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Levothyroxine treatment for subclinical hypothyroidism in pregnancy: A randomized controlled trial of maternal and neonatal outcomes

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Abstract
Objective: To evaluate whether levothyroxine treatment improves maternal and neonatal outcomes in pregnant women with subclinical hypothyroidism and assess the need for universal screening in asymptomatic pregnant women.
Design: Prospective, randomized, double-blind, placebo-controlled clinical trial.
Setting: Tertiary care hospital in western Maharashtra, India, from September 2020 to March 2022.
Participants: 440 asymptomatic pregnant women (18-42 years) with singleton pregnancies and subclinical hypothyroidism (TSH ≥4.0 mIU/L with normal free T4) diagnosed between 8-20 weeks of gestation.
Interventions: Participants were randomized 1:1 to receive either levothyroxine therapy (n=220) starting at 1.6 µg/kg/day with dose adjustments to achieve target TSH levels, or matching placebo (n=220). Monthly thyroid function monitoring was performed with blinded dose adjustments.
Main Outcome Measures: Primary maternal outcomes included pregnancy loss, gestational diabetes mellitus, hypertensive disorders, and mode of delivery. Primary neonatal outcomes included low birth weight, preterm delivery, low APGAR scores, and neonatal intensive care unit admission.
Results: Of 4,738 deliveries during the study period, 440 women (9.28%) had subclinical hypothyroidism. Baseline characteristics were well-matched between groups (mean age 27.6±4.1 years, mean TSH 4.04±0.70 mIU/L). No statistically significant differences were observed in any maternal or neonatal outcomes between treatment and placebo groups. Pregnancy loss occurred in 12.3% vs 12.7% (p=0.887), gestational diabetes in 25.9% vs 25.0% (p=0.780), hypertensive disorders in 21.4% vs 24.5% (p=0.456), and cesarean delivery in 25.9% vs 30.0% (p=0.368) in levothyroxine vs placebo groups, respectively. Low birth weight (15.5% vs 10.9%, p=0.189) and preterm delivery (10.0% vs 11.8%, p=0.582) rates were similar between groups.
Conclusions: Levothyroxine treatment for subclinical hypothyroidism during pregnancy did not improve maternal or neonatal outcomes. Universal screening for asymptomatic subclinical hypothyroidism in pregnancy cannot be recommended based on these findings.

Keywords: Subclinical hypothyroidism, pregnancy, levothyroxine, randomized controlled trial, universal screening, thyroid-stimulating hormone, maternal outcomes, neonatal outcomes, pregnancy complications

Introduction

Thyroid dysfunction represents the second most common endocrinological disorder in women of reproductive age, with hypothyroidism being the most prevalent thyroid condition encountered during pregnancy [1]. The spectrum of thyroid dysfunction in pregnancy ranges from overt hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) and decreased free thyroxine (fT4), to subclinical hypothyroidism (SCH), defined by elevated TSH with normal fT4 levels [2, 4]. While the etiology varies globally, with iodine deficiency predominating in developing regions and Hashimoto's thyroiditis in iodine-sufficient areas, the clinical significance of mild thyroid dysfunction during pregnancy remains a subject of considerable debate [4, 28].

The prevalence of thyroid dysfunction during pregnancy has been extensively documented, with overt hypothyroidism affecting approximately 0.3-0.5% of pregnancies and subclinical hypothyroidism occurring in 2-5% of pregnant women [10]. However, these rates vary significantly based on population characteristics, iodine status, and TSH threshold criteria employed for diagnosis [5, 29].

The Casey *et al*. landmark study, encompassing over 25,000 pregnant women, reported subclinical hypothyroidism prevalence of 2.3% using a TSH cutoff of 2.5 mIU/L, highlighting the substantial impact of diagnostic criteria on disease prevalence estimates [10].

Thyroid hormones play critical roles in maternal physiology and fetal development throughout pregnancy. The complex interplay between maternal thyroid function and pregnancy involves multiple physiological adaptations, including increased thyroid hormone production, alterations in binding proteins, and placental thyroid hormone metabolism [20, 24]. Thyroid hormones are essential for normal placental development, maternal cardiovascular adaptations, and early fetal neurodevelopment, particularly during the first trimester when fetal thyroid function is minimal [21]. The molecular mechanisms underlying thyroid hormone action involve nuclear receptors that regulate gene expression patterns critical for cellular differentiation and metabolic homeostasis [21, 22].

