RESEARCH

Untreated thyroid autoantibody-negative SCH increases the risk of spontaneous abortions

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Abstract

Background: Numerous studies have found that subclinical hypothyroidism (SCH) may increase adverse pregnancy outcomes; however, the benefit of levothyroxine (LT4) treatment remains controversial. The 2017 guidelines of the American Thyroid Association weakly recommended LT4 therapy for serum antithyroid peroxidase antibody (TPOAb)-negative women with thyroid-stimulating hormone (TSH) concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L. Therefore, the primary goal of this study was to investigate the correlation between thyroid autoantibody-negative SCH with or without LT4 treatment and adverse pregnancy outcomes.

Methods: We prospectively enrolled 1868 consecutive pregnant women. Finally, 1344 women were involved in the study according to the inclusion and exclusion criteria. Assays for TSH, free thyroxine (FT4), TPOAb, anti-thyroglobulin antibody, and laboratory indicators were performed. The participants were divided into the euthyroid (ET) group (n = 1250) and the SCH group(n = 94). The SCH group was further divided into LT4 group (n = 40) and non-LT4 group(n = 54). The laboratory indicators and pregnancy outcomes were evaluated during follow-ups.

Results: Maternal age, BMI, parity, and the history of spontaneous abortion did not differ significantly between the ET group and the different SCH groups. There were no significant differences in lipid profile and homocysteine levels between ET and SCH group in the first and third trimester of pregnancy. After adjusting the confounding factors, the non-LT4 group was a risk factor for spontaneous abortion (odds ratio: 3.141, 95% CI: 1.060–9.302). Survival analysis showed that the time of abortion was different between the ET group and SCH group (log-rank P = 0.042). The spontaneous abortion in SCH, especially in non-LT4, group mainly occurred in the first trimester of pregnancy.

Conclusions: Thyroid autoantibody negative-SCH seems to be associated with increased risk of spontaneous abortions during the first trimester of pregnancy. LT4 therapy in this patient population might be beneficial to reduce adverse pregnancy outcomes.

Key Words

- subclinical hypothyroidism
- levothyroxine
- pregnancy outcomes

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Introduction

Maternal subclinical hypothyroidism (SCH), which is defined as an increased thyroid-stimulating hormone (TSH) concentration beyond the upper limit of the pregnancy-specific reference range and a normal free-thyroxine (FT4) concentration, is prevalent in pregnant women (1). Numerous studies have shown that SCH may be associated with adverse pregnancy outcomes, such as spontaneous abortion, premature birth, hypertensive disorders in pregnancy (HDP), gestational diabetes mellitus (GDM), and placental abruption (1, 2, 3). A previous study (4) about

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thyroid disease and pregnancy outcomes showed that SCH increased the odds of adverse pregnancy outcomes and that levothyroxine (LT4) administration improved pregnancy outcomes. However, a prior retrospective cohort study (5) found that there was no difference in the incidence of GDM, intrahepatic cholestasis in pregnancy, premature rupture of membranes (PROM), fetal growth restriction, preterm delivery, fetal respiratory distress, and pregnancy mortality between ET and SCH pregnant women. Thyroid autoimmunity (TAI) is a major risk factor for SCH. Several studies have shown that SCH with TAI increases the risk of miscarriage, preterm birth, and GDM (6, 7). Nevertheless, a previous retrospective study (8) involving 30,015 pregnant women revealed that untreated thyroid autoantibody-negative SCH increased the risk of miscarriage, abnormal blood glucose (GS) tolerance, placenta previa, and placental abnormality. A meta-analysis (9) confirmed that SCH is a risk factor for miscarriage and found that early treatment can reduce the rate of miscarriage. Most studies have found that SCH is associated with adverse pregnancy outcomes; however, the benefit of treatment remains controversial.

The 2017 guidelines of the American Thyroid Association (ATA) (1) strongly recommend LT4 therapy for antithyroid peroxidase antibody (TPOAb)-positive women with TSH concentrations greater than the pregnancy-specific reference range. However, the guidelines of the ATA weakly recommend this therapy for serum TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L. However, there are only several evidences to support this recommendation for TPOAb-negative SCH women. Therefore, the primary goal of this study was to investigate the correlation between thyroid autoantibody-negative SCH with or without LT4 treatment and adverse pregnancy outcomes. Previous studies (10) have also found that SCH is associated with some laboratory indicators of pregnant women, such as blood lipids and homocysteine (Hcy). Therefore, the secondary goal was to explore the association between SCH treatment and laboratory indicators of pregnant women.

