

# Effects of Levothyroxine Therapy on Pregnancy and Neonatal Outcomes in Subclinical Hypothyroidism

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**Purpose:** To assess the effects of levothyroxine (LT4) therapy on pregnancy and neonatal outcomes in pregnant women with subclinical hypothyroidism (SCH) who had different thyroid peroxidase antibody (TPOAb) status.

**Methods:** The data of pregnant women from the Chengdu Hospital of Integrated Traditional Chinese and Western Medicine between January 2017 and August 2019 were collected. SCH was defined as  $11.88 < \text{free thyroxine (FT4)} < 20.06 \mu\text{mol/L}$  in conjunction with thyroid-stimulating hormone (TSH)  $> 4.00 \text{ mU/L}$ . Some clinical characteristics have been collected, including body mass index (BMI) before pregnancy, number of pregnancies, number of miscarriages (spontaneous abortion), parity, family history of diabetes, history of smoking, history of drinking, TSH, FT4, and TPOAb levels. The prevalence of pregnancy and neonatal outcomes in the LT4 and non-LT4 groups, and in the LT4 and euthyroid control groups were compared, respectively. Univariate and multivariate logistic regression analyses were used to assess the effects of LT4 therapy on pregnancy and neonatal outcomes in SCH pregnant women with TPOAb.

**Results:** A total of 985 subjects were enrolled and divided into LT4 group with 478 patients, non-LT4 group with 156 patients and euthyroid control group with 351 patients. The prevalence of amniotic fluid abnormalities and premature delivery in the LT4 group was lower than that in the non-LT4 group in participants with TPOAb-positive (TPOAb<sup>+</sup>). After adjusting age, BMI prior to pregnancy, number of pregnancies, number of miscarriages, parity, TSH and FT4 level, the SCH pregnant women with TPOAb<sup>+</sup> in the LT4 group had a lower risk of amniotic fluid abnormalities and premature delivery than that in the non-LT4 group.

**Conclusion:** LT4 therapy could reduce the risk of premature delivery and amniotic fluid abnormalities in the SCH pregnant women with TPOAb<sup>+</sup>. However, more randomized trials are required to confirm this association before the unequivocal advocacy of LT4 therapy in pregnant women with SCH.

**Keywords:** levothyroxine, subclinical hypothyroidism, pregnant women, pregnancy and neonatal outcomes

## Introduction

Subclinical hypothyroidism (SCH) is a biochemical disturbance in thyroid function, defined as a free thyroxine (FT4) level within the normal range and thyroid-stimulating hormone (TSH) level above the upper limit of the reference range.<sup>1,2</sup> It has been reported that gestational SCH is approximately 0.5% to 0.6% in China.<sup>3</sup> SCH in pregnancy is related to a higher risk of poor pregnancy outcomes, such as abortion and premature delivery.<sup>4,5</sup> Thyroid dysfunction was reported to be caused by thyroid peroxidase antibody (TPOAb), which might increase the risk of SCH during pregnancy.<sup>6</sup> According to the 2017 American Thyroid Association Guidelines for the Diagnosis and Management of Thyroid Disorders during pregnancy and postpartum, up to 18% of pregnant women were positive for thyroid peroxidase antibody (TPOAb).<sup>7</sup> Several studies suggested that the presence of TPOAb-positive (TPOAb<sup>+</sup>) was linked to adverse maternal and fetal outcomes in pregnancy, such as premature delivery, placental abruption, and miscarriage.<sup>7-10</sup> In the study of Pradhan M et al,<sup>11</sup> they pointed out that the

presence of TPOAb+ in pregnant women with hypothyroidism was associated with gestational diabetes, preterm delivery, malformation, intrauterine growth restriction and low apgar and neonatal intensive care unit admission. It cannot be ignored to focus on the prognosis of SCH pregnant women with TPOAb+.

Adequate thyroid hormone (TH) level is one of the critical factors for fetal growth,<sup>12–14</sup> especially during the first trimester.<sup>15,16</sup> Currently, levothyroxine (LT4) is a common non-surgical treatment for SCH. An RCT meta-analysis has found that LT4 therapy could affect pregnancy complications and neonatal outcomes in SCH patients.<sup>17</sup> The study conducted by Spyridoula Maraka et al has revealed that receiving LT4 therapy can decrease the number of neonates with a five-minute Apgar score  $\leq 7$  and low birth weight offspring.<sup>18</sup> However, another study indicated that TSH level and LT4 treatment were not associated with pregnancy outcomes.<sup>19</sup> Although there are clear clinical guidelines for pregnant women with significant hypothyroidism,<sup>7</sup> endocrinologists have not reached consensus on whether to treat SCH of TPOAb, and data on the benefits of treatment in these women are inconclusive. Herein, this study was mainly designed to assess the effects of LT4 therapy on pregnancy and neonatal outcomes in SCH pregnant women with TPOAb, based on the baseline characteristics, pregnancy complications, and neonatal outcomes.

