test was applied for quantitative variables and the chi-square test was applied for categorical variables during significance testing. To analyze the data further, multivariate logistic regression analysis was carried out to measure the odds ratio (OR) for analyzing the chance of SCH occurring in pregnant women with poor glycemic control or obesity. Data were considered to be statistically significant if the *p* value was less than 0.05.

Results

Clinical characteristics of the study subjects

No specific disparities were observed in the maternal age, gravidity and parity history, gestational age at delivery, and delivery modes of the pregnant women in the DM group and the control group. Apart from that, there was a difference between TSH and FT4, but the difference was not statistically significant. So there were no significant differences in the TSH and FT4 levels of pregnant women in the DM group and the control group. ($P > 0.05$, **Table 1**).

Different characteristics of pregnant women in the DM group and the control group

We also found that the BMI, systolic and diastolic blood pressure, FPG, HbA1c, BUN, total cholesterol level, and triglyceride values were higher in pregnant women of the DM group than those of the control group ($P < 0.01$). Additionally, the high-density lipoprotein cholesterol (HDL-C) was lower in pregnant women

Table 1. Clinical characteristics of the study subjects

Characteristic	Control group (n = 65)	DM group (n = 62)	*p* value
Maternal age (years)	25.6 ± 4.4	26.1 ± 4.8	0.61
BMI, kg/m^2	21.6 ± 2.9	27.1 ± 4.5	< 0.010
Parity			
Nulliparity	50 (76.9%)	48 (77.4%)	0.76
Multiparity	15 (23.1%)	14 (22.6%)	
Gestational age at delivery (weeks)	38.4 ± 3.2	38.8 ± 4.2	0.83
Mode of delivery			
Vaginal	41 (63.1%)	38 (61.3%)	0.64
Cesarean	24 (36.9%)	24 (38.7%)	
TSH, mIU/L	2.19 ± 0.43	2.26 ± 0.62	0.15
Free T4, ng/dL	1.41 ± 0.43	1.36 ± 0.51	0.23

Values are presented as mean ± SD or number (%). DM, diabetes mellitus; BMI, body mass index; TSH, thyroid.

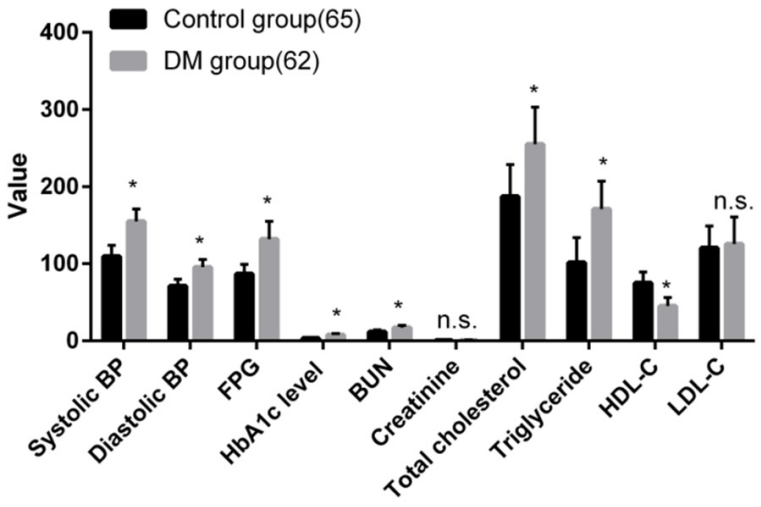

Figure 2. Different characteristics between pregnant women and normal control. DM, diabetes mellitus; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone; T4, thyroxine. *P < 0.05, normal women compared with pregnant women. n.s. P > 0.05, normal pregnant women compare with pregnant women.

of the DM group than those of the control group (P < 0.01) (**Figure 2** and **Table 2**).