Materials and methods

Study population

This cohort study consecutively enrolled 1868 pregnant women in the Department of Gynecology and Obstetrics of Peking University International Hospital from January 2017 to May 2019. The inclusion criteria were as follows: (i) singleton pregnancy, (ii) residency in Beijing for more than 5 years, (iii) 4–8 weeks of gestation as determined using human chorionic gonadotropin (HCG) testing or ultrasonography, and (iv) euthyroidism or SCH (TSH > 4.0 μIU/mL) with thyroid autoantibody negativity in the first trimester of pregnancy. The exclusion criteria were as follows: (i) a history of hypothyroidism and hyperthyroidism, (ii) subclinical hyperthyroidism or hyperthyroidism, (iii) hypothyroidism or other thyroid dysfunction disorders (e.g. hypothyroxinemia and high serum FT4 level) in the first trimester of pregnancy, (iv) hereditary diseases, (v) tumor, (vi) autoimmune disease (e.g. systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, or Sjogren's syndrome), and (vii) treatment with any drug affecting thyroid function (e.g. levothyroxine, methimazole, propylthiouracil, amiodarone, glucocorticoid, interferon, and heparin). Consequently, 1344 pregnant women in their first trimester were included in this study. The participants were followed up until delivery or spontaneous abortion. This study is registered with ClinicalTrials.gov. NCT02966405.

Data collection

All participants completed a medical questionnaire that included questions about a history of thyroid or autoimmune disease, family health history, medication history, and fertility history. The women's last menstrual period, height, weight, and blood pressure and the number of gestational weeks were recorded at their initial visit. Subsequently, BMI was calculated by dividing the weight by the square of height (kg/m^2). The use of LT4 treatment was recorded during pregnancy (from 4 weeks of gestation to delivery). Participants were followed up in the second and third trimesters of their pregnancy until delivery. The mode of birth, delivery weeks, neonatal weight and height, and pregnancy outcomes were recorded.

Blood samples were obtained from each participant in the morning after an overnight fast. The pregnant women were tested for thyroid function in their first, second, and third trimesters of pregnancy. Assays for TSH, FT4, anti-thyroglobulin antibody (TGAb), and TPOAb were performed using automated chemiluminescence immunoassay (COBAS E601, Roche) according to the manufacturer's protocol. TPOAb and TGAb concentrations of >34 IU/mL and >115 IU/mL, respectively, were defined as a positive result, according to the analyzer's manufacturer instructions (Roche). The pregnant women were tested for GS, lipids, and Hcy in the first and third trimesters of their pregnancy. The GS, total cholesterol (TC), triglyceride

(TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and Hcy tests were analyzed using BAKMAN AU5800 auto-analyzer. Glycosylated hemoglobin (HbA1c) tests were analyzed using G8 Hemoglobin A1c instrument.

Patient grouping

A total of 524 pregnant women were excluded, including 23 twin pregnancies, 49 pregnant women with a history of hypothyroidism and hyperthyroidism, 334 pregnant women with TPOAb and/or TGAb positivity, 89 pregnant women with subclinical hyperthyroidism or hyperthyroidism, 9 pregnant women with hypothyroxinemia, and 20 pregnant women with other thyroid dysfunctions. Finally, 1344 pregnant women in their first trimester were included in this study. The patients were divided into the euthyroid (ET) group ($n = 1250$) and the SCH group ($n = 94$). The ET group included pregnant women with TSH concentrations >0.12 mIU/mL and ≤4.0 μIU/mL and normal FT4 levels. The SCH group included women with TSH concentrations >4.0 μIU/mL with normal FT4 levels and thyroid autoantibody negativity in the first trimester of their pregnancy. The women in the SCH group were further divided into the LT4 group ($n = 40$) and the non-LT4 group ($n = 54$) based on whether the women received LT4 treatment in the first trimester of their pregnancy (Fig. 1). LT4 treatment was dependent on regular obstetric examinations and timely detection of SCH by the obstetrician. In the LT4 group, thyroid function was reviewed every 4–6 weeks, and the treatment dose of LT4 was adjusted according to thyroid function.

Definition of pregnancy outcomes

Pregnancy outcomes included GDM, spontaneous abortion, PROM, HDP, preterm delivery, fetal distress, low birth weight, megalomania, and small for gestational age (SGA). Definitions for these adverse pregnancy outcomes are based on previous studies (11).