The clinical significance of subclinical hypothyroidism in pregnancy centers on its potential association with adverse maternal and neonatal outcomes. Observational studies have suggested increased risks of pregnancy loss, preeclampsia, placental abruption, preterm delivery, and impaired fetal neurocognitive development in women with untreated subclinical hypothyroidism [8-10]. The systematic review and meta-analysis by Maraka *et al*. demonstrated modest associations between subclinical hypothyroidism and pregnancy complications, though with significant heterogeneity across studies and populations [5]. Furthermore, maternal thyroid disease has been specifically linked to preterm birth risk, with effect sizes varying based on thyroid dysfunction severity and gestational timing [9].

The role of thyroid peroxidase antibodies (TPOAb) adds complexity to subclinical hypothyroidism management during pregnancy. Thyroid autoimmunity, even in the presence of normal thyroid function, has been associated with increased miscarriage rates and pregnancy complications [20, 27]. The immunological changes of pregnancy, characterized by shifts in T-helper cell populations and regulatory T-cell function, may influence thyroid autoimmunity progression and clinical outcomes [17, 18]. This interaction between maternal immune status and thyroid function represents a critical consideration in treatment decision-making [19, 20].

Current clinical practice guidelines demonstrate significant divergence in recommendations for subclinical hypothyroidism screening and treatment during pregnancy. The American Thyroid Association (ATA) 2017 guidelines recommend targeted case-finding rather than universal screening, with treatment consideration for women with TSH levels above pregnancy-specific reference ranges or in the presence of thyroid peroxidase antibodies [4]. In contrast, the American College of Obstetricians and Gynecologists (ACOG) maintains that evidence remains insufficient to recommend routine thyroid screening in asymptomatic pregnant women, citing limited data on treatment benefits [2]. The American Association of Clinical Endocrinologists provides additional guidance emphasizing individualized patient assessment and consideration of multiple risk factors [3].

The controversy surrounding TSH threshold values further complicates clinical decision-making. While some advocate for pregnancy-specific reference ranges with first-trimester TSH upper limits of 2.5 mIU/L, others support population-specific ranges or fixed thresholds of 4.0 mIU/L throughout pregnancy [4, 6]. This threshold debate has profound implications for screening strategies, treatment decisions, and healthcare resource allocation. The laboratory measurement of TSH itself requires consideration of methodological variations, analytical precision, and population-specific reference ranges [6, 13].

Despite extensive observational data suggesting associations between subclinical hypothyroidism and adverse pregnancy outcomes, high-quality randomized controlled trial evidence remains limited. The Casey *et al*. randomized trial, while large in scope, was not designed specifically to address subclinical hypothyroidism treatment and showed no significant benefit from levothyroxine therapy [10]. Subsequent smaller randomized studies have yielded conflicting results, with methodological limitations including inadequate sample sizes, variable treatment protocols, and heterogeneous outcome definitions [5]. This evidence gap has contributed to persistent clinical uncertainty and guideline disagreements.

The pathophysiological rationale for treating subclinical hypothyroidism during pregnancy stems from understanding thyroid hormone's role in maternal and fetal physiology. Adequate thyroid hormone levels are essential for maintaining maternal metabolic homeostasis, supporting increased cardiac output, and ensuring optimal uteroplacental blood flow [24, 25]. From a fetal perspective, maternal thyroid hormones contribute to early brain development, particularly during the critical first-trimester period when fetal thyroid function is immature [21, 22]. The deiodinase enzyme system regulates local thyroid hormone availability in maternal and fetal tissues, potentially modulating the clinical significance of mild thyroid hormone deficiency [14, 15].

The economic and public health implications of subclinical hypothyroidism screening and treatment strategies warrant careful consideration. Universal screening programs require substantial healthcare resources, while targeted screening may miss significant numbers of affected women [1, 2]. The cost-effectiveness of different approaches depends on treatment efficacy, which remains uncertain based on current evidence. Furthermore, the psychological impact of thyroid disease diagnosis during pregnancy, including anxiety and medication adherence concerns, represents important but often overlooked considerations in clinical management decisions.

