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Effect of levothyroxine treatment on serum lipids and pregnancy outcomes in pregnant women with isolated hypothyroxinemia

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374 pregnant women with isolated hypothyroxinemia (IH) who were ≤ 20 weeks were included retrospectively in this study. Based on the confirmed gestational age and the use of levothyroxine (LT4), the patients were divided into the treated group (T1 group) and untreated group (C1 group) in first trimester (≤ 13^{+6} weeks), the treated group(T2 group) and untreated group (C2 group) in second trimester (14–20 weeks). Data on thyroid function and lipid indices was collected both before and after LT4 treatment. To compare the thyroid function, lipid indices and pregnancy outcomes after LT4 treatment. There was a negative correlation between FT4 levels and TC and LDL levels in the first trimester ($P < 0.05$). FT4 and HDL levels in T1 group were significantly increased, and TSH, TC, TG and LDL levels were decreased, compared to C1 group ($P < 0.05$). FT4 levels in T2 group were higher than C2 group, and there was no significant difference in other indicators. The risk of spontaneous abortion, gestational diabetes mellitus (GDM) and macrosomia in T1 group was significantly decreased ($P < 0.05$), and there was no significant difference between T2 and C2 groups. Thus, LT4 treatment can improve the level of FT4 and lipids and reduce adverse pregnancy outcomes in women with IH in the first trimester.

Keywords Hypothyroxinemia, Lipids, Levothyroxine, Pregnancy outcomes

Thyroid hormone (TH) is essential for maintaining normal metabolism and promoting physical growth and neurodevelopment[1]. Thyroid dysfunction is a common disease in pregnant women. Pregnancy with isolated hypothyroxinemia (IH) refers to pregnant woman with negative thyroid autoantibodies and normal serum thyroid stimulating hormone (TSH) levels, but free thyroxine (FT4) levels below the lower limit of the pregnancy-specific reference range[2]. The prevalence of IH in pregnancy ranges widely from 0.2–31%[3]. Pregnancy-related physiological changes cause an increasing demand for TH until the 20th week of gestation, after which it levels off until delivery. The fetus is dependent on the mother's transplacental transfer of TH before 20 weeks of pregnancy. Notably, FT4 is the main source of FT3 in the embryonic brain because it can cross the fetal blood-brain barrier more easily than free triiodothyronine (FT3). The potential effect of IH on pregnancy outcomes and offspring development remains controversial. Most scholars believe that gestational IH is associated with adverse pregnancy outcomes such as gestational hypertensive disease (HDP), gestational diabetes mellitus (GDM), macrosomia, miscarriage, premature delivery, placental abruption, premature rupture of membranes, fetal distress[4–8]. In addition, gestational IH may increase the risk of offspring autism[9,10].

During pregnancy, it is essential for pregnant women to maintain elevated blood lipid levels to support normal fetal development and provide energy for pregnancy, labor and postpartum lactation[11]. TH plays a crucial role in lipid metabolism. Research conducted by Karbownik et al. identified a negative correlation between FT4 concentrations in women with IH of childbearing age and levels of low-density lipoprotein (LDL) and triglycerides (TG), while demonstrating a positive correlation with high-density lipoprotein (HDL)[12]. Additionally, a study by Xu et al. indicated that pregnant women with IH exhibited increased levels of total cholesterol (TC), TG, and LDL during pregnancy. This study further established that treatment with levothyroxine (LT4) could elevate serum FT4 levels and improve lipid profiles in this population[13]. However, existing literature also suggests that pregnant women with IH do not exhibit dyslipidemia[14]. Currently, there is a paucity of research evaluating the effect of LT4 on lipid metabolism in pregnant women with IH.

