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Original Article

Levothyroxine suppression therapy improves maternal and neonatal outcomes in pregnancy after thyroidectomy for differentiated thyroid carcinoma

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Abstract: Objectives: To evaluate the efficacy of levothyroxine (L-T4) suppression therapy in women with a history of differentiated thyroid carcinoma (DTC), focusing on pregnancy outcome after thyroidectomy. Methods: This retrospective study included 300 pregnancies in women with previous DTC surgery. Participants were divided into an experimental group (n=187) receiving L-T4 doses adjusted based on thyroid-stimulating hormone (TSH) levels and a control group (n=113) following a fixed low-dose L-T4 regimen. We assessed various outcomes, including biochemical values (TSH dynamics, lipid profile, folic acid [FA] levels), obstetric measures (placental function, pregnancy complications), and neonatal outcomes. Results: The experimental group showed consistently lower TSH levels throughout pregnancy and experienced fewer pregnancy and neonatal complications compared to the control group (all P<0.05). Additionally, the experimental group demonstrated significant improvements in lipid profiles, FA levels, and placental function(all P<0.05). Conclusions: TSH-adjusted L-T4 therapy in pregnant women post-DTC thyroidectomy results in better maternal and neonatal outcomes compared to a fixed low-dose L-T4 regimen. This approach optimizes TSH stability, improves lipid and FA profiles, and enhances placental function, leading to improved overall outcomes for both the mother and child.

Keywords: Thyroid carcinoma, post-DTC surgery, pregnancy, L-T4, thyroid-stimulating hormone, blood lipids, folic acid

Introduction

Thyroid cancer (TC), including differentiated thyroid carcinoma (DTC), has been increasingly prevalent, with reproductive-age females exhibiting significantly higher susceptibility than males [1, 2]. The standard treatment for reproductively active female TC patients is thyroidectomy [3], but this results in the loss of thyroid function, either partially or entirely, leading to hypothyroidism [4]. Thyroid hormones, secreted by the thyroid gland, play essential roles in almost all body cells, influencing growth, development, metabolism, and organ functions [5]. Hypothyroidism often leads to an overproduction of thyroid-stimulating hormone (TSH), which can have detrimental effects, particularly on cardiovascular and reproductive health [6].

Pregnant women, influenced by estrogen secretion, have an increased demand for thyroid hormones compared to non-pregnant individuals. A hypothyroid state can adversely affect maternal blood lipid and folic acid (FA) levels, increasing the risk of cardiovascular issues and fetal neurological deficits, leading to unfavorable outcomes for pregnancy, the perinatal period, and neonates [7]. Therefore, TSH suppression in postoperative DTC pregnancies is crucial to reduce adverse pregnancy events and fetal abnormalities.

Levothyroxine (L-T4) suppressive therapy aims to control TSH to a low range through L-T4 ad-

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ministration, maintaining normal metabolic functioning and preventing DTC recurrence [8]. L-T4 is a synthetic thyroid hormone commonly used in the treatment of hypothyroidism [9]. Following thyroidectomy for DTC, which eliminates the thyroid gland's hormone-secreting capacity, lifelong L-T4 replacement is required [10]. During postoperative DTC pregnancies, L-T4 therapy becomes particularly challenging as clinicians must maintain preconception TSH levels, prevent maternal hypothyroidism, and meet the elevated thyroid hormone demands of embryogenesis [11]. Studies on L-T4 therapy in pregnancies following thyroidectomy for DTC are limited. Therefore, this study aims to investigate L-T4 suppressive therapy in these patients, providing a scientific basis for pharmacotherapy in postoperative DTC pregnancies and laying the groundwork for future clinical research.