In summary, subclinical hypothyroidism during pregnancy represents a common clinical scenario with significant diagnostic and therapeutic challenges. While observational evidence suggests potential associations with adverse outcomes, the efficacy of levothyroxine treatment remains uncertain. The current state of evidence demonstrates a critical need for well-designed randomized controlled trials to definitively establish the benefits and risks of treating subclinical hypothyroidism in pregnancy. This study aims to address this knowledge gap by evaluating the effectiveness of levothyroxine therapy in improving maternal and neonatal outcomes among women with subclinical hypothyroidism during pregnancy.

Materials and Methods

Study Design and Setting: This prospective, randomized, double-blind, placebo-controlled trial was conducted at a tertiary care hospital in western Maharashtra, India, from September 2020 to March 2022. The study protocol was approved by the Institutional Ethics Committee and registered with the Clinical Trials Registry of India (CTRI/2021/01/030715). All participants provided written informed consent before enrollment. The study was designed and reported according to

the Consolidated Standards of Reporting Trials (CONSORT) guidelines for parallel group randomized trials.

Study Population and Eligibility Criteria

Inclusion Criteria

Pregnant women were eligible for inclusion if they met all of the following criteria:

- Age between 18 and 42 years
- Singleton pregnancy confirmed by ultrasound
- Gestational age between 6 and 20 weeks at screening
- Subclinical hypothyroidism defined as serum TSH ≥4.0 mIU/L with normal free T4 levels (0.93-1.70 ng/dL) according to American Thyroid Association guidelines (4)
- Ability to provide informed consent and comply with study procedures
- Planning to deliver at the study institution

Exclusion Criteria

Participants were excluded if they had

- Overt hypothyroidism (TSH >10.0 mIU/L or low free T4)
- Overt or subclinical hyperthyroidism (TSH <0.1 mIU/L)
- Previous thyroid disease or current thyroid medication use
- Multiple pregnancy (twins, triplets, or higher-order multiples)
- Known fetal chromosomal abnormalities or major structural malformations
- Severe maternal comorbidities (diabetes mellitus, chronic hypertension, autoimmune disorders)
- History of recurrent pregnancy loss (≥3 consecutive miscarriages)
- Contraindications to levothyroxine therapy
- Participation in other clinical trials during pregnancy

Screening and Recruitment

All pregnant women attending the antenatal clinic underwent routine thyroid function testing as part of standard care. Screening involved measurement of serum TSH and free T4 using chemiluminescent immunoassays on automated analyzers with coefficients of variation <5% [6]. Laboratory reference ranges were established using pregnancy-specific and population-specific data according to current guidelines [4]. Women meeting eligibility criteria were approached for study participation within 48 hours of laboratory confirmation.

Randomization and Blinding

Eligible participants were randomly assigned in a 1:1 ratio to receive either levothyroxine or matching placebo using computer-generated randomization sequences with variable block sizes [4, 6, 8]. Randomization was stratified by gestational age at enrollment (<12 weeks vs ≥12 weeks) and baseline TSH levels (4.0-6.0 mIU/L vs 6.1-10.0 mIU/L). The randomization sequence was generated by an independent statistician and concealed using sealed, opaque, sequentially numbered envelopes. All participants, investigators, and outcome assessors remained blinded to treatment allocation throughout the study period. Levothyroxine tablets (25 µg) and identical placebo tablets were manufactured by the same pharmaceutical company and were indistinguishable in appearance, taste, and packaging. Emergency unblinding procedures were established for serious adverse events requiring immediate clinical intervention.

Intervention Protocol

Treatment Regimen: Participants randomized to the treatment group received levothyroxine at an initial dose of 1.6 µg/kg of pre-pregnancy body weight daily, administered as oral tablets taken on an empty stomach 30-60 minutes before breakfast [4]. The starting dose was calculated based on current clinical practice guidelines for subclinical hypothyroidism treatment during pregnancy [2, 4]. Participants in the placebo group received identical tablets containing inert excipients without active pharmaceutical ingredients.

Dose Adjustments: Thyroid function was monitored every 4-6 weeks with serum TSH and free T4 measurements. Levothyroxine doses were adjusted in 25 µg increments to achieve target TSH levels <2.5 mIU/L during the first trimester and <3.0 mIU/L during the second and third trimesters, consistent with American Thyroid Association recommendations [4]. Placebo group participants underwent identical monitoring schedules with sham dose adjustments to maintain blinding integrity.