Sample size calculation

This was a cohort study designed for grouping. There were two groups: the ET and SCH groups. According to previous literature reports (7), the abortion rates of the two groups were 2.2 and 7.1%. Assuming a power value of 0.90 and an α value of 0.05, the sample size of this study was 644 using PASS version 11, and it was hypothesized that the rate of no

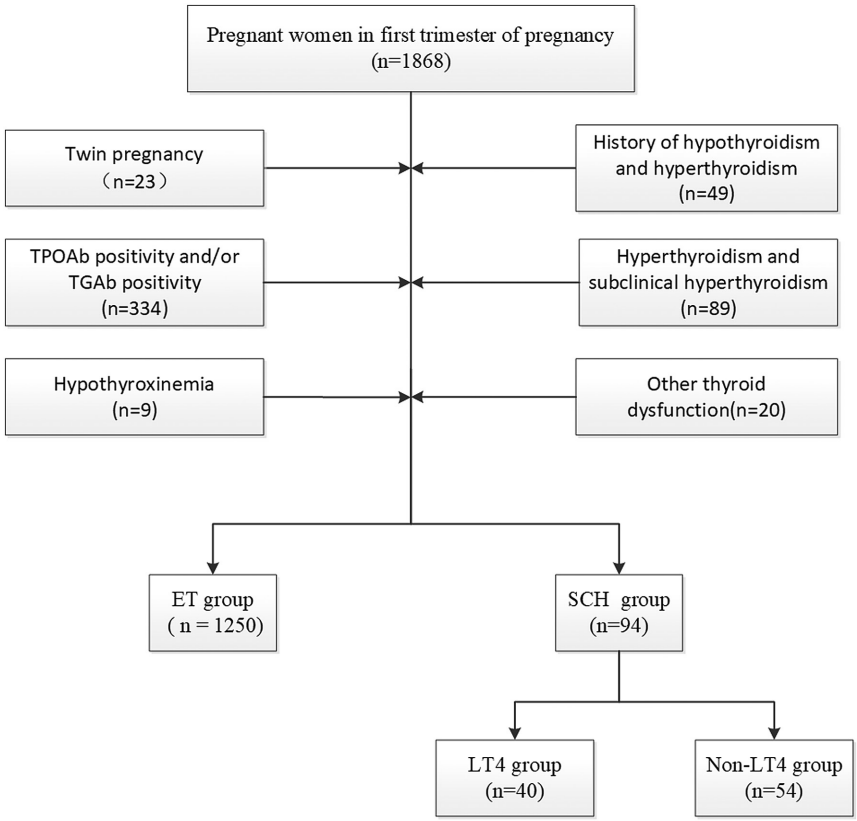

Figure 1
Patient enrollment flowchart. TPOAb, antithyroid peroxidase antibody; TGAb, anti-thyroglobulin antibody; LT4, levothyroxine; ET, euthyroid; SCH, subclinical hypothyroidism.

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response in this study was 10%. Thus, the sample size was 715 ($n = 644/0.9$) patients.

Statistical analyses

We used SPSS version 22.0 (SPSS, IBM) for all statistical analyses. Normally distributed data are expressed as mean and S.D. (x ± S.D.), and non-normally distributed data are expressed as median (interquartile range). Comparisons between groups were made using the ANOVA for normally distributed data and using non-parametric tests for non-normally distributed data. Categorical variables are described as the composition ratio or rate and compared using the chi-squared test or Fisher test. The multivariate logistic regression analysis was performed to assess the association between SCH and adverse pregnancy outcomes and presented as odds ratio (OR) and 95% CIs. All statistical tests were two-sided (test level, $\alpha = 0.05$), and a P value of <0.05 was considered statistically significant.

Ethics and consent

This study was approved by the Ethics Committee of Peking University International Hospital. Written informed consent was obtained from each participant before enrollment into the study and sample collection. The study procedures conformed to the principles of the Declaration of Helsinki.

Results

Clinical and laboratory characteristics of the study participants

The clinical and laboratory characteristics of the study participants are shown in Table 1. Maternal age, BMI, parity, and the history of spontaneous abortion did not differ significantly between the ET group and the different SCH groups. Meanwhile, there were no significant differences in GS, HbA1c, TG, TC, HDL-C, LDL-C, and Hcy levels between ET group and different SCH group in the first and third trimester of pregnancy.

Figures 2 and 3 present the changes in TSH and FT4 levels during pregnancy in the LT4 and non-LT4 SCH groups. In the first trimester of pregnancy, TSH levels in the LT4 group were higher than those in the non-LT4 group (5.804 ± 0.252 vs 4.936 ± 0.217, $P < 0.05$). There was no difference in FT4 level between the two groups. In the second and third trimesters of pregnancy, there was no difference in TSH and FT4 levels between the two groups. In the LT4 group, the TSH level in the first trimester of pregnancy was higher than those in the second and third trimesters of pregnancy (5.804 ± 0.252 μIU/mL vs 3.101 ± 0.266 μIU/mL and 3.364 ± 0.262 μIU/mL, $P < 0.05$). Meanwhile, the FT4 level in the first trimester of pregnancy was higher than those in the second and third trimesters of pregnancy (15.269 ± 0.299 pmol/L vs 13.335 ± 0.315 pmol/L and 12.905 ± 0.310 pmol/L, $P < 0.05$). In the non-LT4 group, TSH and FT4 levels in the first trimester of pregnancy were higher than those in the second and third trimesters of pregnancy (4.936 ± 0.217 μIU/mL vs 3.651 ± 0.235 μIU/mL and 3.493 ± 0.269 μIU/mL, $P < 0.05$; 15.938 ± 0.257 pmol/L vs 13.022 ± 0.278 pmol/L and 13.439 ± 0.319 pmol/L, $P < 0.05$).