Materials and methods

Case selection

From July 2015 to September 2024, 300 pregnant women with a history of DTC who underwent pregnancy check-ups at Chongming Hospital Affiliated to Shanghai University of Medicine & Health Sciences, Shanghai Chongming District Maternal and Child Health Center, and Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine were enrolled in this study. Sample size calculation was based on the formula in Practical Medical Statistics [12]. With α=0.05 ($Z_{\alpha/2}$=1.96), β=0.1 (Z_{β}=1.282) and using the formula: $n=(p_1(1-p_1)+p_2(1-p_2))[(1.96+1.282)/(p_1-p_2)]^2$, where p1 and p2 are the efficacy rates of the experimental and control groups, respectively, we estimated a sample size of 250. This was increased to 300 to account for a 20% attrition rate. Participants were categorized based on their L-T4 suppressive therapy regimens. The experimental group (n=187) received L-T4 doses adjusted to their TSH levels, while the control group (n=113) followed a consistent low-dose L-T4 regimen. Ethical approval was granted by the institutional review board, with strict adherence to the principles of respect, informed consent, non-maleficence, beneficence, and justice throughout the study.

Inclusion criteria: ① Age range: 25~35 years; ② Diagnosed with TC according to the ATA 2015 Guidelines for Diagnosis and Management of Thyroid Cancer [13]; ③ TSH <2.5 mIU/L for >3 months under L-T4 treatment; ④ Singleton pregnancy confirmed by color Doppler ultrasound; ⑤ No cognitive, communication, or expressive impairments; ⑥ Full participation in all pregnancy stages; ⑦ Primigravid women with spontaneous pregnancies; ⑧ A history of total/near-total thyroidectomy with pathologically confirmed absence of distant metastasis; ⑨ Availability of complete clinical data. Exclusion criteria: ① Cardio-cerebrovascular disorders; ② Diabetes; ③ Non-compliance with medical advice during pregnancy; ④ Severe mental or psychological disorders; ⑤ Significant organ pathologies; ⑥ Coexisting chronic hypertension or autoimmune disorders (e.g., systemic lupus erythematosus, antiphospholipid syndrome); ⑦ Histopathologic findings of medullary or undifferentiated thyroid carcinoma post-surgery; previous radioactive iodine treatment for thyroid remnant elimination; ⑧ Gastrointestinal pathologies affecting hormone absorption (e.g., untreated celiac disease, prior sleeve gastrectomy), or concurrent intake of agents known to reduce L-T4 bioavailability (e.g., calcium or iron supplements taken less than 4 hours apart from L-T4); ⑨ Prenatal diagnosis of major fetal congenital anomalies or chromosomal disorders.

Inerventional treatments

Treatments

Daily protective education was provided to both study groups.

Experimental group: Regular thyroid function testing: Participants were required to adhere to prescribed prenatal visit schedules and thyroid assessments, with fortnightly tests during early pregnancy (<14 weeks) and monthly tests in later gestation (28-40 weeks).

L-T4 titration: Oral L-T4 (Euthyrox; Shanghai Aladdin Biochemical Technology Co., Ltd., T106193) was administered based on TSH levels to meet maternal-fetal thyroid requirements. Therapy was discontinued postpartum.

Control group: Regular pregnancy check-ups: Patients were instructed to attend check-ups regularly, with thyroid function assessed at