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In recent years, there have been limited and controversial literatures on whether LT4 therapy can improve adverse maternal and fetal outcomes in pregnant women with IH. The study by Li et al. found that LT4 treatment reduced the risk of miscarriage and the likelihood of the neonatal intensive care unit (NICU) admission in pregnant women with IH[15]. Conversely, Casey et al. showed that LT4 intervention did not improve adverse pregnancy outcomes and offspring cognition[16]. Despite these conflicting findings, domestic and international guidelines vary in their recommendations for the management of IH during pregnancy. In 2014, the European Thyroid Association (ETA) recommended LT4 treatment for women with IH during the first trimester[17], while the 2017 American Thyroid Association (ATA) did not recommend intervention[18]. The Chinese Guidelines for the Diagnosis and Treatment of Thyroid Diseases in Pregnancy and Postpartum (2nd edition) published in 2019 and the recent 2022 Guidelines for the Prevention and Management of Thyroid Diseases during pregnancy did not definitively recommend or oppose the use of LT4 in the first trimester for pregnant women with IH[2,19].

Therefore, the objective of this study was to investigate the effect of LT4 treatment on blood lipid levels and pregnancy outcomes in pregnant women with IH during the first half of pregnancy.

Materials and methods

Research target

This is a retrospective study. Clinical data were collected from pregnant women diagnosed with IH during the first half of pregnancy who delivered at the Third Affiliated Hospital of Zhengzhou University between January 2021 and October 2023.

The inclusion criteria were established as follows: (1) Participants were required to be between the age of 18 and 35. (2) The thyroid function levels of the pregnant women must have met the diagnostic criteria outlined in the 2019 Guidelines for the Diagnosis and Treatment of Thyroid Diseases in Pregnancy and Postpartum (2nd edition)[2], as well as the reference-range criteria established by the Department of Clinical Laboratory of the Third Affiliated Hospital of Zhengzhou University [TSH: 0.27–4.2mIU/L, FT4 < 12.3pmol/L, thyroid peroxidase antibody(TPOAb)<34 IU/ml, thyroglobulin antibody (TgAb)<115 IU/ml].(3) The gestational age of pregnant women diagnosed with IH was less than 20 weeks.

The exclusion criteria were delineated as follows: (1) Patients with multiple pregnancies. (2) Patients who conceived through assisted reproductive technology. (3) Patients with a history of hyperthyroidism, Hashimoto's thyroiditis, subacute thyroiditis, clinical hypothyroidism, subclinical hypothyroidism, prior thyroid surgery, hypertension, diabetes mellitus, cardiovascular disease, autoimmune disease or psychiatric disease prior to enrollment.(4) Previous use of drugs that may affect blood lipids or thyroid function; (5) Patients with incomplete data.

In this study, a cohort of 374 pregnant women with IH during the first half of pregnancy was identified through electronic medical records. These women were classified into different groups according to their gestation week and whether or not they received levothyroxine (LT4) treatment. Specifically, the groups included the first trimester (gestational age ≤ 13^{+6} weeks) treated group (80 patients, T1 group), the first trimester untreated group (98 patients, C1 group), the second trimester (gestational age 14–20 week) treated group (95 patients, T2 group), and the second trimester untreated group (101 patients, C2 group). In the treatment groups, LT4 therapy was initiated upon diagnosis, with dosage adjustments made based on FT4 and TSH levels. Treatment was sustained throughout the entirety of the pregnancy until delivery.

Statement. (1) This study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (Approval No. 2023-041-01). The need for informed consent was waived by the ethics committee of The Third Affiliated Hospital of Zhengzhou University. (2) All methods were carried out in accordance with relevant guidelines and regulations.

Method

1. The age, pre-pregnancy body mass index (BMI), confirmed gestational week, timing of cesarean section, serum fasting blood glucose (FPG) and glycosylated hemoglobin (HbA1c) levels of pregnant women with IH were collected by consulting through the electronic medical record system.
2. Thyroid function indexes and blood lipid indexes, including FT4, TSH, TC, TG, HDL and LDL were collected in pregnant women with IH before and after LT4 treatment. These metabolic indicators were monitored with a minimum interval of four weeks.
3. Maternal and neonatal outcomes were collected, including miscarriage, GDM, premature rupture of membranes (PROM), HDP, placental abruption, cesarean section, postpartum hemorrhage, gestational week of delivery, neonatal birth weight (BW), length, 1-minute and 5-minute Apgar scores, preterm labor, fetal distress, macrosomia, neonatal asphyxia, and admission to NICU.