Prevalence of SCH in GDM, pre-GDM and control group

We divided our subjects with DM (n = 62) into two groups, as those with gestational DM (GDM, n = 28) and pregestational DM (pre-GDM, n = 34). Among the 28 patients with GDM, 26 (92.9%) subjects exhibited normal thyroid function, while the rest (n = 2, 7.1%) had SCH. Among the 34 individuals with pre-GDM, 30 (88.2%) exhibited normal thyroid function and 4 (11.8%) had SCH (**Table 3**). Among the 65 patients with GDM, 63 subjects exhibited normal thyroid function, while the remaining 2 (n = 2, 3.1%) had SCH. These data suggested that the prevalence of SCH in the GDM group did not differ significantly from that in the control group (*P* = 0.13). On the contrary, differences existed between the pre-GDM and control groups (*P* < 0.01).

Clinical characteristics of pregnant women between Euthyroidism and Subclinical hypothyroidism in the DM group

The pregnant subjects with DM were also categorized into the SCH and euthyroid groups. Diabetic pregnant women that had poor blood glucose control and SCH were distinctively characterized by higher TSH (P < 0.01), HbA1c, (P < 0.01) and BMI (P < 0.01) levels (**Figure 3**). There were no significant differences between groups with regard to the parameters that were listed in the questionnaires, including parity, maternal age, gestational age, delivery method, blood pressure, hypertension, creatinine, triglyceride, total cholesterol, FT4, FPG, BUN, HDL-C, LDL-C, etc. (**Table 4**). These findings indicate that poor blood glucose control and higher BMI increased the possibility of occurrence of SCH in pregnant women with diabetes.

The association of SCH with glycemic control and BMI in pregnant women with DM

The study further explored the correlation of poor blood glucose control and obesity with

Table 2. Different characteristics between pregnant women with DM and normal control

Characteristic	Control group (n = 65)	DM group (n = 62)	*p* value
Hypertension	7 (10.8%)	16 (25.8%)	0.0013
Systolic BP, mmHg	109.5 ± 14.3	155.2 ± 16.1	0.0087
Diastolic BP, mmHg	71.2 ± 8.7	95.5 ± 10.1	0.0076
FPG, mg/dL	86.7 ± 12.5	132.3 ± 22.8	0.0065
HbA1c level (%)	3.4 ± 0.6	7.8 ± 1.6	0.0068
BUN, mg/dL	11.7 ± 2.6	17.1 ± 3.2	0.0076
Creatinine, mg/dL	0.87 ± 0.2	0.91 ± 0.3	0.0053
Total cholesterol, mg/dL	187.4 ± 41.3	255.3 ± 47.9	0.0051
Triglyceride, mg/dL	101.4 ± 32.7	171.2 ± 35.8	0.00225
HDL-C, mg/dL	75.2 ± 14.1	45.3 ± 10.7	0.0036
LDL-C, mg/dL	120.4 ± 28.6	125.5 ± 35.2	0.0049

Values are presented as mean ± SD or number (%). DM, diabetes mellitus index; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 3. Prevalence of subclinical hypothyroidism in GDM, pre-GDM and control group

Groups	No. of Normal Thyroid function (%)	No. of Subclinical Hypothyroid (%)	*p* value (vs control)
Control group	63 (96.9%)	2 (3.1%)	
GDM	26 (92.9%)	2 (7.1%)	0.130
Pre-GDM	30 (88.2%)	4 (11.8%)	< 0.010

GDM, gestational diabetes mellitus.