The adverse pregnancy outcomes of the ET and SCH groups are demonstrated in Table 2. Significant differences in the rate of PROM were found among the ET and different SCH groups. Meanwhile, the incidence rate of PROM in the non-LT4 group was higher than those in the LT4 group (27.8% vs 7.5%, $\chi^2 = 6.783$, $P < 0.05$). The percentage of spontaneous abortion in the non-LT4 group was higher than those in the ET and LT4 groups. However, there was no significant difference between the ET group and the different SCH groups (7.4% vs 2.6% and 2.5%, $\chi^2 = 3.057$, $P > 0.05$). The incidence rates of GDM in the ET and non-LT4 groups were higher than that in the LT4 group. However, there was no significant difference (19.5% vs 20.4% and 10.0%, $\chi^2 = 2.302$, $P > 0.05$). There were no significant differences in the incidence of HDP, preterm birth, fetal distress, low birth weight, fetal macrosomia, SGA, and birth weight and height between the ET and different SCH groups.

Risk of adverse pregnancy outcomes

The association between SCH and adverse pregnancy outcomes was calculated by logistic regression analysis and is shown in Table 3. After adjusting the confounding factors, such as age, parity, BMI, and the history of spontaneous abortion, the non-LT4 group was a risk factor for spontaneous abortion (OR: 3.141; 95% CI: 1.060–9.302). However, there was no association between the SCH and adverse pregnancy outcomes, including GDM, PROM, HDP, preterm birth, fetal distress, low birth weight, macrosomia, and SGA.

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Table 1 Clinical and laboratory characteristics in the ET groups and SCH group. Data are presented as the median (IQR) or *n* (%) as appropriate.

	ET group (n = 1250)	SCH group		F/χ^2	P
		LT4 group (n = 40)	Non-LT4 group (n = 54)		
Maternal age (years), median (Q25, Q75)	30 (28,33)	30 (28, 33)	30 (28, 34)	0.071	0.965
BMI (kg/m^2), median (Q25, Q75)	21.41 (19.67, 23.49)	21.15 (20.13, 23.50)	21.19 (19.76, 24.64)	0.023	0.989
Parity, *n* (%)					
Primipara	745 (63.0)	24 (60.0)	29 (53.7)	0.753	0.686
Multipara	505 (37.0)	16 (40.0)	25 (46.3)		
History of spontaneous abortion, *n* (%)	160 (12.8)	3 (7.5)	6 (11.1)	1.100	0.577
In the first trimester of pregnancy					
GS (mmol/L), median (Q25,Q75)	4.88 (4.64,5.12)	4.94 (4.73,5.12)	4.90 (4.70,5.15)	1.048	0.592
HbA1c (%), median (Q25,Q75)	5.10 (5.00,5.30)	5.15 (5.00,5.38)	5.10 (4.90,5.30)	1.007	0.604
Hcy (μmol/L), median (Q25,Q75)	6.30 (5.60,7.20)	6.70 (5.73,7.10)	6.70 (5.90,7.30)	2.664	0.264
TC (mmol/L), median (Q25,Q75)	3.89 (3.51,4.32)	3.83 (3.45,4.21)	3.95 (3.57,4.44)	1.592	0.451
TG (mmol/L), median (Q25,Q75)	0.83 (0.64,1.15)	0.93 (0.68,1:08)	0.96 (0.72,1.22)	1.927	0.382
HDL (mmol/L), median (Q25,Q75)	1.40 (1.22,1.58)	1.37 (1.22,1.61)	1.43 (1.23,1.60)	0.179	0.914
LDL (mmol/L), median (Q25,Q75)	2.00 (1.67,2.37)	1.88 (1.67,2.22)	2.04 (1.69,2.47)	2.900	0.235
In the third trimester of pregnancy					
GS (mmol/L), median (Q25,Q75)	4.50 (4.23,4.80)	4.41 (4.10,4.67)	4.52 (4.34,4.80)	2.900	0.235
HbA1c (%), median (Q25,Q75)	5.20 (5.00,5.40)	5.20 (5.00,5.40)	5.15 (4.90,5.40)	0.193	0.908
Hcy (μmol/L), median (Q25,Q75)	5.80 (5.10,6.70)	5.65 (5.03,6.40)	5.50 (5.10,6.68)	0.796	0.672
TC (mmol/L), median (Q25,Q75)	6.16 (5.49,6.91)	5.96 (5.30,6.88)	5.91 (5.33,6.78)	0.535	0.765
TG (mmol/L), median (Q25,Q75)	2.27 (2.33,3.61)	3.15 (2.66,3.80)	3.13 (2.57,3.67)	4.743	0.093
HDL (mmol/L), median (Q25,Q75)	1.76 (1.53,2.01)	1.72 (1.57,1.98)	1.72 (1.54,1.94)	0.078	0.962
LDL (mmol/L), median (Q25,Q75)	3.25 (2.68,3.92)	3.17 (2.53,3.67)	3:03 (2.72,3.72)	1.677	0.432