## Methods

### Study Population

The data of 1008 pregnant women from the Chengdu Hospital of Integrated Traditional Chinese and Western Medicine between January 2017 and August 2019 were collected. SCH was defined as  $11.88 < \text{free thyroxine (FT4)} < 20.06 \mu\text{mol/L}$  in conjunction with  $\text{TSH} > 4.00 \text{ mU/L}$ .<sup>7</sup> TPOAb was measured using an E-Anti-TPO kit (Beckman Diagnostics), and TPOAb+ was defined as TPOAb levels above 9 IU/mL. Participants were divided into three groups: LT4, non-LT4, and euthyroid control groups. The LT4 group referred to the SCH patients with LT4 therapy; the non-LT4 group was the SCH patients without LT4 therapy; the euthyroid control group was the normal thyroid function participants. This study was approved by the Ethics Committee of Chengdu Integrated TCM & Western Medicine Hospital (Ref. No.2021-WZ-002.). For these patients who accepting treatment with levothyroxine, verbal informed consent has been obtained. This study was in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows: (1) age  $\geq 18$  years; (2) singleton gestation; (3) subjects with complete demographics clinical data; (3) patients who had conceived naturally without assisted reproductive technology; and (4) patients without autoimmune diseases or polycystic ovarian syndrome.

The exclusion criteria were as follows: (1) individuals who had taken drugs that affect thyroid function, including TH preparations, amiodarone, propylthiouracil, or methimazole; (2) subjects with obvious hypothyroidism or hyperthyroidism; (3) patients with previous thyroid diseases; (4) patients having pre-existing diabetes or hypertension before pregnancy; (5) subjects who had taken any drugs within one month before the study or participated in another drug clinical trial; and (6) patient who was judged unsuitable for this clinical trial participation by the physician in charge.

### LT4 Therapy

Subjects were given LT4 (Euthyrox, 50  $\mu\text{g}$ /tablet), with an initial dose ranging from 25 to 50  $\mu\text{g}$  according to gestational weeks and TSH level. It was administered as 1 tablet once a day orally in the morning or empty stomach from the first trimester until delivery. TSH and FT4 were measured every 14 days, and dose adjustments were conducted according to the changes of TSH, FT4 levels, and gestational weeks, with each adjusted at a dose range of 25–50  $\mu\text{g}$ . After the TSH level was recovered ( $0.1 \text{ mU/L} < \text{TSH} < 2.5 \text{ mU/L}$ ), the levels of TSH and FT4 were measured every 4 weeks.

### Data Collection

Baseline data were collected, including age, body mass index (BMI) before pregnancy, number of pregnancies, number of miscarriages, parity (the sum of the number of term births and the number of preterm delivery), family history of diabetes, history of smoking, history of alcohol intake, TSH level, FT4 level and TPOAb level.

Pregnancy outcomes were recorded, including gestational diabetes, gestational hypertension, placenta previa, pre-eclampsia, intrahepatic cholestasis of pregnancy, premature rupture of membranes, chorioamnionitis, pelvic inflammatory

disease, preterm delivery, amniotic fluid abnormalities, miscarriage (spontaneous abortion), and postpartum hemorrhage. Adverse pregnancy outcome was defined as the occurrence of any of the above pregnancy outcomes.

Neonatal outcomes were monitored, such as low birth weight, intrauterine growth restriction, macrosomia, neonatal asphyxia, neonatal respiratory distress syndrome, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, and admitted to intensive care unit (ICU). Adverse neonatal outcome was defined as the occurrence of any of the above neonatal outcomes.

## Statistical Analysis

All statistical analyses were performed by SAS 9.4 (SAS Institute, Cary, NC, USA). The continuous variable was represented by the mean  $\pm$  standard deviation (Mean  $\pm$  SD) or the median with interquartile spacing [M (Q<sub>1</sub>, Q<sub>3</sub>)], and the analysis of variance was applied for intergroup comparison. Categorical variables were described by the number of cases (constituent ratio) [n (%)], and  $\chi^2$  test or Fisher's exact test was adopted for intergroup comparison. Two-tailed tests were utilized for all analyses, and  $P < 0.05$  was considered statistically significant.

We summarized the prevalence of pregnancy and neonatal outcomes in the LT4 and non-LT4 groups, and in the LT4 and euthyroid control groups. Univariate and multivariate logistic regression analyses were used to assess the effects of LT4 therapy on pregnancy and neonatal outcomes in SCH pregnant women with TPOAb. Three regression models were carried out in this study. Model 1 was unadjusted; model 2 was adjusted for age and BMI prior to pregnancy; model 3 was adjusted for age, BMI prior to pregnancy, number of pregnancies, number of miscarriages, parity, TSH level and FT4 level.

## Results

### Baseline Data

In this study, after excluding 23 patients without TPOAb information, a total of 985 subjects were enrolled eventually with LT4 group 478 (48.53%) patients, non-LT4 group 156 (15.84%) patients, and the euthyroid control group 351 patients (35.63%). The study participants' average age was  $29.06 \pm 3.67$  years for the women in the LT4 group, with  $28.51 \pm 3.63$  and  $28.62 \pm 3.90$  years in the non-LT4 group and the euthyroid control group, respectively. The mean BMI prior to the pregnancy in the LT4 group was  $21.19 \text{ kg/m}^2$ , with  $20.88 \text{ kg/m}^2$  in the non-LT4 group and  $21.10 \text{ kg/m}^2$  in the euthyroid control group. The mean TSH levels in the LT4 group, non-LT4 group, and euthyroid control group were 5.15 mU/L, 4.44 mU/L, and 1.71 mU/L. The TPOAb<sup>+</sup> rate of the LT4 group was 38.91%, with 7.69% in the non-LT4 group and 9.12% in the euthyroid control group. The results of the baseline data of study participants are shown in Table 1.