Main instruments and testing methods

LDL and HDL levels were determined by a uniform phase assay (Beckman Coulter automatic biochemical analyzer, Beckman Coulter Experimental System, Suzhou), and TC and TG levels were determined by an enzymatic method (Beckman Coulter automatic biochemical analyzer, Beckman Coulter Experimental System, Suzhou). TSH, FT4, TPOAb and TgAb levels were measured by an electroluminescence immunoassay (Roche, Shanghai, China). Thyroid function indices and blood lipid indices were detected by the same instrument and detection method before and after LT4 treatment.

General characteristics and baseline serological indicators	C1 group (*n* = 98)	T1 group (*n* = 80)	*P*
Age(year)	32(30, 33)	31(30, 33)	0.090
BMI(kg/m^2)	22.59(21.06, 24.81)	22.63(20.55, 25.39)	0.801
cesarean section time(n)	0(0, 0)	0(0, 0)	0.668
confirmed gestational week(week)	9.0(7.1, 11.6)	9.6(8.0, 11.5)	0.489
FPG(mmol/l)	4.77 ± 0.04	4.79 ± 0.04	0.782
HbA1C(%)	5.0(4.8, 5.3)	5.0(4.6, 5.2)	0.343
FT4(pmol/L)	11.75(11.00, 12.10)	11.90(11.23, 12.10)	0.287
TSH(mIU/L)	1.72(1.21, 2.69)	2.09(1.43, 2.68)	0.226
TC(mmol/L)	4.23(3.87, 5.11)	4.43(4.02, 4.92)	0.623
TG(mmol/L)	1.35(1.04, 1.86)	1.34(1.04, 2.06)	0.913
HDL(mmol/L)	1.61(1.39, 1.78)	1.62(1.46, 1.87)	0.410
LDL(mmol/L)	2.59(2.28, 3.20)	2.74(2.32, 3.21)	0.598

Table 1. General characteristics and baseline serological indicators of pregnant women with IH in the first trimester.

General characteristics and baseline serological indicators	C2 group (*n* = 101)	T2 group (*n* = 95)	*P*
Age(year)	31(30, 33)	31(29, 32)	0.417
BMI(kg/m2)	22.96(21.48, 24.92)	22.94(21.58, 25.32)	0.625
cesarean section time(n)	0(0, 1)	0(0, 0)	0.109
confirmed gestational week(week)	18.0(17.0, 19.0)	18.0(16.4, 18.9)	0.379
FPG(mmol/l)	4.71 ± 0.43	4.72 ± 0.41	0.779
HbA1C(%)	5.0(4.8, 5.3)	5.0(4.7, 5.2)	0.789
FT4(pmol/L)	11.60(11.00, 11.90)	11.60(11.20, 11.90)	0.805
TSH(mIU/L)	1.78(1.29, 2.54)	2.28(1.40, 3.21)	0.056
TC(mmol/L)	5.02(4.48, 5.93)	4.92(4.34, 5.69)	0.299
TG(mmol/L)	1.88(1.48, 2.43)	1.89(1.52, 2.36)	0.953
HDL(mmol/L)	1.89(1.61, 2.14)	1.90(1.59, 2.12)	0.770
LDL(mmol/L)	3.07(2.70, 3.68)	3.00(2.53, 3.51)	0.411

Table 2. General characteristics and baseline serological indicators of pregnant women with IH in the second trimester.

Statistical analysis

Statistical analysis was conducted using SPSS version 26.0. The Kolmogorov-Smirnov (K-S) and Shapiro-Wilk (S-W) tests were employed to assess the normality of the measurement data. For data that conformed to a normal distribution, results were presented as mean ± standard deviation, and comparisons between groups were performed using the independent samples t-test. Conversely, for data that did not meet the criteria for normal distribution, results were reported as median (25th percentile, 75th percentile), and the rank sum test was utilized for group comparisons. Categorical data were expressed in terms of frequency and percentage (%), with the chi-square test or Fisher's exact test applied for intergroup comparisons. Spearman correlation analysis was used to investigate the relationship between FT4 and TC, TG, LDL and HDL. Two-sided test. $P < 0.05$ was established to determine statistical significance.