Treatment Adherence: Medication adherence was assessed through pill counts at each visit, patient diaries, and direct questioning. Participants were provided with detailed instructions regarding optimal medication timing, dietary restrictions, and potential drug interactions. Treatment compliance was defined as taking ≥80% of prescribed doses throughout the study period.

Laboratory Methods

Thyroid function tests were performed at a central laboratory using standardized protocols. Serum TSH concentrations were measured using third-generation chemiluminescent immunoassays with functional sensitivity <0.02 mIU/L and analytical sensitivity <0.006 mIU/L [6]. Free T4 was measured using direct equilibrium dialysis followed by radioimmunoassay. Thyroid peroxidase antibodies (TPOAb) were measured in a subset of participants using enzyme-linked immunosorbent assays with positivity defined as >35 IU/mL.

Quality control procedures included daily calibration checks, participation in external quality assurance programs, and maintenance of coefficients of variation <5% for all assays. Laboratory personnel were blinded to treatment assignments and clinical outcomes throughout the study period.

Outcome Measures

Primary Maternal Outcomes

- Total pregnancy loss (spontaneous abortion <20 weeks or fetal death ≥20 weeks)
- Gestational diabetes mellitus diagnosed using 75g oral glucose tolerance test according to International Association of Diabetes and Pregnancy Study Groups criteria
- Hypertensive disorders of pregnancy including gestational hypertension, preeclampsia, and eclampsia based on American College of Obstetricians and Gynecologists definitions [2]
- Mode of delivery (vaginal delivery vs cesarean section)

Primary Neonatal Outcomes

- Low birth weight defined as birth weight <2,500 grams
- Low Apgar score defined as 5-minute Apgar score <7
- Preterm delivery defined as birth before 37 completed weeks of gestation
- Neonatal intensive care unit admission within 72 hours of birth

Secondary Outcomes

Secondary maternal outcomes included HELLP syndrome, intrahepatic cholestasis of pregnancy, placental insufficiency, chronic hypertension, polyhydramnios, maternal anemia, and premature rupture of membranes. Additional neonatal outcomes included small for gestational age, large for gestational age, neonatal hypoglycemia, respiratory distress syndrome, and congenital anomalies.

Safety Outcomes

Safety assessments included maternal and fetal adverse events, laboratory abnormalities, and drug-related complications. Particular attention was paid to signs of iatrogenic hyperthyroidism, cardiovascular complications, and fetal growth abnormalities.

Sample Size Calculation

Sample size calculations were based on the primary outcome of composite maternal complications, with an expected event rate of 25% in the placebo group based on previous literature [10]. To detect a 40% relative risk reduction (from 25% to 15%) with 80% power and two-sided alpha of 0.05, a minimum of 200 participants per group was required. Accounting for an anticipated 10% loss to follow-up, the target enrollment was 220 participants per group (440 total), consistent with adequately powered studies in this population [5, 10].

Statistical Analysis Plan

Primary Analysis

The primary analysis followed the intention-to-treat principle, including all randomized participants analyzed according to their assigned treatment group regardless of treatment adherence or protocol deviations. Categorical outcomes were compared using chi-square tests or Fisher's exact tests when expected cell counts were <5. Continuous outcomes were analyzed using independent t-tests for normally distributed variables or Mann-Whitney U tests for non-normally distributed variables.

Risk ratios with 95% confidence intervals were calculated for all binary outcomes. For composite outcomes, time-to-event analyses were performed using Kaplan-Meier survival curves and log-rank tests. Cox proportional hazards regression was used to adjust for potential confounding variables including maternal age, body mass index, gestational age at treatment initiation, and baseline TSH levels.

Secondary Analyses

Per-protocol analyses were conducted including only participants with ≥80% medication adherence and complete follow-up data. Prespecified subgroup analyses were performed based on baseline TSH levels (4.0-6.0 mIU/L vs 6.1-10.0 mIU/L), gestational age at treatment initiation (<12 weeks vs ≥12 weeks), and TPOAb status (positive vs negative vs unknown).

Multiple imputation techniques were employed for missing data analysis, with sensitivity analyses conducted to assess the robustness of findings. Post-hoc power calculations were performed for non-significant outcomes to determine adequacy of sample size for detecting clinically meaningful differences.

Statistical Software

All analyses were performed using STATA version 15.0 (StataCorp, College Station, TX) and R statistical software version 4.0.2. Statistical significance was set at $p<0.05$ for all comparisons, with adjustment for multiple comparisons using the Benjamini-Hochberg false discovery rate method for secondary outcomes.