**Table 1** The Baseline Data of Study Participants

Variables	Total (n=985)	LT4 Therapy Group (n=478)	Non-LT4 Therapy Group (n=156)	Euthyroid Control Group (n=351)
Age, Mean $\pm$ SD	28.82 $\pm$ 3.75	29.06 $\pm$ 3.67	28.51 $\pm$ 3.63	28.62 $\pm$ 3.90
BMI before pregnancy, kg/m <sup>2</sup> , Mean $\pm$ SD	21.11 $\pm$ 2.90	21.19 $\pm$ 2.96	20.88 $\pm$ 2.40	21.10 $\pm$ 3.01
Number of pregnancies, M (Q <sub>1</sub> , Q <sub>3</sub> )	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Number of miscarriages, M (Q <sub>1</sub> , Q <sub>3</sub> )	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Parity*, M (Q <sub>1</sub> , Q <sub>3</sub> )	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Family history of diabetes, yes, n (%)	12 (1.22)	7 (1.46)	3 (1.92)	2 (0.57)
History of smoking, yes, n (%)	3 (0.30)	2 (0.42)	1 (0.64)	0 (0.00)
History of drinking, yes, n (%)	2 (0.20)	2 (0.42)	0 (0.00)	0 (0.00)
TSH, M (Q <sub>1</sub> , Q <sub>3</sub> )	4.29 (2.16, 5.21)	5.15 (4.46, 6.14)	4.44 (4.19, 4.81)	1.71 (1.10, 2.33)
FT4, Mean $\pm$ SD	15.41 $\pm$ 1.62	15.09 $\pm$ 1.61	15.23 $\pm$ 1.70	15.92 $\pm$ 1.46
TPOAb <sup>+</sup> , n (%)	230 (23.35)	186 (38.91)	12 (7.69)	32 (9.12)

**Note:** \*Parity was defined as the sum of the number of term births and the number of preterm delivery.

**Abbreviations:** LT4, levothyroxine; BMI, body mass index; TSH, thyroid-stimulating hormone; FT4, free thyroxine; TPOAb<sup>+</sup>, thyroid peroxidase antibody-positive; Mean  $\pm$  SD, mean  $\pm$  standard deviation; M (Q<sub>1</sub>, Q<sub>3</sub>), median with interquartile spacing; n (%), number of cases (constituent ratio).

## Prevalence of Pregnancy and Neonatal Outcomes

### LT4 Group vs Non-LT4 Group

The pregnancy and neonatal outcomes of the LT4 and non-LT4 groups are shown in Table 2. For the study participants with TPOAb<sup>+</sup>, the prevalence of amniotic fluid abnormalities and premature delivery in the LT4 group was lower than that in the non-LT4 group (5.38% vs 25.00%,  $P < 0.05$ ; 5.38% vs 25.00%,  $P < 0.05$ ).

### LT4 Group vs Euthyroid Control Group

The prevalence of chorioamnionitis in the LT4 group was higher than that in the euthyroid control group (13.84% vs 9.14%,  $P < 0.05$ ). The pregnancy and neonatal outcomes of the LT4 and euthyroid control group are shown in Table 3.

## Effects on Pregnancy and Neonatal Outcomes of LT4 Therapy in the Pregnant Women with SCH

### Amniotic Fluid Abnormalities

The effects on amniotic fluid abnormalities of LT4 therapy in SCH pregnant women with TPOAb<sup>+</sup> are presented in Figure 1. The three models conducted in this study showed that, the SCH pregnant women with TPOAb<sup>+</sup> in the LT4 group had a lower risk of amniotic fluid abnormalities than that in the non-LT4 group (model 1: OR = 0.214, 95% CI: 0.059–0.782,  $P < 0.05$ ; model 2: OR = 0.212, 95% CI: 0.058–0.780,  $P < 0.05$ ; model 3: OR = 0.176, 95% CI: 0.045–0.683,  $P < 0.05$ ). Additionally, the three models showed no difference between the LT4 and euthyroid control group ( $P > 0.05$ ). All the results indicated that LT4 therapy could reduce the risk of amniotic fluid abnormalities in SCH pregnant women with TPOAb<sup>+</sup>.

### Premature Delivery

The effects on premature delivery of LT4 therapy in SCH pregnant women with TPOAb<sup>+</sup> are presented in Figure 2. For patients with TPOAb<sup>+</sup>, model 1 showed that the risk of premature delivery in the LT4 group was decreased in comparison with the non-LT4 group (OR = 0.170, 95% CI: 0.040–0.729,  $P < 0.05$ ), with similar results in model 2 (OR = 0.178, 95% CI: 0.041–0.775,  $P < 0.05$ ) and model 3 (OR = 0.172, 95% CI: 0.036–0.829,  $P < 0.05$ ). The results also displayed that LT4 therapy might be associated with a reduced risk of premature delivery in SCH pregnant women with TPOAb<sup>+</sup>.

### Chorioamnionitis

The effects on chorioamnionitis of LT4 therapy in pregnant women with SCH are presented in Figure 3. Model 1 showed that the risk of chorioamnionitis in the LT4 group was 1.596-fold than that in the euthyroid control group (OR = 1.596, 95% CI: 1.021–2.495,  $P < 0.05$ ), with a similar result in model 2 (OR = 1.596, 95% CI: 1.020–2.498,  $P < 0.05$ ). However, after adjusting age, BMI before pregnancy, number of pregnancies, number of miscarriages (spontaneous abortion), parity, TSH level and FT4 level, model 3 demonstrated that there was no difference between the LT4 and euthyroid control groups (OR = 1.690, 95% CI: 0.959–2.977,  $P > 0.05$ ).