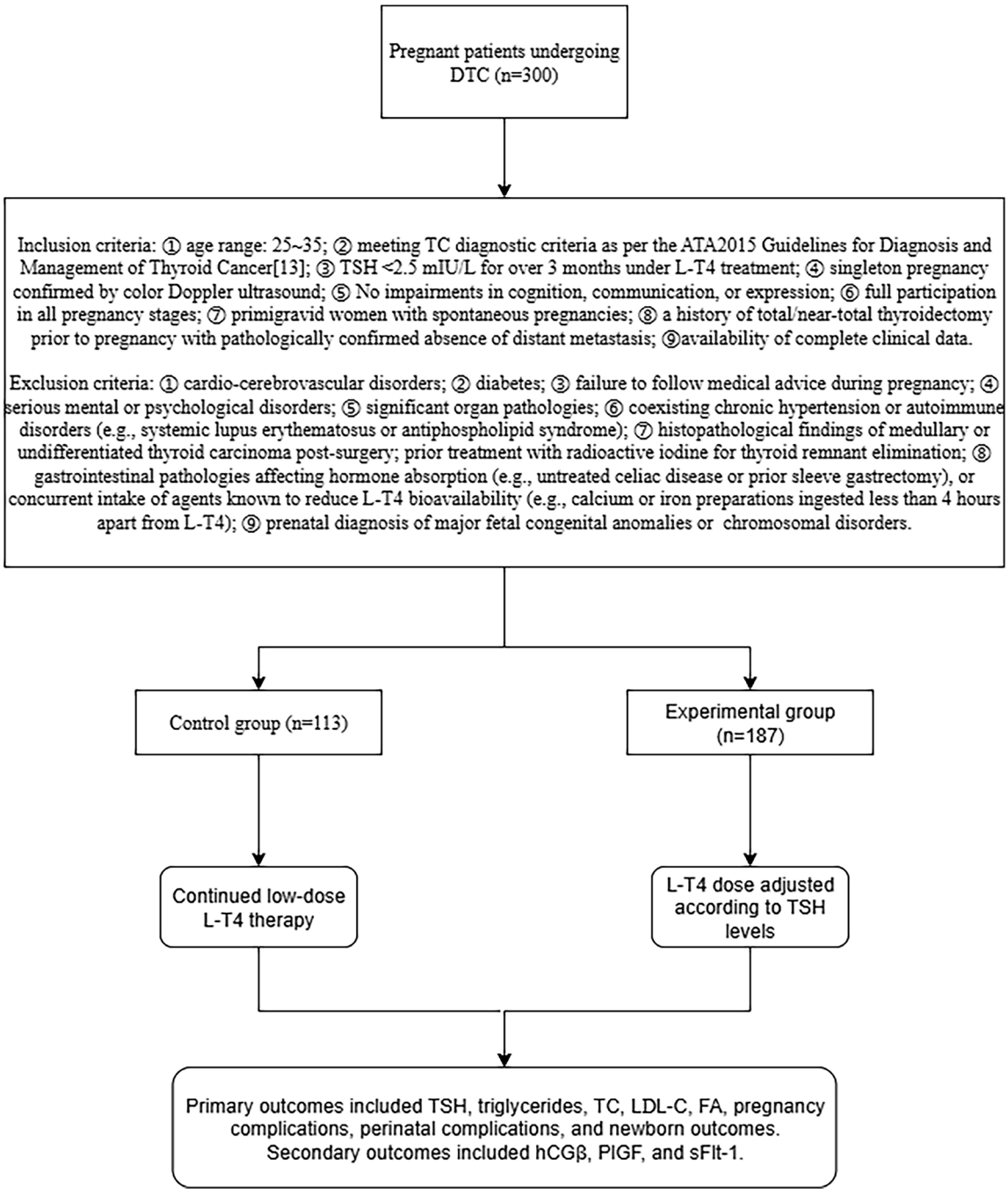

Figure 1. Research flow chart. DTC, Differentiated thyroid cancer; L-T4, postoperative Levothyroxine; TSH, thyroid-stimulating hormone; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; FA, folic acid; hCGβ, human chorionic gonadotropin β; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1.

least once per trimester (early, mid, and late pregnancy stages).

Low-dose L-T4: Patients received 25 μg daily initially, with dosage escalation (25-50 μg increments) after 8 days, reaching 50-100 μg/day. Therapy was discontinued at delivery.

A graphical representation of the patient enrollment process is shown in **Figure 1**.

Blood sampling methods

A 5-mL fasting venous blood sample was collected and centrifuged at 3500 rpm for 10-15

Table 1. General data comparison ($\bar{x}$ ± s, n, %)

Category		Experimental group (n=187)	Control group (n=113)	t/χ^2	*P*
Average age		28.65±2.31	28.92±2.89	0.891	0.373
Surgical modality	Total thyroidectomy	93 (49.73)	94 (50.27)	0.107	0.744
	Unilateral thyroidectomy	54 (47.79)	59 (52.21)		

minutes. The supernatant was extracted and stored at -70°C.