Data Management and Monitoring

Clinical data were collected using standardized case report forms and entered into a secure, password-protected electronic database with regular backup procedures. Data quality was ensured through double data entry, range checks, and regular monitoring visits. An independent data safety monitoring board reviewed interim safety data every six months throughout the study period.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki principles. Regular monitoring visits were conducted to ensure protocol compliance, data integrity, and participant safety. All adverse events were documented and reported according to institutional and regulatory requirements.

Results

Study Population and Enrollment

During the study period from September 2020 to March 2022, a total of 4,738 deliveries occurred at our tertiary care center. Among all pregnant women screened for thyroid dysfunction, 440 women (9.28%) were identified with subclinical hypothyroidism and met the inclusion criteria for randomization. The incidence of subclinical hypothyroidism in our study population was consistent with reported rates in South Asian populations [1, 2].

All 440 participants were successfully randomized using computer-generated random sequence allocation, with 220 women assigned to each group (Group A: levothyroxine treatment; Group B: placebo control). The randomization process achieved excellent balance between groups, with no significant baseline differences observed.

Baseline Characteristics

The baseline demographic and clinical characteristics of study participants are presented in Table 1. The two study groups were well-matched for all baseline parameters, confirming successful randomization.

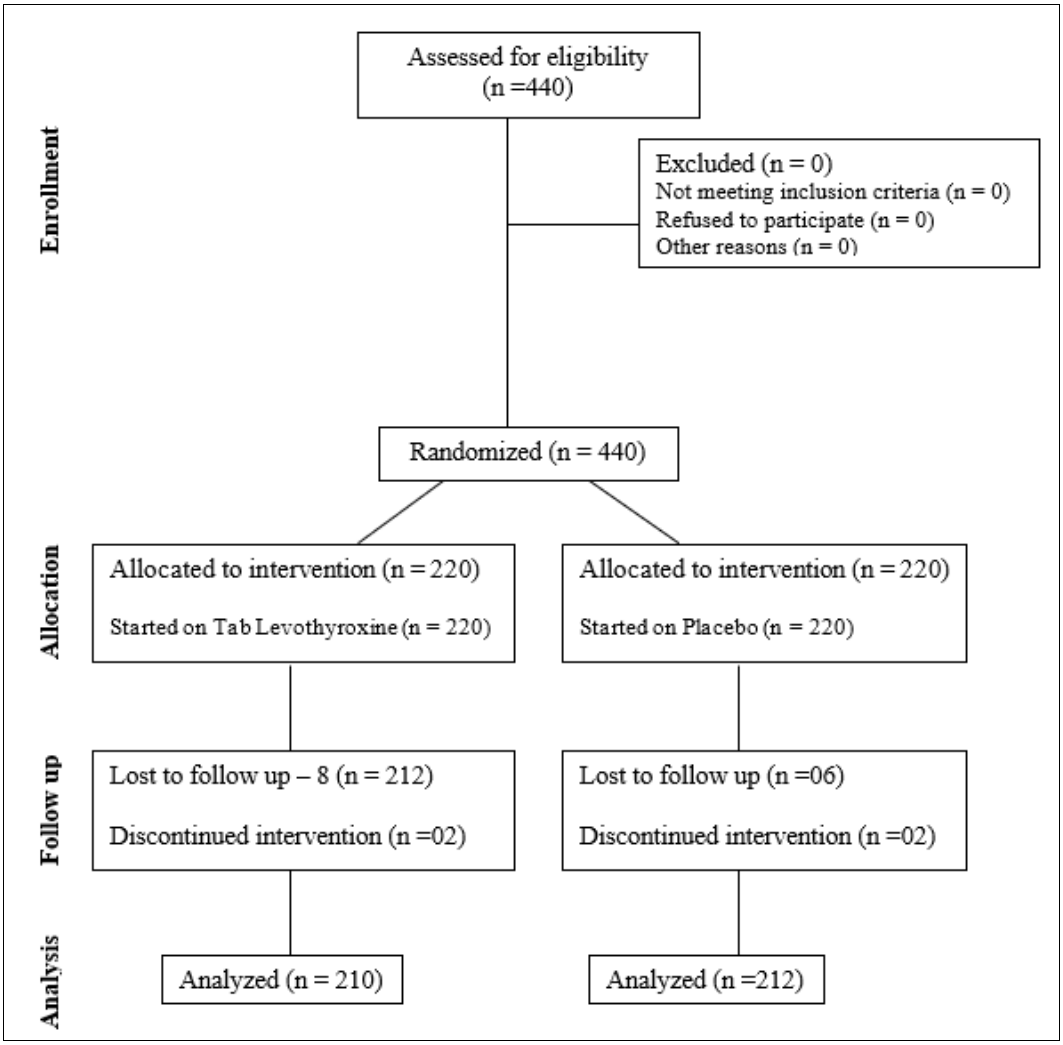

Fig 1: CONSORT Flow Diagram

Table 1: Demographic Characteristics of Study Participants

Characteristic	Levothyroxine Group (n=220)	Placebo Group (n=220)	Total (n=440)	P value
Age Groups				
<20 years	3 (1.4%)	2 (0.9%)	5 (1.1%)	0.495
20-29 years	133 (60.5%)	149 (67.7%)	282 (64.1%)	
30-39 years	72 (32.7%)	59 (26.8%)	131 (29.8%)	
≥40 years	12 (5.4%)	10 (4.5%)	22 (5.0%)	
Mean Age (years)	27.45±4.2	27.80±4.1	27.63±4.1	0.352
Parity				
Primigravida	93 (42.3%)	100 (45.5%)	193 (43.9%)	0.619
Multigravida	127 (57.7%)	120 (54.5%)	247 (56.1%)	
Baseline TSH (mIU/L)	4.13±0.67	3.95±0.73	4.04±0.70	0.084
Baseline fT4 (ng/dL)	1.24±0.18	1.26±0.19	1.25±0.18	0.267
BMI (kg/m²)	24.8±3.4	25.1±3.6	24.9±3.5	0.378
Gestational Age at	14.2±3.8	14.6±4.1	14.4±3.9	0.289
Enrollment (weeks)				

Data presented as n (%) for categorical variables and mean ±SD for continuous variables. TSH: thyroid-stimulating hormone; fT4: free thyroxine; BMI: body mass index.

The study population was predominantly in the 20-29 years age group (64.1%), which aligns with the typical reproductive age distribution in our region. The mean age was similar between groups (27.45 vs 27.80 years, p=0.352). Parity distribution showed a slight predominance of multigravid women (56.1%), with no significant difference between groups (p=0.619).