ET, euthyroid; GS, blood glucose; HbA1c, glycated hemoglobin; Hcy, homocysteine; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG triglyceride, SCH, subclinical hypothyroidism.

Comparison of spontaneous abortion time between the euthyroid and subclinical hypothyroidism groups

Differences between the ET group and different SCH groups in the time of abortion were assessed by survival analysis (log-rank P = 0.042). The spontaneous abortion in SCH group, especially the non-LT4 group, mainly occurred in the first trimester of pregnancy, whereas the spontaneous abortion in the ET group occurred before 20 weeks of gestation (Fig. 4).

Discussion

The correlation between thyroid autoantibody-negative SCH with or without LT4 treatment and adverse pregnancy outcomes remains controversial. The 2017 guidelines of the ATA (1) weakly recommend LT4 therapy for serum TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L. Therefore, the primary goal of this study was to investigate the correlation between thyroid autoantibody-negative SCH with or without LT4 therapy and adverse pregnancy outcomes. In this study, although there was no significant difference in the frequency of spontaneous abortion between the ET and different SCH groups, the percentage of spontaneous abortion in the non-LT4 group was higher than those in the ET and LT4 groups. A logistic regression analysis showed that the non-LT4 group was a risk factor for spontaneous abortion (OR: 3.141; 95% CI: 1.060–9.302) after adjusting age, parity, BMI, and the history of spontaneous abortion. In the present study, autoantibody-negative SCH seems to be associated with increased risk of spontaneous abortions during the first trimester of pregnancy. This finding is consistent with the findings of many previous studies. A meta-analysis (9) reviewed 225 cohort studies from January 1980 to December 2015 and showed that miscarriage was significantly more common in patients with SCH than in women with ET and that the risk of miscarriage was significantly increased in patients without intervention. A separate systematic analysis (12) found that compared with women with ET, pregnant women with SCH were at a higher risk for pregnancy loss. A nested case-control study (13) showed that higher TSH was associated with miscarriage in early pregnancy. The rate of spontaneous abortion was increased by 78% for every unit

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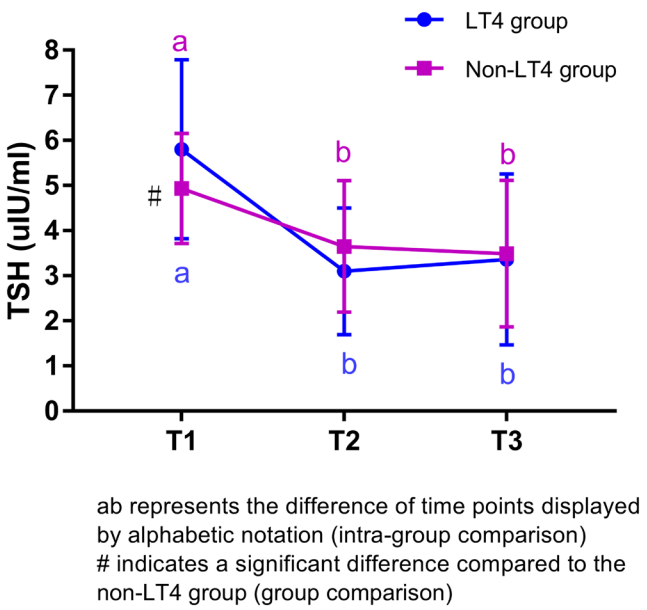

Figure 2
Changes of TSH during pregnancy in the LT4 and non-LT4 SCH groups. TSH, thyroid-stimulating hormone; LT4, levothyroxine; SCH, subclinical hypothyroidism.