Data collection and outcome measurement

TSH levels

TSH levels were measured using an automatic biochemical analyzer (Shanghai Yuzhuo Biotech, V503800) during preconception and throughout the three pregnancy trimesters (early, mid, late) for comparative analyses.

Blood lipid and FA levels

Blood lipid markers (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C]) and FA levels were quantified using automated biochemical analysis, with data recorded and compared between groups.

Placental function-related indexes

Serum human chorionic gonadotropin β (hCGβ) levels were measured pre- and post-intervention (mid-pregnancy) using enzyme-linked immunosorbent assay (ELISA). Serum placental growth factor (PlGF) and soluble Fms-like tyrosine kinase-1 (sFlt-1) levels were measured pre-intervention and in the third trimester, using ELISA kits (Shanghai YuanMu Biotech, YM-SZ0787, YM-SZ0099; Shanghai Lingkeyuan Biotech, ELH1787), following standardized protocols.

Pregnancy complications

Complications such as pregnancy-induced hypertension, gestational diabetes, anemia, and premature rupture of membranes (PROM) were monitored throughout pregnancy and up to one week post-delivery.

Perinatal complications

Perinatal adverse events, including amniotic fluid abnormalities, placental abruption, and postpartum hemorrhage, were tracked in both groups.

Newborn outcomes

Neonatal outcomes, including prematurity, malformations, and intrauterine demise, were compared between groups.

Primary outcomes included TSH, TG, TC, LDL-C, FA, pregnancy/perinatal complications, and newborn outcomes. Secondary outcomes included hCGβ, PlGF, and sFlt-1 levels.

Statistical analysis

Data were processed using SPSS 22.0 and visualized with GraphPad Prism 7.0. Continuous data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and compared using independent sample t-tests (for inter-group comparisons) or paired sample t-tests (for within-group comparisons). Categorical data were expressed as n (%) and compared using χ^2 tests. Statistical significance was defined as $P<0.05$.

Results

Comparison of baseline data

Initial assessment confirmed the clinical comparability of the study cohorts, with no significant differences in baseline characteristics (e.g., mean age, surgical modality) between the groups (all $P>0.05$; **Table 1**).

Comparison of TSH level

Pre-intervention TSH levels did not differ significantly between the groups ($P>0.05$). After the intervention, the experimental group showed significantly lower TSH levels at each gestational stage compared to the control group ($P<0.05$; **Figure 2**).

Comparison of blood lipid and FA levels

There were no significant pre-treatment differences in lipid and FA levels (all $P>0.05$). The experimental group showed more significant reductions in TG, TC, and LDL-C and, along with a greater increase in FA levels compared to the control group (all $P<0.05$; **Table 2**).

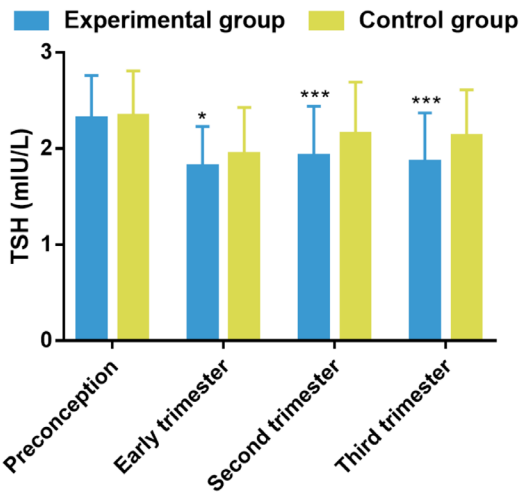

Figure 2. TSH levels across gestational periods. Note: TSH, thyroid-stimulating hormone. *P<0.05, ***P<0.001, compared with the control group at the same time point.

Comparison of placental function-related indexes

Placental function markers were comparable between the groups before treatment (all P>0.05). After the intervention, both groups showed decreases in hCGβ and increases in PlGF and sFlt-1 levels. However, the experimental group exhibited lower hCGβ and sFlt-1 levels and higher PlGF concentrations compared to the control group (all P<0.05; **Figure 3**).