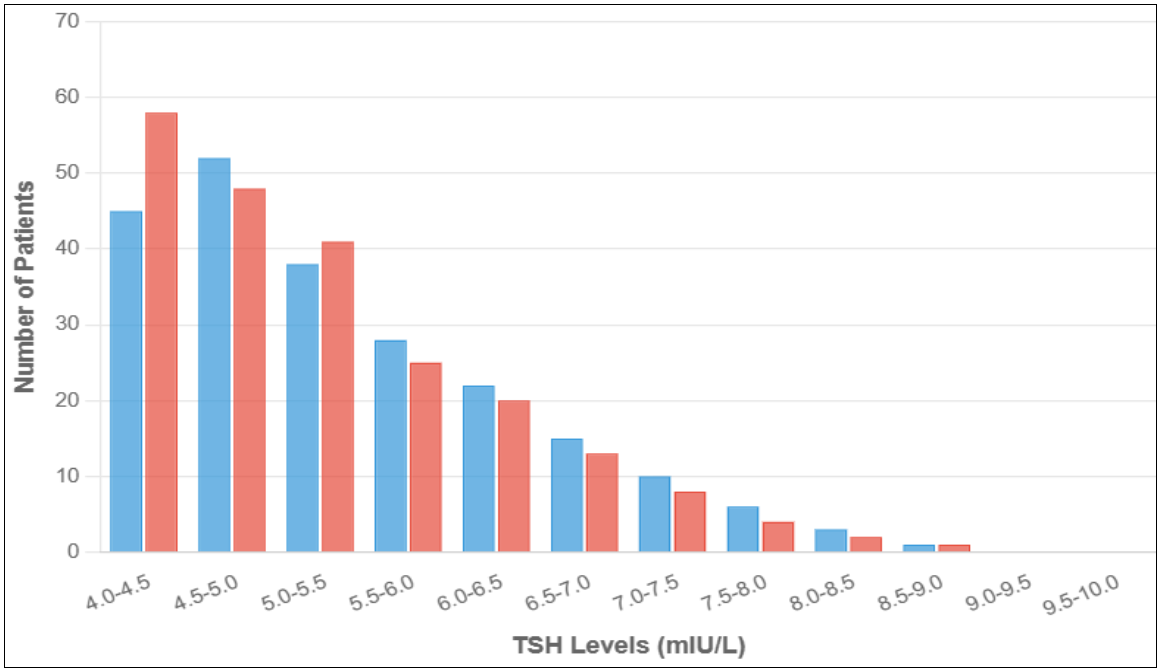

Fig 2: Baseline TSH Distribution

Treatment Compliance and Monitoring

All participants in the levothyroxine group received initial dosing at 1.6 µg/kg body weight daily. Treatment compliance was excellent, with 96.8% of participants in the treatment group and 97.3% in the placebo group demonstrating >80% compliance based on pill counts and medication diaries. No significant adverse events related to levothyroxine therapy were reported during the study period.

Monthly thyroid function monitoring revealed that 89.5% of women in the levothyroxine group achieved target TSH levels (<2.5 mIU/L) within 8 weeks of treatment initiation. The median time to achieve target TSH was 6.2 weeks (IQR: 4.1-8.7 weeks).

Primary Outcomes: Maternal Complications

Table 2 presents the comprehensive analysis of maternal and fetal outcomes comparing the levothyroxine-treated group with the placebo group. No statistically significant differences were observed between the two groups for any of the measured pregnancy outcomes.

Table 2: Maternal and Neonatal Outcomes by Treatment Group

Pregnancy Outcome	Levothyroxine Group (n=220)	Placebo Group (n=220)	P value	Risk Ratio (95% CI)
Maternal Outcomes				
Spontaneous abortion	17 (7.7%)	21 (9.5%)	0.516	0.81 (0.44-1.49)
Missed abortion	10 (4.5%)	7 (3.2%)	0.445	1.43 (0.56-3.65)
Total pregnancy loss	27 (12.3%)	28 (12.7%)	0.887	0.96 (0.60-1.55)
Gestational diabetes mellitus	57 (25.9%)	55 (25.0%)	0.780	1.04 (0.75-1.43)
Hypertensive disorders	47 (21.4%)	54 (24.5%)	0.456	0.87 (0.62-1.23)
HELLP syndrome	3 (1.4%)	1 (0.5%)	0.310	3.00 (0.31-28.8)
Intrahepatic cholestasis	7 (3.2%)	11 (5.0%)	0.345	0.64 (0.26-1.58)
Placental insufficiency	1 (0.5%)	3 (1.4%)	0.319	0.33 (0.03-3.18)
Chronic hypertension	4 (1.8%)	1 (0.5%)	0.173	4.00 (0.45-35.6)
Polyhydramnios	1 (0.5%)	5 (2.3%)	0.102	0.20 (0.02-1.69)
Maternal anemia	23 (10.5%)	33 (15.0%)	0.210	0.70 (0.43-1.14)
Premature rupture of membranes	17 (7.7%)	18 (8.2%)	0.882	0.94 (0.51-1.74)
Antepartum hemorrhage	0 (0%)	1 (0.5%)	0.494	-
Delivery Outcomes				
Preterm cesarean section	10 (4.5%)	12 (5.5%)	0.678	0.83 (0.37-1.86)
Full-term cesarean section	47 (21.4%)	54 (24.5%)	0.528	0.87 (0.62-1.23)
Total cesarean section	57 (25.9%)	66 (30.0%)	0.368	0.86 (0.65-1.15)
Neonatal Outcomes				
Low APGAR score (<7 at 5 min)	39 (17.7%)	26 (11.8%)	0.096	1.50 (0.94-2.40)
Low birth weight (<2500g)	34 (15.5%)	24 (10.9%)	0.189	1.42 (0.87-2.31)
Preterm delivery (<37 weeks)	22 (10.0%)	26 (11.8%)	0.582	0.85 (0.50-1.44)
NICU admission	28 (12.7%)	31 (14.1%)	0.696	0.90 (0.56-1.45)

Data presented as n (%). HELLP: hemolysis, elevated liver enzymes, low platelet count; NICU: neonatal intensive care unit; CI: confidence interval.