increase in SD of TSH concentration (14). This study and previous studies suggested that SCH was associated with spontaneous abortion. Previous studies have found that SCH is not associated with adverse pregnancy outcomes. A study in Japan (15) showed that elevated TSH level was not associated with spontaneous abortion. One study (16) comprising 10,990 pregnant women showed that SCH was not associated with adverse outcomes. The association

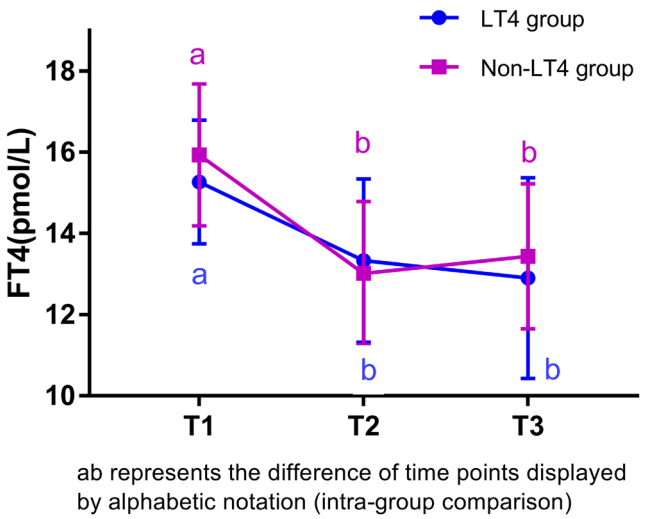

Figure 3
Changes of FT4 during pregnancy in the LT4 and non-LT4 SCH groups. FT4, free thyroxine; LT4, levothyroxine.

between SCH and spontaneous abortion has been reported; however, the conclusions remain controversial. Inter-study differences may be caused by different cutoffs to define an elevated TSH concentration, sample size, iodine nutrition level, or varying thyroid risk factors. A meta-analysis (17) involving 685 articles worldwide from 2005 to 2018 showed that the prevalence of SCH ranged from 1.50 to 42.90%, depending on the diagnostic criteria of SCH. The diagnostic criteria for SCH in pregnancy have changed according to the different guidelines over time. The 2017 ATA guidelines (1) recommend that the population-based trimester-specific reference ranges for serum TSH should be defined. If pregnancy-specific TSH reference ranges are not available, an upper reference limit of 4.0 mU/L may be used (1). Therefore, 4.0 mU/L was used as the lower limit of the TSH reference value for diagnostic SCH in this study. With a TSH cutoff of above 4.0 mIU/L, the prevalence of SCH in pregnant women is estimated to range from 1.50 to 19.60% (17).

The 2017 ATA (1) guidelines strongly recommend LT4 therapy for TPOAb-positive women with SCH; however, these guidelines weakly recommend LT4 therapy for serum TPOAb-negative women with SCH. The main participants of this study were women with SCH with negative thyroid autoantibodies. Few studies have focused on thyroid autoantibody-negative SCH and adverse pregnancy outcomes. A study involving SCH with negative thyroid autoantibodies showed that receiving LT4 therapy reduced the risk of preterm birth (18). This study found an increased risk of spontaneous abortion in the non-LT4 SCH group but not in the LT4 SCH group. LT4 therapy in autoantibody-negative SCH might be beneficial to reduce adverse pregnancy outcomes. This is consistent with the results of previous studies. A meta-analysis about miscarriage and SCH found that the risk of miscarriage was significantly increased in patients without intervention (9). A prospective population-based cohort study (14) showed that the rate of miscarriages in the treated group by LT4 was lower than in the untreated group.

Different from previous studies, the time of spontaneous abortion was also analyzed in this study. Survival analysis showed that the spontaneous abortion in SCH, especially the non-LT4 group, mainly occurred in the first trimester of pregnancy, whereas the spontaneous abortion in the ET group occurred before 20 weeks of gestation. It may be important to receive LT4 treatment for SCH with thyroid autoantibody negativity in the first trimester of pregnancy. This finding is consistent with the results of previous studies. A study (19) about initiation

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Table 2 Adverse pregnancy outcomes between the ET group and SCH groups. Data are presented as *n* (%). In pairwise comparison, the variance is homogeneous and continuous variables are corrected by SNK method. Classification variables can be corrected by Bonferroni method for *P* value.