Result

General characteristics and baseline serological indicators of pregnant women with IH in the first and second trimesters

There were no significant differences in the confirmed gestational week, age, pre-pregnancy BMI, cesarean section time, the levels of FPG, HbA1c, FT4, TSH, TC, TG, HDL and LDL at diagnosis between the T1 and C1 groups ($P > 0.05$) (Table 1). Similarly, no significant differences were found in these parameters between the T2 and C2 groups ($P > 0.05$) (Table 2).

Correlation analysis of serum FT4 and blood lipid indexes in pregnant women with IH at the time of diagnosis

As shown in Table 3, Spearman correlation analysis showed that FT4 level in pregnant women with IH at the time of diagnosis were negatively correlated with TC (ρ=-0.369,P = 0.004) and LDL (ρ=-0.326,P = 0.011) levels,

lipid indexes	the first trimester		the second trimester	
	ρ	P	ρ	P
TC(mmol/L)	-0.369	0.004*	0.114	0.292
TG(mmol/L)	-0.016	0.901	0.075	0.489
LDL(mmol/L)	-0.326	0.011*	0.094	0.389
HDL(mmol/L)	-0.252	0.052	0.001	0.990

Table 3. Correlation analysis of serum FT4 and blood lipid indexes in pregnant women with IH at the time of diagnosis.ρ(Spearman's rank correlation coefficient).*($P<0.05$).

Thyroid function and lipid indexes	C1 group($n=98$)	T1 group($N=80$)	P
FT4(pmol/L)	10.00(9.46, 11.10)	11.35(9.88, 12.20)	<0.001*
TSH(mIU/L)	2.30(1.98, 3.20)	2.10(1.59, 2.50)	<0.001 *
TC(mmol/L)	5.85(5.08, 6.40)	5.77(4.67, 6.21)	0.029 *
TG(mmol/L)	2.28(1.69, 2.92)	1.97(1.79, 2.25)	0.019*
LDL(mmol/L)	3.66(3.12, 3.95)	3.35(2.79, 3.79)	0.016 *
HDL(mmol/L)	1.77(1.53, 2.00)	1.87(1.59, 2.14)	0.019 *

Table 4. Thyroid function and lipid indexes of pregnant women with IH after LT4 treatment in the first trimester. *($P<0.05$).

Thyroid function and lipid indexes	C2 group($n=101$)	T2 group($n=95$)	P
FT4(pmol/L)	10.40(9.56, 11.40)	11.3(10.40, 11.80)	0.001*
TSH(mIU/L)	2.10(1.54, 2.68)	2.19(1.57, 3.17)	0.480
TC(mmol/L)	6.24(5.57, 6.90)	6.07(5.39, 6.52)	0.082
TG(mmol/L)	2.59(1.85, 3.47)	2.38(1.88, 3.31)	0.174
LDL(mmol/L)	3.82(3.48, 4.38)	3.84(3.47, 4.03)	0.533
HDL(mmol/L)	1.82(1.57, 2.04)	1.77(1.59, 1.99)	0.718

Table 5. Thyroid function and lipid indexes of pregnant women with IH after LT4 treatment in the second trimester. *($P<0.05$).

and had no correlation with TG and HDL in the first trimester($P>0.05$). There was no correlation between FT4 levels and TC, TG, LDL and HDL in pregnant women with IH in the second trimester($P>0.05$).

Thyroid function and lipid indexes of pregnant women with IH after LT4 treatment in the first trimester

The levels of FT4 and HDL in T1 group after LT4 treatment were higher than C1 group, and the levels of TSH, TC, TG and LDL were lower than C1 group($P<0.05$) (Table 4).

Thyroid function and lipid indexes of pregnant women with IH after LT4 treatment in the second trimester

FT4 levels in T2 group were higher than C2 group ($P<0.05$), and there was no significant difference in TSH, TC, TG, LDL and HDL levels between T2 and C2 group($P>0.05$) (Table 5).

Pregnancy outcomes of pregnant women with IH in the first and second trimesters

The incidence of miscarriage, GDM and macrosomia in T1 group was lower than that in C1 group, and the difference was statistically significant ($P<0.05$). There was no statistically significant difference in the incidence of pregnancy outcomes such as HDP, cesarean section, postpartum hemorrhage, fetal distress, premature delivery and NICU transfer rate between C1 and T1 groups ($P>0.05$) (Table 6). There was no significant difference in pregnancy outcomes between T2 and C2 groups ($P>0.05$) (Table 7).