## Discussion

SCH is recognized as mild thyroid dysfunctions, reflecting a relatively lower thyroid functional capacity. For pregnant women with SCH, there is an apparent imbalance in the supply and demand for TH, especially in the early of pregnancy,<sup>20</sup> which has been demonstrated to be associated with increased risk of pregnancy outcomes, such as placental abruption, miscarriage, and preterm birth.<sup>7,21</sup> LT4 therapy might be clinically significant for pregnant women with SCH during the first trimester. In the study, we investigated the effects of LT4 on pregnancy and neonatal outcomes in pregnant women with SCH. The results showed that LT4 therapy was associated with a lower risk of premature delivery and amniotic fluid abnormalities in the SCH pregnant women with TPOAb<sup>+</sup>. It was indicated that SCH pregnant women with TPOAb<sup>+</sup> could benefit from the LT4 therapy.

In this research, LT4 therapy was related to a lower risk of premature delivery and amniotic fluid abnormalities in SCH pregnant women with TPOAb<sup>+</sup>. The associations between LT4 and premature delivery or amniotic fluid

**Table 2** The Pregnancy and Neonatal Outcomes Between the LT4 and Non-LT4 Therapy Groups

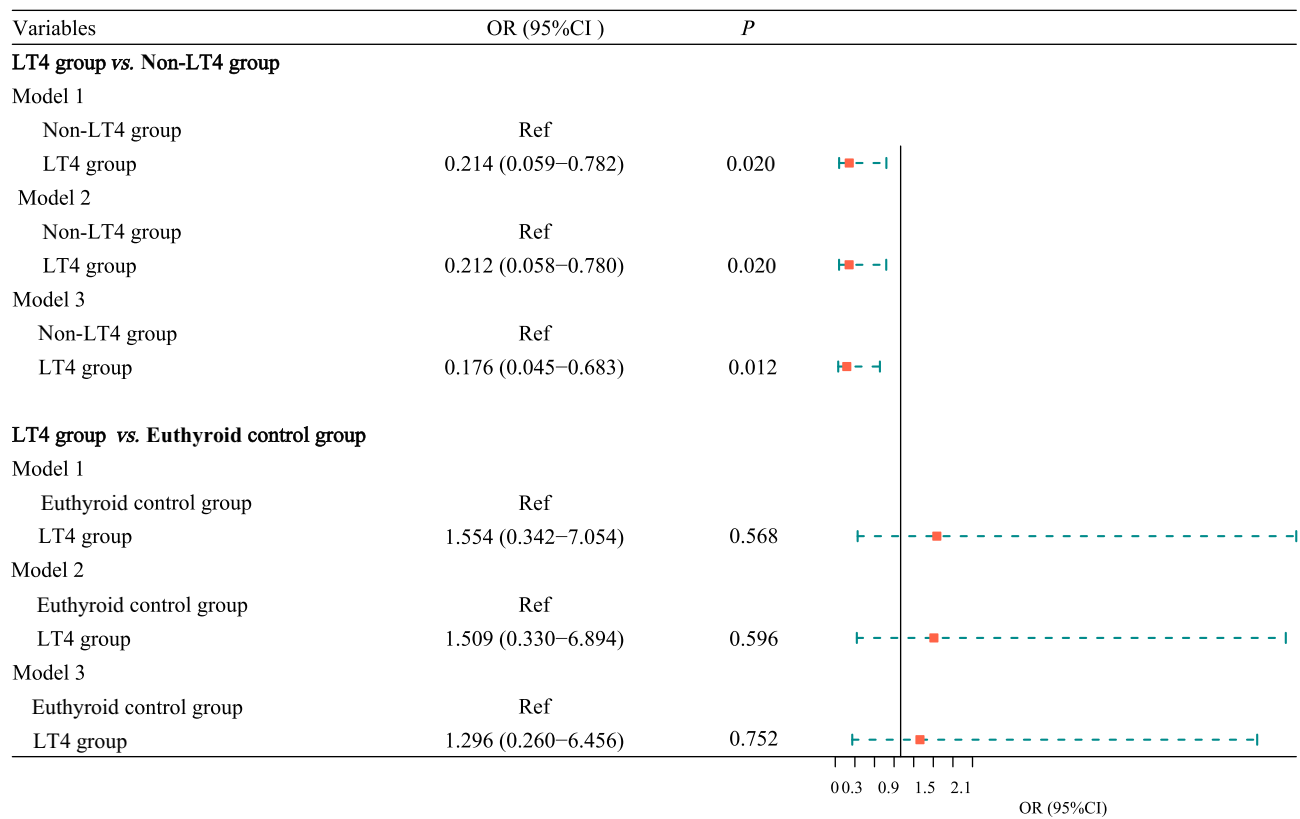
Variables	TPOAb <sup>-</sup> /TPOAb <sup>+</sup>			$\chi^2$	p	TPOAb <sup>-</sup>			$\chi^2$	p	TPOAb <sup>+</sup>			p
	Total	LT4 Therapy Group	Non-LT4 Therapy Group			Total	LT4 Therapy Group	Non-LT4 Therapy Group			Total	LT4 Therapy Group	Non-LT4 Therapy Group	
<b>Pregnancy outcomes</b>														
Gestational diabetes, n (%)	133 (21.04)	95 (19.92)	38 (24.52)	1.490	0.222	90 (20.74)	56 (19.24)	34 (23.78)	1.198	0.274	43 (21.72)	39 (20.97)	4 (33.33)	0.296
Gestational hypertension, n (%)	11 (1.74)	8 (1.68)	3 (1.94)	-	0.736	6 (1.38)	3 (1.03)	3 (2.10)	-	0.401	5 (2.53)	5 (2.69)	0 (0.00)	1.000
Placenta previa, n (%)	7 (1.11)	6 (1.26)	1 (0.65)	-	1.000	3 (0.69)	2 (0.69)	1 (0.70)	-	1.000	4 (2.02)	4 (2.15)	0 (0.00)	1.000
Preeclampsia, n (%)	8 (1.27)	5 (1.05)	3 (1.94)	-	0.413	6 (1.38)	3 (1.03)	3 (2.10)	-	0.401	2 (1.01)	2 (1.08)	0 (0.00)	1.000
Intrahepatic cholestasis of pregnancy, n (%)	49 (7.75)	32 (6.71)	17 (10.97)	2.967	0.085	37 (8.53)	22 (7.56)	15 (10.49)	1.055	0.304	12 (6.06)	10 (5.38)	2 (16.67)	0.158
Premature rupture of membranes, n (%)	129 (20.41)	93 (19.50)	36 (23.23)	1.001	0.317	86 (19.82)	55 (18.90)	31 (21.68)	0.466	0.495	43 (21.72)	38 (20.43)	5 (41.67)	0.139