		SCH group			
	ET group (n = 1250)	LT4 group (n = 40)	Non-LT4 group (n = 54)	F/χ^2	*P*
GDM (%)	244 (19.5)	4 (10.0)	11 (20.4)	2.302	0.316
Spontaneous abortion (%)	33 (2.6)	1 (2.5)	4 (7.4)	3.057	0.217
PROM (%)	216 (17.3)	3 (7.5)	15 (27.8)[a]	6.783	0.034[b]
HDP(%)	31 (2.5)	2 (5.0)	2 (3.7)	1.239	0.538
Preterm birth (%)	57 (4.6)	1 (2.5)	5 (8.9)	2.359	0.307
Fetal distress (%)	80 (6.4)	2 (5.0)	3 (5.6)	0.195	0.907
Low birth weight (%)	22 (1.8)	1 (2.5)	1 (1.9)	0.110	0.941
Fetal macrosomia (%)	73 (5.8)	2 (5.0)	NA	0.050	0.823
SGA (%)	19 (1.52)	NA	NA		
Infant					
Birthweight (kg) median (Q25, Q75)	3.35 (3.07, 3.59)	3.42 (3.14, 3.68)	3.32 (3.04, 3.70)	0.846	0.655
Height (cm) median (Q25, Q75)	50 (49, 51)	50 (49, 51)	50 (49, 51)	0.059	0.971

[a]$P < 0.05$ vs the LT4 group; [b]$P < 0.05$.
ET, euthyroid; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; LT4, levothyroxine; PROM, premature rupture of membranes; SCH, subclinical hypothyroidism.

timing effect of LT4 treatment on SCH showed that LT4 administered in the first trimester was associated with decreased risk of adverse obstetric event.

Although the guidelines (1) recommend treatment for pregnant women with SCH with thyroid autoantibody negativity, there are still some untreated women in real-

Table 3 Logistic regression analysis.

	Unadjusted			Adjusted[a]		
	OR	95% CI	*P*	OR	95% CI	*P*
GDM						
LT4 group	0.458	0.162–1.299	0.142	0.615	0.201–1.882	0.395
Non-LT4 group	1.055	0.536–2.075	0.877	0.869	0.342–2.212	0.769
Spontaneous abortion						
LT4 group	0.946	0.126–7.092	0.957	1.004	0.132–7.616	0.997
Non-LT4 group	4.541	1.006–8.649	0.049	3.141	1.060–9.302	0.039
PROM						
LT4 group	0.388	0.118–1.272	0.118	0.537	0.159–1.814	0.317
Non-LT4 group	0.828	0.385–1.782	0.629	1.004	0.405–2.491	0.993
HDP						
LT4 group	2.084	0.481–9.034	0.327	1.240	0.158–9.727	0.838
Non-LT4 group	1.512	0.352–6.491	0.578	1.185	0.154–9.123	0.870
Preterm birth						
LT4 group	0.537	0.072–3.976	0.542	0.757	0.100–5.700	0.787
Non-LT4 group	1.231	0.373–4.065	0.733	1.317	0.305–5.677	0.712
Fetal distress						
LT4 group	0.771	0.183–3.257	0.771	1.238	0.285–5.378	0.776
Non-LT4 group	0.856	0.261–2.804	0.797	1.578	0.465–5.354	0.465
Low birth weight						
LT4 group	1.430	0.188–10.880	0.730	1.473	0.192–11.291	0.709
Non-LT4 group	1.052	0.139–7.955	0.961	1.093	0.144–8.311	0.931
Fetal macrosomia						
LT4 group	0.849	0.201–3.587	0.823	1.135	0.257–5.010	0.868
Non-LT4 group		NA			NA	
SGA						
LT4 group		NA			NA	
Non-LT4 group		NA			NA	

[a]Adjusted for age, parity, and the history of spontaneous abortion.
GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; OR, odds ratio; PROM, premature rupture of membranes.

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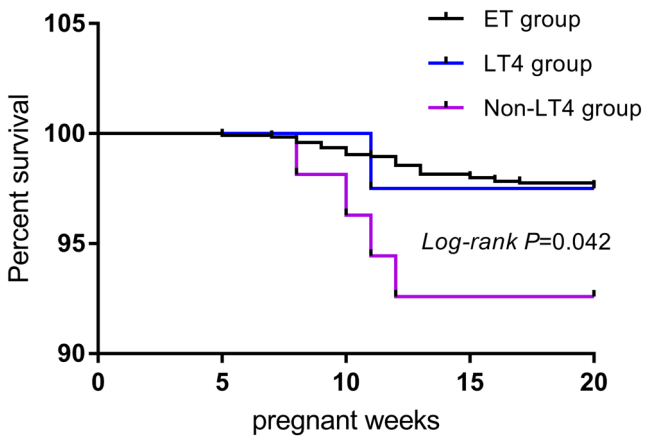

Figure 4
Comparison of spontaneous abortion time between ET group and SCH group. ET, euthyroid; SCH, subclinical hypothyroidism.

world clinical settings. The possible reasons are as follows. First, negative thyroid autoantibodies combined with slightly elevated TSH level in pregnant women failed to attract the attention of physicians and patients. Secondly, in the first trimester of pregnancy, pregnant women completed the detection of thyroid function and thyroid autoantibodies; however, SCH was not diagnosed until the next obstetric examination. Finally, screening for thyroid function is not emphasized in pregnant women with no history of thyroid disease.