Discussion

Normal TH levels facilitate a dynamic equilibrium between the synthesis and catabolism of serum lipids in pregnant women. Studies suggest that IH during pregnancy may be associated with adverse perinatal outcomes[5]. However, there is limited research on the treatment of IH in pregnancy Casey et al. conducted a randomized study involving patients diagnosed with hypothyroxinemia, assigning them to receive either levothyroxine replacement therapy or a placebo. The objective of the study was to examine the relationship between iodine

Pregnancy outcome	C1 group($n = 98$)	T1 group($n = 80$)	P
Miscarriage(n/%)	8(8.2)	1(1.3)	0.043*
HDP(n/%)	6(6.7)	3(3.8)	0.505
GDM(n/%)	18(20.0)	7(8.9)	0.021*
PROM(n/%)	14(15.6)	12(12.2)	0.948
placental abruption(n/%)	2(2.2)	2(2.5)	1.000
Caesarean section(n/%)	33(36.7)	33(41.8)	0.497
Postpartum hemorrhage(n/%)	2(2.2)	0(0)	0.499
Gestational week of delivery(week)	39.1(38.2, 40.0)	39.4(38.9, 39.9)	0.159
Newborn birth weight (kg)	3.36(3.10, 3.57)	3.48(3.26, 3.68)	0.100
Length (cm)	51(50, 52)	51(50, 52)	0.612
1-minute Apgar scores	10(10, 10)	10(10, 10)	0.318
5-minute Apgar scores	10(10, 10)	10(10, 10)	0.184
Fetal distress(n/%)	10(11.1)	4(5.1)	0.155
Preterm labor(n/%)	4(4.4)	4(5.1)	0.850
Macrosomia(n/%)	7(7.8)	0(0)	0.015*
Neonatal asphyxi(n/%)	2(2.2)	0(0)	0.499
NICU(n/%)	11(12.2)	10(12.7)	0.932

Table 6. Pregnancy outcomes of pregnant women with IH in the first trimester. Apgar scores: it is the scoring method made according to the child's physical condition after birth, composed of five clinical components: activity, pulse, Grimace, Appearance, and respiration. Each component receives 0, 1, or 2 points based on predetermined criteria, with a maximum score of 10.*($P<0.05$).

Pregnancy outcome	C2 group($n = 101$)	T2 group($n = 95$)	P
Miscarriage(n/%)	4(4.0)	1(1.1)	0.370
HDP(n/%)	9(9.3)	7(7.4)	0.648
GDM(n/%)	16(16.5)	20(21.3)	0.398
PROM(n/%)	15(15.5)	13(13.8)	0.750
placental abruption(n/%)	3(3.1)	0(0)	0.246
Caesarean section(n/%)	38(39.2)	33(35.1)	0.561
Postpartum hemorrhage(n/%)	2(2.1)	1(1.1)	1.000
Gestational week of delivery(week)	39.3(38.9, 40.3)	39.3(38.7, 40.1)	0.278
Newborn birth weight (kg)	3.44(3.17, 3.72)	3.40(3.15, 3.56)	0.152
Length (cm)	51(50, 52)	51(50, 52)	0.447
1-minute Apgar scores	10(10, 10)	10(10, 10)	0.196
5-minute Apgar scores	10(10, 10)	10(10, 10)	0.619
Fetal distress(n/%)	11(11.3)	14(14.9)	0.467
Preterm labor(n/%)	5(5.2)	10(10.6)	0.159
Macrosomia(n/%)	8(8.2)	2(2.1)	0.101
Neonatal asphyxia(n/%)	0(0)	1(1.1)	0.492
NICU(n/%)	20(20.6)	20(21.3)	0.911

Table 7. Pregnancy outcomes of pregnant women with IH in the second trimester.

status in pregnant women with hypothyroxinemia during the first trimester and various behavioral and neurodevelopmental indicators in children under the age of five. The findings indicated that irrespective of the maternal iodine levels, treatment with levothyroxine did not demonstrate a significant association with neurodevelopmental or behavioral outcomes in the offspring[20]. This study retrospectively analyzed the thyroid function indexes, lipid indexes and maternal and infant outcomes of pregnant women with IH treated with LT4 at different gestational weeks, and aimed to investigate the effect of LT4 treatment on lipid metabolism and pregnancy outcomes of pregnant women with IH.