Chorioamnionitis, n (%)	91 (14.40)	66 (13.84)	25 (16.13)	0.499	0.480	57 (13.13)	34 (11.68)	23 (16.08)	1.627	0.202	34 (17.17)	32 (17.20)	2 (16.67)	1.000
Pelvic inflammatory disease, n (%)	21 (3.32)	16 (3.35)	5 (3.23)	0.006	0.938	17 (3.92)	12 (4.12)	5 (3.50)	0.100	0.752	4 (2.02)	4 (2.15)	0 (0.00)	1.000
Amniotic fluid abnormalities, n (%)	71 (11.23)	54 (11.32)	17 (10.97)	0.015	0.904	49 (11.29)	36 (12.37)	13 (9.09)	1.030	0.310	22 (11.11)	18 (9.68)	4 (33.33)	0.031
Preterm delivery, n (%)	28 (4.43)	19 (3.98)	9 (5.81)	0.918	0.338	15 (3.46)	9 (3.09)	6 (4.20)	-	0.582	13 (6.57)	10 (5.38)	3 (25.00)	0.035
Miscarriage (spontaneous abortion), n (%)	2 (0.32)	1 (0.21)	1 (0.64)	-	0.432	2 (0.46)	1 (0.34)	1 (0.69)	-	0.552	0 (0.00)	0 (0.00)	0 (0.00)	-
Postpartum hemorrhage, n (%)	72 (11.36)	53 (11.09)	19 (12.18)	0.139	0.709	46 (10.55)	28 (9.59)	18 (12.50)	0.866	0.352	26 (13.13)	25 (13.44)	1 (8.33)	1.000
<b>Neonatal outcomes</b>														
Low birth weight, n (%)	23 (3.63)	16 (3.35)	7 (4.49)	0.437	0.509	17 (3.90)	11 (3.77)	6 (4.17)	0.041	0.839	6 (3.03)	5 (2.69)	1 (8.33)	0.316
Macrosomia, n (%)	32 (5.05)	23 (4.81)	9 (5.77)	0.225	0.635	22 (5.05)	14 (4.79)	8 (5.56)	0.117	0.733	10 (5.05)	9 (4.84)	1 (8.33)	0.473
Neonatal asphyxia, n (%)	14 (2.21)	11 (2.30)	3 (1.92)	-	1.000	8 (1.83)	5 (1.71)	3 (2.08)	-	0.723	6 (3.03)	6 (3.23)	0 (0.00)	1.000
Intrauterine growth restriction, n (%)	3 (0.47)	3 (0.63)	0 (0.00)	-	1.000	1 (0.23)	1 (0.34)	0 (0.00)	-	1.000	2 (1.01)	2 (1.08)	0 (0.00)	1.000
Neonatal respiratory distress syndrome, n (%)	3 (0.47)	1 (0.21)	2 (1.28)	-	0.151	2 (0.46)	0 (0.00)	2 (1.39)	-	0.109	1 (0.51)	1 (0.54)	0 (0.00)	1.000
Retinopathy of prematurity, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-
Necrotizing enterocolitis, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-
Bronchopulmonary dysplasia, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-
Admitted to ICU, n (%)	64 (10.13)	45 (9.45)	19 (12.18)	0.959	0.327	41 (9.45)	25 (8.62)	16 (11.11)	0.698	0.404	23 (11.62)	20 (10.75)	3 (25.00)	0.150

**Abbreviations:** TPOAb<sup>-</sup>, thyroid peroxidase antibody-negative; TPOAb<sup>+</sup>, thyroid peroxidase antibody-positive; LT4, levothyroxine; ICU, intensive care unit. Mean  $\pm$  SD, mean  $\pm$  standard deviation; M (Q1, Q3), median with interquartile spacing; n (%), number of cases (constituent ratio).