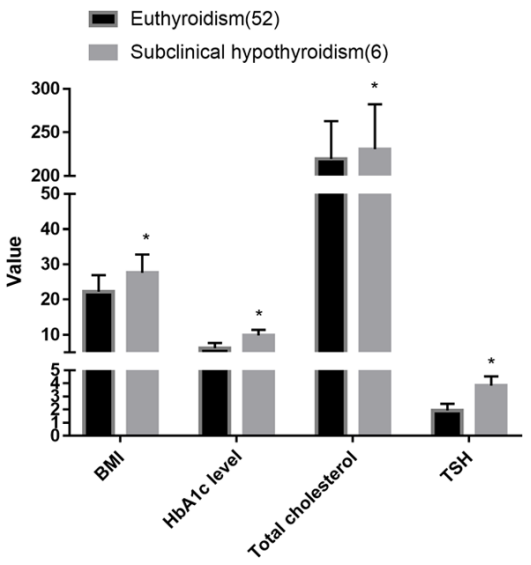

Figure 3. Different characteristics of pregnant women with or without subclinical hypothyroidism. BMI (kg/m^2), body mass index; HbA1c (%), glycosylated hemoglobin (mg/dL); TSH (mIU/L), thyroid stimulating hormone; *P < 0.05, Euthyroidism compared with Subclinical hypothyroidism.

SCH in pregnant women with DM. After the adjustment of parameters (parity, maternal age, gestational age, delivery method, hypertension, blood pressure, creatinine, total cholesterol, triglyceride, FT4, FPG, BUN, HDL-C, and LDL-C), the regression analysis demonstrated a positive correlation between SCH and poor blood glucose control/obesity. As shown in **Table 5**, the RRs for poor blood glucose control and obesity were 3.24 (95% CI, 1.94 to 6.63; P < 0.01) and 2.16 (95% CI, 1.35 to 4.32; P < 0.01). These data suggest a correlation between weak blood glucose control, obesity, and SCH in pregnant women.

Discussion

There is an association between the occurrence of thyroid disorders and impaired neurodevelopment in the offspring. Specifically, subclinical or mild hypothyroidism is linked to mental retardation in the newborn [14]. This study has found a significant difference in the prevalence of SCH between pregnant women with pre-GDM and the control group, but the GDM group and the control group showed no significant differences in the prevalence of SCH. In addition, the results showed that SCH is associated with poor blood glucose control and obesity in pregnant women with DM.

It is important for pregnant women to do the thyroid function screening, so that the occurrence of patients with SCH may be reduced in the clinic. Some clinicians suggest a universal testing in all women by their 9th week of pregnancy, while others argue that only pregnant women at high risk are fit to take this examination. However, research has found that a considerable proportion of pregnant women with the SCH were overlooked when the targeted testing method was used. A recent study of pregnant women revealed a one-third missed diagnosis rate for hypothyroidism or SCH when the targeted testing method was used [15]. Additional research also suggested an omission rate of 50% [16]. In this study, a significant

Table 4. Clinical characteristics of pregnant women between Euthyroidism and Subclinical hypothyroidism in the DM group

Characteristic	Euthyroidism (n = 56)	Subclinical hypothyroidism (n = 6)	*p* value
Maternal age (years)	25.9 ± 5.3	26.3 ± 4.6	0.612
BMI, kg/m^2	22.2 ± 4.7	27.6 ± 5.2	< 0.01
Parity			
Nulliparity	44 (78.6%)	5 (83.3%)	0.293
Multiparity	12 (21.4%)	1 (16.7%)	
Gestational age at delivery (weeks)	38.6 ± 4.4	39.1 ± 5.3	0.561
Mode of delivery			
Vaginal	35 (62.5%)	3 (50.0%)	0.213
Cesarean	21 (37.5%)	3 (50.0%)	
Hypertension	56 (9.0%)	5 (10.6%)	0.624
Systolic BP, mmHg	124.3 ± 15.1	125.8 ± 17.6	0.519
Diastolic BP, mmHg	78.7 ± 9.3	80.2 ± 12.5	0.301
FPG, mg/dL	130.2 ± 20.7	134.5 ± 23.4	0.167
HbA1c level (%)	6.2 ± 1.5	9.8 ± 1.6	< 0.01
BUN, mg/dL	14.9 ± 2.8	15.5 ± 3.4	0.163
Creatinine, mg/dL	0.88 ± 0.27	0.93 ± 0.32	0.331
Total cholesterol, mg/dL	219.6 ± 43.2	230.7 ± 51.6	0.092
Triglyceride, mg/dL	167.3 ± 33.8	175.2 ± 38.9	0.133
HDL-C, mg/dL	54.3 ± 10.1	56.8 ± 11.4	0.114
LDL-C, mg/dL	124.6 ± 32.4	126.7 ± 37.2	0.672
TSH, mIU/L	1.93 ± 0.52	3.83 ± 0.71	< 0.01
Free T4, ng/dL	1.34 ± 0.35	1.38 ± 0.44	0.461

Values are presented as mean ± SD or number (%). DM, diabetes mellitus; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone; T4, thyroxine.