Comparison of pregnancy complications

The experimental group experienced a significant reduction in pregnancy complications (including pregnancy-induced hypertension, gestational diabetes, anemia, and PROM compared to the control group (P<0.05; **Table 3**).

Comparison of perinatal complications

Fewer perinatal complications (such as amniotic fluid abnormalities, placental abruption, anemia, and postpartum hemorrhage) were observed in the experimental group than in the control group after treatment (*P*<0.05; **Table 4**).

Comparison of neonatal outcomes

The experimental group demonstrated significantly better neonatal outcomes, with lower incidences of malformations, neonatal asphyxia, fetal intrauterine distress, prematurity, and intrauterine demise compared to the control group post-intervention (*P*<0.05; **Table 5**).

Discussion

Thyroid cancer (TC), though accounting for less than one-tenth of all thyroid disorders, is the most commonly diagnosed endocrine malignancy [14]. Studies have shown a steady increase in TC incidence, with an annual growth rate exceeding 6%. As a major subtype of TC, DTC poses significant risks to patients' health and safety [15]. Thyroidectomy, an effective treatment for DTC, often leads to hypothyroidism due to the resection of thyroid tissue [16]. L-T4 therapy has been shown to enhance thyroid function by supplementing thyroid hormones and inhibiting TSH production. For post-surgical DTC patients, long-term L-T4 suppressive therapy is required to normalize thyroid hormone levels. During pregnancy, maternal thyroid hormone needs increase, which results in elevated TSH levels. However, excessively high TSH concentrations can lead to blood lipid and FA alterations, negatively affecting maternal health, fetal growth, and development, and significantly impacting maternal-fetal outcomes, perinatal complications, and neonatal prognosis [17]. This study argues that L-T4 suppressive therapy adjusted according to thyroid function levels provides better outcomes than consistent low-dose regimens by regulating TSH, blood lipids, and FA levels, reducing pregnancy/perinatal complications, and improving neonatal outcomes, thereby providing reliable clinical evidence.

In pregnant women with a history of DTC surgery, reduced thyroid hormone secretion leads to TSH elevation, causing symptoms such as mental sluggishness, depressive mood, and cold intolerance. These symptoms are associated with unfavorable pregnancy outcomes and fetal dysplasia. Maternal hypothyroidism has been linked to multiple negative consequences for pregnancy and fetal development [18]. To support maternal survival and fetal growth, the body's demand for thyroid hormones increases, leading to a parallel rise in TSH levels. Research has shown that the thyroid hormone requirement varies across different stages of pregnancy [19]. This study demonstrated that the experimental group, with titrated L-T4 dosing, exhibited significantly lower TSH levels than the control group at all stag-

Table 2. Inter-group comparison of blood lipid indices and folic acid levels ($\bar{x} \pm s$)

Value	Experimental group (n=187)	Control group (n=113)	*t*	*P*
TG (mmol/L)				
Before intervention	1.78±0.28	1.76±0.26	0.616	0.539
After intervention	1.48±0.24***	1.62±0.21***	5.127	<0.001
TC (mmol/L)				
Before intervention	6.24±0.62	6.21±0.59	0.414	0.680
After intervention	4.47±0.57***	4.73±0.54***	3.904	0.001
LDL-C (mmol/L)				
Before intervention	3.37±0.48	3.40±0.47	0.529	0.597
After intervention	2.86±0.35***	3.12±0.33***	6.369	<0.001
FA (ng/mL)				
Before intervention	9.39±1.69	9.37±1.58	0.102	0.919
After intervention	13.79±2.18***	11.76±2.06***	7.977	<0.001

Note: ***P<0.001 vs. pre-intervention values within the same group.