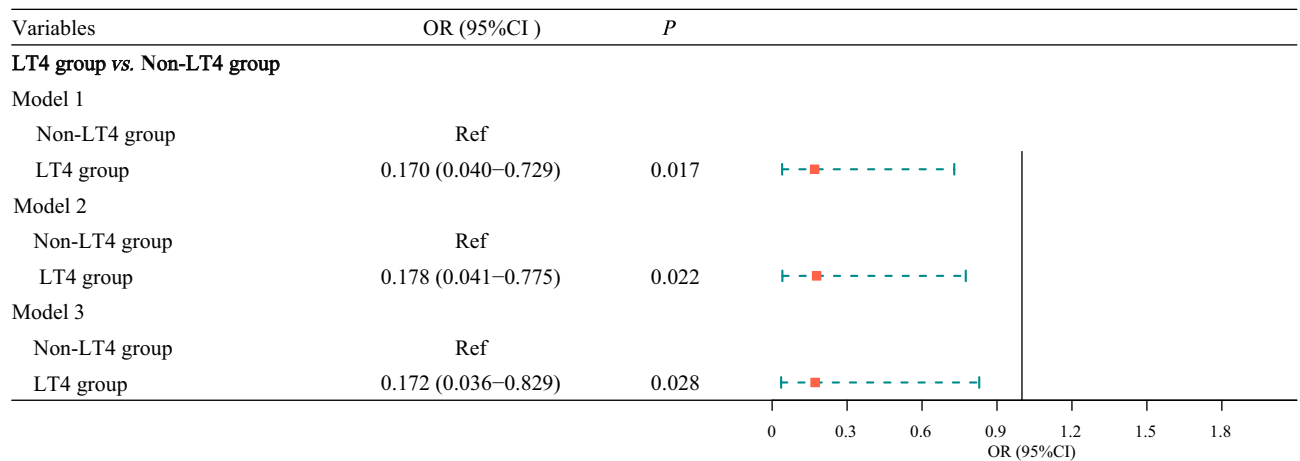
**Table 3** The Pregnancy and Neonatal Outcomes Between the LT4 Therapy and Euthyroid Control Groups

Variables	TPOAb <sup>-</sup> /TPOAb <sup>+</sup>			$\chi^2$	p	TPOAb <sup>-</sup>			$\chi^2$	p	TPOAb <sup>+</sup>			$\chi^2$	p
	Total	LT4 Therapy Group	Euthyroid Control Group			Total	LT4 Therapy Group	Euthyroid Control Group			Total	LT4 Therapy Group	Euthyroid Control Group		
<b>Pregnancy outcomes</b>															
Gestational diabetes, n (%)	156 (18.86)	95 (19.92)	61 (17.43)	0.816	0.366	109 (17.87)	56 (19.24)	53 (16.61)	0.717	0.397	47 (21.66)	39 (20.97)	8 (25.81)	0.367	0.545
Gestational hypertension, n (%)	16 (1.93)	8 (1.68)	8 (2.29)	0.394	0.530	11 (1.80)	3 (1.03)	8 (2.51)	1.875	0.171	5 (2.30)	5 (2.69)	0 (0.00)	-	1.000
Placenta previa, n (%)	12 (1.45)	6 (1.26)	6 (1.71)	0.294	0.588	8 (1.31)	2 (0.69)	6 (1.88)	-	0.290	4 (1.84)	4 (2.15)	0 (0.00)	-	1.000
Preeclampsia, n (%)	9 (1.09)	5 (1.05)	4 (1.14)	-	1.000	7 (1.15)	3 (1.03)	4 (1.25)	-	1.000	2 (0.92)	2 (1.08)	0 (0.00)	-	1.000
Intrahepatic cholestasis of pregnancy, n (%)	54 (6.53)	32 (6.71)	22 (6.29)	0.059	0.808	41 (6.72)	22 (7.56)	19 (5.96)	0.625	0.429	13 (5.99)	10 (5.38)	3 (9.68)	-	0.405
Premature rupture of membranes, n (%)	175 (21.16)	93 (19.50)	82 (23.43)	1.871	0.171	132 (21.64)	55 (18.90)	77 (24.14)	2.462	0.117	43 (19.82)	38 (20.43)	5 (16.13)	0.309	0.578
Chorioamnionitis, n (%)	98 (11.85)	66 (13.84)	32 (9.14)	4.257	0.039	61 (10.00)	34 (11.68)	27 (8.46)	1.753	0.185	37 (17.05)	32 (17.20)	5 (16.13)	0.022	0.883
Pelvic inflammatory disease, n (%)	37 (4.47)	16 (3.35)	21 (6.00)	3.306	0.069	32 (5.25)	12 (4.12)	20 (6.27)	1.410	0.235	5 (2.30)	4 (2.15)	1 (3.23)	-	0.541
Amniotic fluid abnormalities, n (%)	93 (11.25)	54 (11.32)	39 (11.14)	0.006	0.936	73 (11.97)	36 (12.37)	37 (11.60)	0.086	0.769	20 (9.22)	18 (9.68)	2 (6.45)	-	0.746
Preterm delivery, n (%)	29 (3.51)	19 (3.98)	10 (2.86)	0.757	0.384	19 (3.11)	9 (3.09)	10 (3.13)	0.001	0.976	10 (4.61)	10 (5.38)	0 (0.00)	-	0.364
Miscarriage (spontaneous abortion), n (%)	2 (0.24)	1 (0.21)	1 (0.28)	-	1.000	1 (0.16)	1 (0.34)	0 (0.00)	-	0.478	1 (0.46)	0 (0.00)	1 (3.13)	-	0.147
Postpartum hemorrhage, n (%)	100 (12.06)	53 (11.09)	47 (13.39)	1.011	0.315	69 (11.29)	28 (9.59)	41 (12.85)	1.621	0.203	31 (14.22)	25 (13.44)	6 (18.75)	-	0.417
<b>Neonatal outcomes</b>															
Low birth weight, n (%)	24 (2.90)	16 (3.35)	8 (2.29)	0.809	0.368	19 (3.11)	11 (3.77)	8 (2.51)	0.802	0.370	5 (2.30)	5 (2.69)	0 (0.00)	-	1.000
Macrosomia, n (%)	41 (4.95)	23 (4.81)	18 (5.14)	0.047	0.828	31 (5.07)	14 (4.79)	17 (5.33)	0.090	0.764	10 (4.61)	9 (4.84)	1 (3.23)	-	1.000
Neonatal asphyxia, n (%)	17 (2.05)	11 (2.30)	6 (1.71)	0.346	0.556	11 (1.80)	5 (1.71)	6 (1.88)	0.024	0.876	6 (2.76)	6 (3.23)	0 (0.00)	-	0.597
Intrauterine growth restriction, n (%)	5 (0.60)	3 (0.63)	2 (0.57)	-	1.000	3 (0.49)	1 (0.34)	2 (0.63)	-	1.000	2 (0.92)	2 (1.08)	0 (0.00)	-	1.000
Neonatal respiratory distress syndrome, n (%)	2 (0.24)	1 (0.21)	1 (0.29)	-	1.000	1 (0.16)	0 (0.00)	1 (0.31)	-	1.000	1 (0.46)	1 (0.54)	0 (0.00)	-	1.000
Retinopathy of prematurity, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Necrotizing enterocolitis, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Bronchopulmonary dysplasia, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Admitted to ICU, n (%)	76 (9.20)	45 (9.45)	31 (8.86)	0.086	0.769	56 (9.20)	25 (8.62)	31 (9.72)	0.219	0.640	20 (9.22)	20 (10.75)	0 (0.00)	-	0.086