We first analyzed the correlation between FT4 levels and blood lipid indexes in pregnant women with IH in the first and second trimesters. Our findings indicated that serum FT4 levels in the first trimester were negatively correlated with TC and LDL levels, and had no significant correlation with TG and HDL levels. There was no correlation between serum FT4 level and lipid indexes in the second trimester. The study conducted by Liu et al. also indicated a negative correlation between FT4 levels and TC in pregnant women with IH during the first trimester, which aligns with our findings[21]. These results imply that pregnant women with IH may experience

dyslipidemia. TH plays a key role in the process of cholesterol synthesis and catabolism. In instances of TH deficiency, although the synthesis rate of TC may decline, the rates of TC degradation and excretion decrease even more markedly, resulting in a significant increase in TC levels.

Secondly, we analyzed the thyroid function and lipid indexes of pregnant women with IH after LT4 treatment, and the results showed that the FT4 levels of pregnant women with LT4 treatment in the first trimester group were higher, and the TSH levels were lower, compared to the untreated group. This suggests that oral administration of LT4 may enhance the body's thyroxine (T4) level, consequently increasing FT4 concentration. Furthermore, T4 undergoes deiodination to form triiodothyronine (T3), which exerts a negative feedback effect on the hypothalamic-pituitary-thyroid axis, thereby reducing TSH synthesis and secretion[22]. We also found that the levels of TC, TG and LDL in the first trimester treated group were lower than the untreated group, and the level of HDL was higher. Current literature on LT4 treatment for IH during early pregnancy is limited. Zhao et al. reported that LT4 treatment in non-pregnant women with hypothyroidism resulted in decreased LDL level[23]. Similarly, Yang et al. observed that LT4 administration in pregnant women with subclinical hypothyroidism during the first trimester led to improvements in LDL and TC levels[24]. We speculate that LT4 supplementation may influence lipid metabolism through several mechanisms: (1) LT4 supplementation may increase the expression of cholesterol 7α-hydroxylase, promoting the conversion of TC to bile acid, reducing the level of serum TC[25]. (2) FT4 may bind to the corresponding sites in LDL, inhibiting the formation of oxidized LDL (ox-LDL), which is not recognized by LDL receptors, leading to cellular accumulation of LDL[26]. The supplementation of LT4 can stimulate the expression of LDL receptor and inhibit the oxidation of LDL, so that it can be easily recognized and cleared by LDL receptor, and then reduce the serum LDL levels. (3) LT4 can increase the basal metabolic rate, up-regulate the activity of lipoprotein esterase, and promote the hydrolysis of TG[27]. (4) Supplementation with LT4 reduces the concentration of cholesterol ester transfer protein (CETP)[28], potentially resulting in increased HDL levels in plasma. Therefore, we believe that LT4 treatment can improve serum FT4 and lipid levels in pregnant women with IH in the first trimester.

The result of the second trimester showed that the level of FT4 in the treated group was higher than that in the untreated group, and the levels of TSH and lipids had no significant alterations. Xu et al. 's study which included 77 pregnant women with IH in the treated group and 87 patients in the untreated group found that after LT4 supplementation, FT4, TSH, TC and LDL were significantly improved compared with the untreated group, but the changes of TG and HDL were not significantly difference[13]. This is not exactly consistent with our results, potentially due to variations in gestational age. Research indicates that FT4 levels in healthy pregnant women typically rise during the first trimester, gradually decline in the second and third trimesters, and revert to non-pregnant levels around 20 weeks of gestation. Conversely, TSH levels generally decrease during the first trimester and progressively increase after the second trimester[2]. We tested that supplementation of LT4 in the second trimester increased the level of T4 in vivo and directly increased the level of FT4, but indirectly acted on the regulation of TSH, so the change of TSH in the second trimester after LT4 treatment was not significant. The study has shown that after LT4 treatment in patients with clinical or subclinical hypothyroidism, TSH level returns to normal, but TC and LDL levels are still higher than those in the general population[29]. It may be due to the persistence of subnormal levels of triiodothyronine (T3)[30]. In addition, blood lipids during pregnancy will gradually increase with the progress of pregnancy, reaching a peak in the third trimester[31]. Therefore, LT4 supplementation alone may not be sufficient to alter lipid levels in the second trimester.