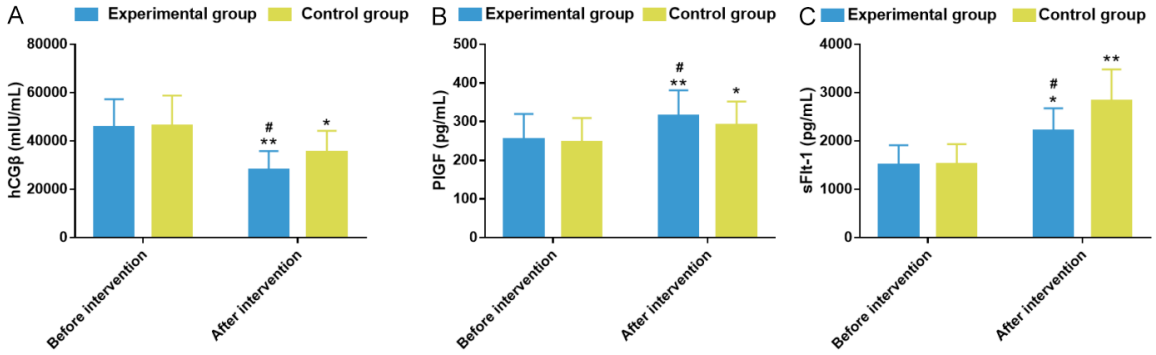

Figure 3. Comparison of placental function-related indexes. A. Changes in serum hCGβ levels pre- and post-intervention. B. Variations in serum PlGF levels before and after treatment. C. Differences in serum sFlt-1 levels between groups over time. Note: hCGβ, human chorionic gonadotropin β; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1; *P<0.05, **P<0.01 (vs. pre-intervention); #P<0.05 (vs. control group at the same time point).

Table 3. Pregnancy complication frequency in both groups (n, %)

Item	Experimental group (n=187)	Control group (n=113)	χ^2	*P*
Pregnancy-induced hypertension	7 (3.74)	18 (15.93)	13.690	<0.001
Gestational diabetes	6 (3.21)	19 (16.81)	17.070	<0.001
Anemia	5 (2.67)	13 (11.50)	9.379	0.002
Premature rupture of membranes	5 (2.67)	11 (9.73)	6.955	0.008
Total incidence	23 (12.30)	61 (53.98)	60.701	<0.001

Table 4. Perinatal complication rates (n, %)

Item	Experimental group (n=187)	Control group (n=113)	χ^2	*P*
Amniotic fluid abnormalities	6 (3.21)	14 (12.39)	3.089	0.002
Placental abruption	9 (4.81)	17 (15.04)	9.315	0.023
Anemia	5 (2.67)	20 (17.70)	4.563	<0.001
Postpartum hemorrhage	2 (1.07)	11 (9.73)	3.572	<0.001
Total incidence	22 (11.76)	62 (54.87)	64.911	<0.001

Table 5. Comparative analysis of neonatal outcomes (n, %)

Item	Experimental group (n=187)	Control group (n=113)	χ^2	*P*
Malformations	2 (1.07)	13 (11.50)	4.018	<0.001
Neonatal asphyxia	3 (1.60)	11 (9.73)	10.471	0.001
Fetal intrauterine distress	5 (2.67)	19 (16.81)	4.374	<0.001
Prematurity	12 (6.42)	23 (20.35)	13.281	<0.001
Intrauterine demise	0 (0.00)	9 (7.96)	3.918	<0.001
Adverse neonatal outcome rate	22 (11.76)	75 (66.37)	96.001	<0.001

es of pregnancy, indicating a superior efficacy of adjusted L-T4 therapy compared to consistent low-dose L-T4 in managing pregnant patients after DTC surgery. L-T4 therapy compensates for insufficient thyroid hormone by binding to triiodothyronine receptors, facilitating biological processes and suppressing TSH production. According to Abalovich et al. [20], the fetal thyroid is not fully functional in early pregnancy, relying exclusively on maternal thyroxine. However, as the fetal thyroid matures in mid-to-late pregnancy, L-T4 dosage should be reduced. Consistent low-dose L-T4 therapy, with incremental adjustments, can maintain basic stability, but excessive dosing during mid-to-late pregnancy may increase maternal-fetal risks. In contrast, timely L-T4 dose adjustments based on TSH monitoring ensure optimal thyroid function, supporting maternal health and fetal development.