**Abbreviations:** TPOAb<sup>-</sup>, thyroid peroxidase antibody-negative; TPOAb<sup>+</sup>, thyroid peroxidase antibody-positive; LT4, levothyroxine; ICU, intensive care unit. Mean  $\pm$  SD, mean  $\pm$  standard deviation; M (Q1, Q3), median with interquartile spacing; n (%), number of cases (constituent ratio).

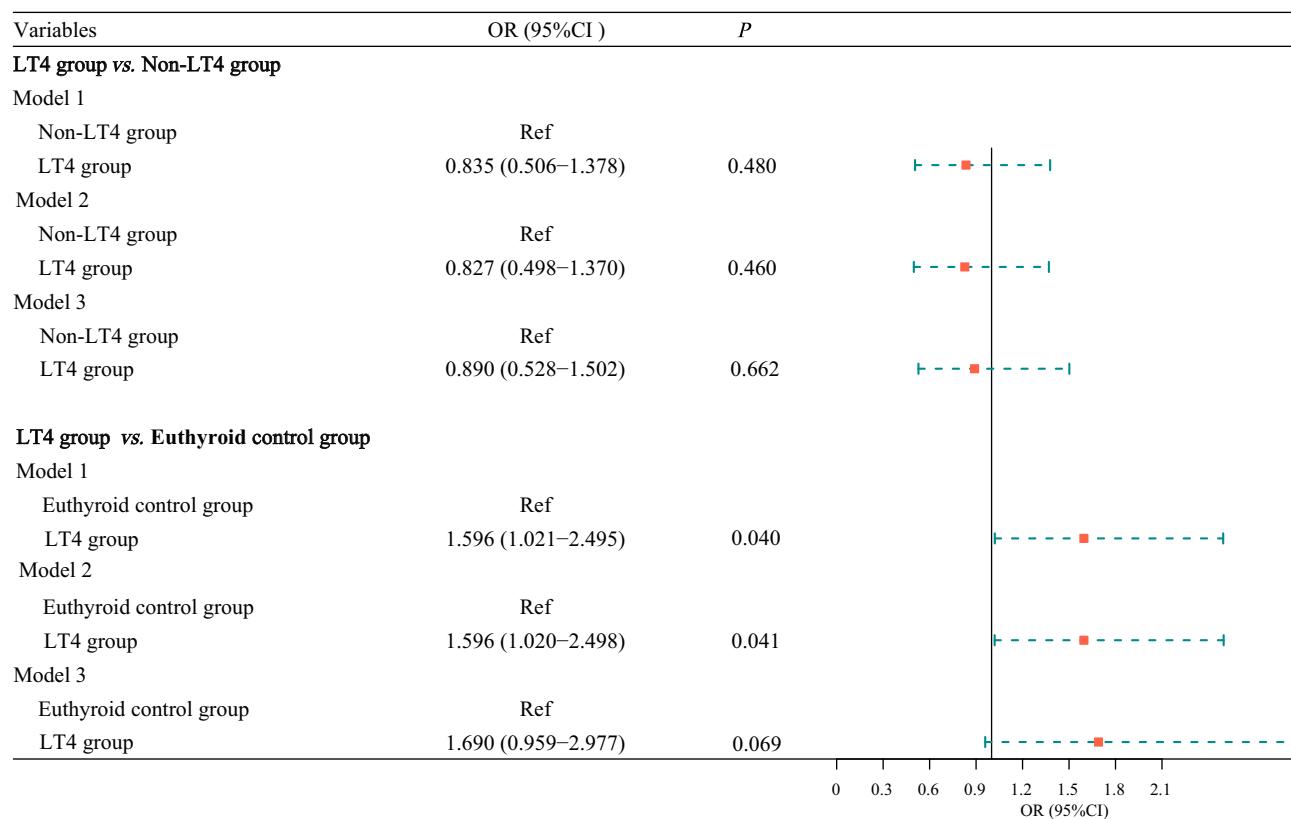


**Figure 1** The effects on amniotic fluid abnormalities of LT4 therapy in SCH pregnant women with TPOAb<sup>+</sup>.



**Figure 2** The effects on premature delivery of LT4 therapy in SCH pregnant women with TPOAb<sup>+</sup>.

abnormalities were no longer apparent in SCH women with TPOAb<sup>-</sup>, indicating that TPOAb<sup>+</sup> forms the basis for any treatment effects of LT4 in pregnant women with SCH. Our results indicated that TPOAb should be considered when treating pregnant women with SCH using LT4, which is in keeping with the American Thyroid Association.<sup>22</sup> Two studies have shown that, after pretreatment of euthyroid TPOAb<sup>+</sup> pregnant women with LT4, the risk of premature delivery and any other neonatal outcomes was not reduced.<sup>23,24</sup> It should be pointed out that the TSH of the subjects in the above two studies was within the normal range. Another randomized clinical trial showed LT4 could only reduce the premature delivery rate in TPOAb<sup>+</sup> women with TSH > 4.0 mU/L,<sup>25</sup> which was consistent with our results.



**Figure 3** The effects of LT4 therapy on chorioamnionitis in pregnant women with SCH.

In the present study, we found that LT4 was associated with a lower risk of premature delivery in the SCH pregnant women with TPOAb<sup>+</sup>. Casey et al retrospectively investigated 25,756 pregnant women, and the pregnancy outcomes were collected.<sup>21</sup> Their results showed that the risk of premature delivery in pregnant women with SCH was two-fold more than that of euthyroid participants, and it was statistically significant. SCH with TPOAb<sup>+</sup> represents a mild deficiency in thyroid functional capacity, leading to a relatively insufficient TH during pregnancy. In the human body, TH could be involved in multiple physiological processes associated with premature delivery, including maintaining adequate placental function<sup>26</sup> and promoting fetal growth,<sup>27,28</sup> so the effects of low TH on premature delivery might be accounted for by affecting placental function, fetal growth, or both. Additionally, lower TH was associated with premature delivery by increasing oxytocin and decreasing vasopressin levels,<sup>29,30</sup> or the specific effects of thyroxine on the cervix, endothelium, and fetal membrane.<sup>30</sup> So LT4 may reduce the risk of premature delivery by ameliorating the adverse effects of insufficient TH.