We further compared maternal and infant outcomes after treatment. This study found that LT4 treatment reduced the risk of miscarriage in the first trimester. In a non-randomized intervention study by Li et al., involving 964 pregnant women with IH in the first trimester, it was demonstrated that LT4 treatment markedly decreased the miscarriage rate[15]. This is consistent with our results. A Spanish study showed that in women with IH with FT4 levels < 7.5 pg/mL, LT4 treatment given prior to 9 weeks of pregnancy reduced the risk of miscarriage by over 40% before 12 weeks and between 14 and 40% before 18 weeks[32], which is consistent with our findings. The study had shown that ox-LDL level increase and HDL level decrease in pregnant women with spontaneous abortion[33]. ox-LDL can promote the secretion of inflammatory cytokines, leading to vascular endothelial cell damage[26]. HDL can promote the catabolism of cholesterol and is a protective factor of blood vessels. Consequently, LT4 supplementation may contribute to a reduction in LDL and ox-LDL levels in pregnant women with IH during the first trimester, while simultaneously increasing HDL levels. This may help to mitigate damage to placental vascular endothelial cells, thereby enhancing fetal blood supply and decreasing the incidence of miscarriage. Moreover, LT4 supplementation may also play a role in regulating maternal immune tolerance, facilitating embryo implantation and placental development, and further reducing the likelihood of miscarriage by promoting the secretion of progesterone, human chorionic gonadotropin, vascular endothelial growth factor, and placental growth factor from trophoblast cells of the placenta[34].

The findings of this study showed that LT4 treatment reduced the risk of GDM in pregnant women with IH in the first trimester. Currently, there is a paucity of research examining the effects of LT4 therapy on GDM and macrosomia in this population. Notably, Sitoris's study found that LT4 treatment reduced the prevalence of GDM in subclinical hypothyroidism during pregnancy[35]. The studies had revealed a significant correlation between the incidence of GDM and elevated TG level in early pregnancy, suggesting that lipid metabolism disorders may contribute to or exacerbate insulin resistance[36,37]. LT4 supplementation may reduce insulin resistance by indirectly lowering TG levels, and increase T3 levels in vivo. T3 promotes the secretion of glucagon-like peptide-1 and insulin by inhibiting the intestinal farnesol X receptor signaling pathway, and reduces the occurrence of GDM[38]. Furthermore, our study found that LT4 treatment reduces the risk of macrosomia in women with IH in the first trimester. A prospective intervention study conducted by Gong et al. reported that LT4 treatment did not improve adverse pregnancy outcomes in women with IH during the first trimester and noted an increased risk of macrosomia in those with IH during the second trimester, although no intervention was performed on this latter group[39]. This finding contradicts our results. A study had shown that the use of

LT4 in pregnant women with hypothyroidism can reduce the risk of macrosomia[40]. Supplementation of LT4 may reduce the occurrence of macrosomia by decreasing maternal plasma TG levels, decreasing the activity of placental lipase, and limiting the entry of free fatty acids into the fetus[41].

In summary, this study retrospectively analyzed the effect of LT4 treatment on thyroid function, lipid levels and pregnancy outcomes in pregnant women with IH. Subgroup analysis based on gestational age showed that LT4 treatment could improve the serum lipid levels and adverse pregnancy outcomes of pregnant women in the first trimester to a certain degree. However, several limitations must be acknowledged: Firstly, this study is retrospective. Secondly, the sample size of this study is relatively small, which may cause some bias into the results. In addition, the study did not assess the cognitive development of the offspring of women with IH, highlighting an area for future investigation. In the future, multicenter, large sample, and randomized intervention studies are still needed to further determine whether LT4 therapy can improve pregnancy outcomes and offspring neurodevelopment in pregnant women with IH.

Data availability

The data are not publicly available due to their containing information that could compromise the privacy of research participants. The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

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Author contributions

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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