Blood lipid abnormalities in pregnant women are associated with increased risks of maternal thrombosis, myocardial ischemia, and cardiovascular injury. FA is essential for fetal growth and neurodevelopment. Elevated blood lipids and decreased FA levels are common in hypothyroidism. Clinical evidence highlights the importance of monitoring blood lipid and FA levels in pregnant women with hypothyroidism [21], as this condition delays LDL particle clearance, resulting in elevated LDL-C and TC levels, which contribute to hyperlipidemia. Lipid metabolism dysfunction increases blood viscosity, causes thrombosis, and can lead to placental vasculopathy, adversely affecting pregnancy outcomes. Research has shown that FA deficiencies during pregnancy can lead to adverse outcomes, such as fetal malformations, premature delivery, and neurodevelopmental impairments [22]. In this study, the experimental group showed lower blood lipid levels and higher FA levels compared to controls, indicating that TSH-adjusted L-T4 dosing is more effective than consistent low-dose L-T4 in improving blood lipid profiles and FA levels in pregnant patients after DTC surgery. As the mainstay of thyroid hormone replacement, L-T4 helps adjust TSH levels and offers lipid-lowering benefits. Clinical evidence links hypothyroidism to arterial stiffening and myocardial infarction. In the hypothyroid state, reduced LDL receptor activity and cholesterol clearance elevate the risk of hyperlipidemia. L-T4 suppressive therapy, by supplementing thyroid hormones, effectively treats hypothyroidism and reduces elevated lipid profiles [23]. Pregnant women with hypothyroidism also experience slowed metabolism and poor nutritional absorption, leading to FA deficiencies. Stagi et al. [24] reported that adequate L-T4 supplementation restores thyroid hormone levels, alleviates hypothyroidism symptoms, and modulates FA levels, which aligns with our findings. Therefore, regular thyroid function testing and tailored L-T4 dosing based on these results can achieve better TSH control, alleviate dyslipidemia, raise FA levels, and improve treatment outcomes.

Moreover, placental function-related indices were more effectively regulated in the experimental group, with enhanced hCG-mediated thyroid stimulation and improved placental angiogenesis under titrated L-T4 dosing according to TSH levels. Additionally, the incidence of pregnancy/perinatal complications and adverse neonatal outcomes was significantly lower in the experimental group compared to the control group, supporting the superior effectiveness of TSH-adjusted L-T4 therapy in reducing adverse outcomes. The thyroid is a critical endocrine organ that influences female reproductive function. TSH receptors are present in various systems and tissues, maintaining normal growth, differentiation, and development. Excessive TSH release during pregnancy can cause pregnancy and perinatal complications, affecting neonatal outcomes. Studies have

identified TSH as a high-risk factor for gestational diabetes and pregnancy-induced hypertension [25, 26]. Overexpression of TSH increases the incidence of pregnancy/perinatal complications, affects fetal growth, and leads to poor neonatal outcomes. L-T4, functioning similarly to endogenous thyroid hormones, inhibits TSH elevation, corrects thyroid dysfunction, and reduces the incidence of pregnancy/perinatal complications and poor neonatal outcomes. Therefore, TSH-adjusted L-T4 therapy, driven by maternal thyroid needs, can help post-surgical DTC patients supplement thyroid hormones during pregnancy, reduce TSH production, mitigate hypothyroidism's impact on both mother and fetus, and reduce pregnancy/perinatal complications and adverse neonatal outcomes.

In conclusion, compared to consistent low-dose L-T4 suppressive therapy, titrated L-T4 dosing based on TSH levels in pregnant patients after DTC surgery can significantly control TSH levels, improve blood lipid profiles, FA levels, and placental function, and reduce pregnancy/perinatal complications, with better neonatal outcomes and promising clinical value. However, the study's conclusions may be constrained by its small sample size and limited population. Future research will aim to expand participant recruitment and optimize quality control to further explore the effects of L-T4 suppressive therapy in pregnant women after DTC surgery.

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Disclosure of conflict of interest

None.

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