Most studies have suggested that SCH is associated with spontaneous abortion. However, the mechanism and etiology of spontaneous abortion remain heterogeneous and unclear.

Thyroid hormones may influence trophoblast invasion. A previous study (20) suggested that epidermal growth factor (EGF) and T3 may act synergistically to regulate both proliferation and differentiated function of the human trophoblast. Thyroid hormones are directly involved in endometrial physiology (21). Thyroid hormones can regulate dendritic cell maturation and function to affect implantation and placentation (22). The α subunit of HCG is similar to that of TSH. A decrease in HCG level may lead to spontaneous abortion. More studies are required to investigate the mechanisms underlying the association between SCH and spontaneous abortion.

In this study, there were no significant differences in the incidence of GDM, PROM, HDP, preterm birth, fetal distress, low birth weight, fetal macrosomia, and SGA between the ET and SCH groups. The association between SCH and adverse pregnancy is inconsistent. A retrospective cohort study (5) showed that SCH only increases the risk of gestational hypertension but does not increase the incidence of GDM, intrahepatic cholestasis in pregnancy, PROM, fetal growth restriction, and preterm delivery. A retrospective study (8) revealed that thyroid autoantibody-negative SCH increased the risk of miscarriage, abnormal GS tolerance, HDP, and placenta previa. A meta-analysis (23) involving SCH and GDM showed that SCH with positive antithyroid autoantibodies in pregnancy is associated with an increased risk of GDM. A cohort study (24) showed that pregnant women with SCH had increased risks of gestational hypertension and PROM. However, there was no significant difference between GDM and SCH. Above all, the association between SCH and adverse pregnancy outcomes varied in population, region, race, age, and other factors. Therefore, it is necessary to explore the influence of SCH and adverse pregnancy outcomes.

In this study, the correlation between SCH and lipid profile was analyzed. However, there was no correlation between SCH with/without LT4 treatment and lipid profile. Previous studies have found that SCH affects the terms of lipid metabolism in pregnant women. However, current studies are limited, and the correlation between lipid metabolism disorders and the pathogenesis of SCH pregnancy women remains unclear. Li *et al.* (25) found that 143 lipid molecules were expressed differently between the SCH and control groups. A study (26) about fatty acids and SCH showed that there was a correlation between serum fatty acid composition and pregnant Chinese women with SCH during the second and third trimesters of pregnancy. This abnormality may be different from the inclusion criteria of pregnant women with SCH and the indexes of lipid profile. Except for this, in this study, no significant correlation was found between SCH with/without LT4 treatment and Hcy level. However, a meta-analysis (27) showed that patients with SCH aged between 18 and 65 years were associated with a slightly increased Hcy level compared with ET controls. A study conducted on pregnant women (10) found that the Hcy levels in the SCH group were markedly higher than those in the ET group. The correlation between SCH and Hcy level in this study is different from those of previous studies, which may be related to the possible influence of various factors on Hcy during pregnancy. More studies are required to further explore the effects of SCH on lipid metabolism and Hcy.

This study has certain limitations. First, this study was a single-center study and involved only a few pregnant women with SCH. This may limit the generalization of this study. Secondly, spontaneous abortions in the first trimester may be omitted because the inclusion criteria are pregnant women at 4–8 weeks of gestation. However, in Beijing, China, pregnant women are routinely examined

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during the first 4–6 weeks of gestation. Thirdly, this study performed a subgroup analysis based on whether or not LT4 replacement therapy was performed in early pregnancy, ignoring the effect of LT4 therapy on pregnancy outcomes in the second and third trimesters of pregnancy.

Conclusion

Thyroid autoantibody-negative SCH seems to be associated with an increased risk of spontaneous abortions during the first trimester of pregnancy. LT4 therapy in this patient population might be beneficial to reduce adverse pregnancy outcomes.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethics approval and consent to participate
This study was approved by the Ethics Committee of Peking University International Hospital [2017-021(BMR)].

Author contribution statement
X M Z and N Y conceived and designed research and wrote the manuscript. X M Z, N Y, and J B S recruited the patients and collected the samples. J B S, D J, N M, X Z, and Q L Z contributed to data acquisition. X M Z and N Y collected, and analyzed data, and revised the manuscript. All authors read and approved the final manuscript.

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