Table 5. The association of SCH with glycemic control and BMI in pregnant women with diabetes mellitus was evaluated by multivariate logistic regression analysis

Outcome	Adjusted RR	95% CI	*p* value
HbA1c level	3.24	1.94-6.63	< 0.01
BMI	2.16	1.35-4.32	< 0.01

SCH, subclinical hypothyroidism; OR, odds ratio; CI, confidence interval. Adjusted for maternal age, parity, gestational age at delivery, mode of delivery, systolic and diastolic blood pressure, fasting plasma glucose, blood urea nitrogen, creatinine, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglyceride.

difference in the prevalence of SCH was found between the pre-GDM group and control group; the differences between the GDM and control groups were insignificant. Therefore, a universal thyroid function test should be prescribed to pregnant women with pre-GDM during their first few prenatal visits.

This study found that the risk of SCH increased with poor glycemic control, especially in pregnant women with pre-GDM. Insulin resistance possibly explains this correlation. Research has found that patients with SCH had fasting hyperinsulinemia and insulin resistance [17], and this previous study suggested that the impaired translocation of GULT4 was associated with SCH, leading to deteriorated insulin-stimulated glucose disposal [18]. Another study of diabetic patients found that subjects with SCH have a higher HOMA-IR than their counterparts with normal thyroid function [19]. Further, El-Eshmawy et al. [17] revealed that TSH levels are positively correlated with HOMA-IR levels. However, a study of diabetic rats found that rising TSH levels relieve some symptoms caused by diabetes, indicating the increasing incidence of SCH may be a physiological adaption [20]. Recent studies also showed that TSH reference levels differed with geographic districts and ethical considerations [21]. Considering the ref-

erence TSH interval provided by Li et al. [22], this study suggests that increased TSH levels are linked with poor blood glucose control in patients with pre-GDM. However, further research is required to reveal the complicated interactions between SCH and pregnant with pre-GDM.

The study also found that the TSH level was positively correlated with BMI in patients with DM. Euthyroid adults tended to have higher TSH and lower FT4 levels when the subcutaneous fat increased considerably [23]. Obese pregnant women were at a higher risk of having maternal hypothyroxinemia (women with low blood FT4 and normal blood TSH during pregnancy) than their counterparts with normal weight [24]. Research has found that increased energy consumption caused by obesity leads to an increased conversion of FT4 to FT3, resulting in low FT4 levels [25]. On the other hand, weight-loss interventions are associated with decreased FT3 levels. Therefore, pregnant women should be encouraged to maintain a reasonable BMI to prevent maternal hypothyroxinemia.

We found that SCH was associated with poor blood glucose control and obesity in patients with DM. However, further sequential research is required to determine if there is a causal relationship between them.

This study had several other limitations. Follow-up thyroid function tests were not conducted in subjects. Though dietary guidance was given at the first visit, the dietary record was not tracked further. Since diet is an important factor influencing GDM, the reliability of the results might be adversely affected due to this factor. The size of the control group was relatively small, due to limited funds being available for research, which is a limitation of this study. Future studies should include a much bigger number of samples to obtain results that are more convincing.

In conclusion, this study showed the prevalence of SCH in normal, GDM, and pre-GDM pregnant women. These results indicate that the pre-GDM group is at a higher risk of having thyroid dysfunction; the prevalence of SCH is similar in women with GDM and normal pregnant women. Moreover, the increased risk of SCH is associated with poor blood glucose control and obesity in pregnant women with DM. Therefore, this study suggests that obese pregnant women with poor blood glucose control are at high risk of SCH as a comorbidity.

Disclosure of conflict of interest

None.

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