In this research, we found that LT4 could reduce the risk of amniotic fluid abnormalities in the SCH pregnant women with TPOAb<sup>+</sup>. Oligohydramnios can occur in all phases during the pregnancy, usually in the third trimester, which has been associated with an increased risk of fetal distress, stillbirth, and fetal malformations.<sup>31</sup> Previous studies have indicated that oligohydramnios was related to apoptosis regulation disorders.<sup>32</sup> It has indicated that the excessive apoptosis of amniotic tissue cells resulted in insufficient expression of aquaporin 1 protein, decreasing maternal-fetal exchange, fetal blood volume, and fetal urine production, which contributed to the reduced amniotic fluid volume. LT4 as an artificial synthetic TH could promote the proliferation of amniotic tissue cells with anti-apoptosis roles. It was speculated LT4 might decrease the risk of oligohydramnios by regulating apoptosis.

Some limitations of this study could not be ignored. Firstly, the present research was a single-center retrospective study, without taking the geographical differences into account. Multicenter and large sample studies are looking forward to being performed. Secondly, only LT4 adopted in the first trimester of pregnancy was considered. The effects of LT4 in the second and third trimesters should also be studied. Thirdly, neonatal outcomes might not be comprehensive enough



without considering the therapeutic effect of LT4 on infants' intellectual development. Lastly, it must be acknowledged that urinary iodine concentration<sup>7</sup> and disease history may be an important covariate. However, in this retrospective study, we did not collect information on patients taking iodine supplements during pregnancy nor estimate urinary iodine concentration in these patients. More prospective studies will be conducted in the future to verify the result of this study.

## Conclusion

LT4 therapy during the first trimester was associated with the lower risk of premature delivery and amniotic fluid abnormalities in the SCH pregnant women with TPOAb<sup>+</sup>, which indicated that SCH pregnant women with TPOAb<sup>+</sup> could benefit from the LT4 therapy. However, more randomized trials are required to confirm this association before the unequivocal advocacy of LT4 in pregnant women with SCH.

## Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Chengdu Integrated TCM & Western Medicine Hospital (Ref. No.2021-WZ-002). Informed consent has been obtained from all participants.

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## Disclosure

The authors report no conflicts of interest in this work.

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