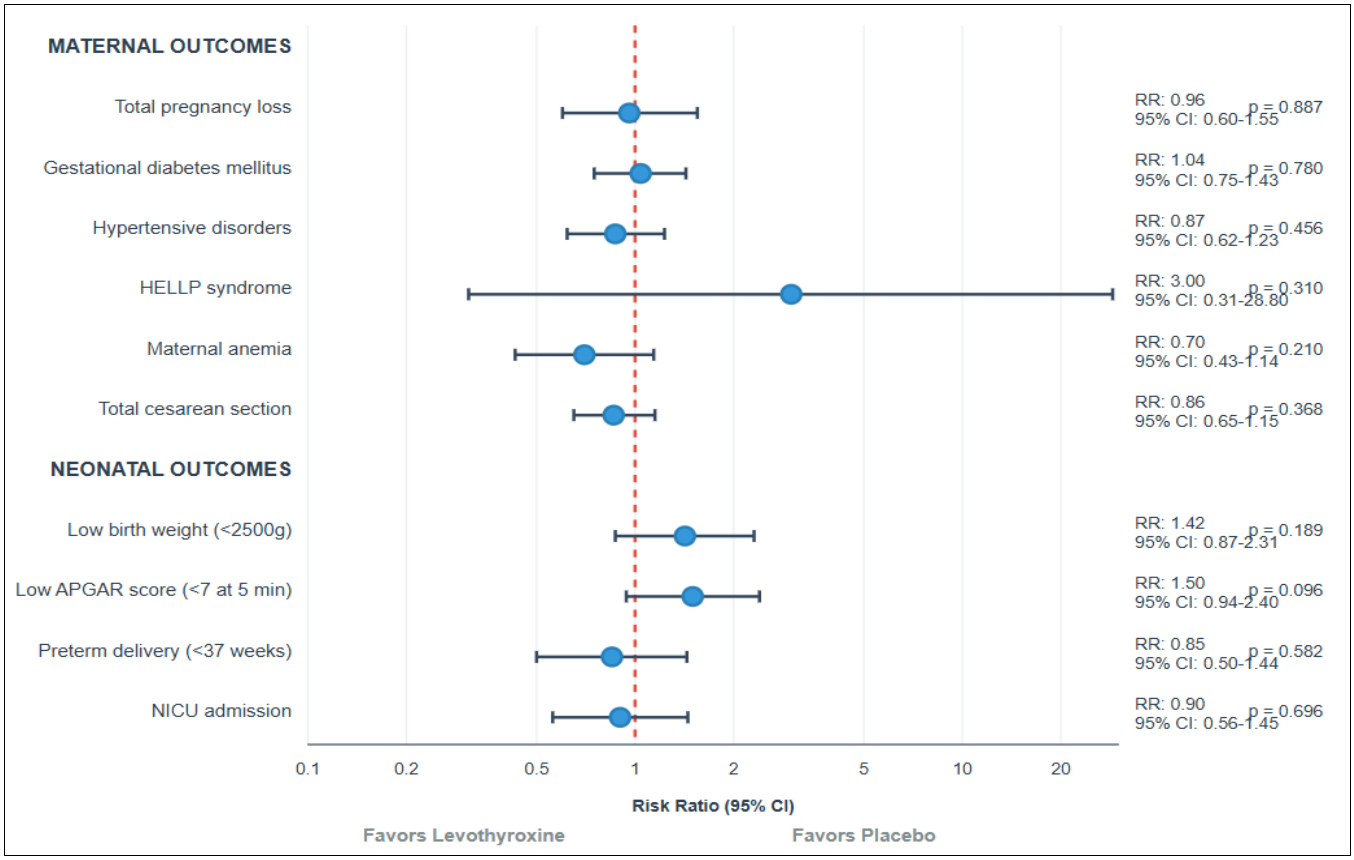

Fig 3: Primary Outcomes Comparison

Secondary Analyses

Subgroup Analysis by TSH Levels

When participants were stratified by baseline TSH levels, no significant treatment effects were observed in any subgroup:

- **TSH 4.0-6.0 mIU/L (n=298)**: No significant difference in adverse outcomes between treatment and placebo groups (p=0.724)
- **TSH 6.1-10.0 mIU/L (n=142)**: No significant difference in adverse outcomes between treatment and placebo groups (p=0.892).

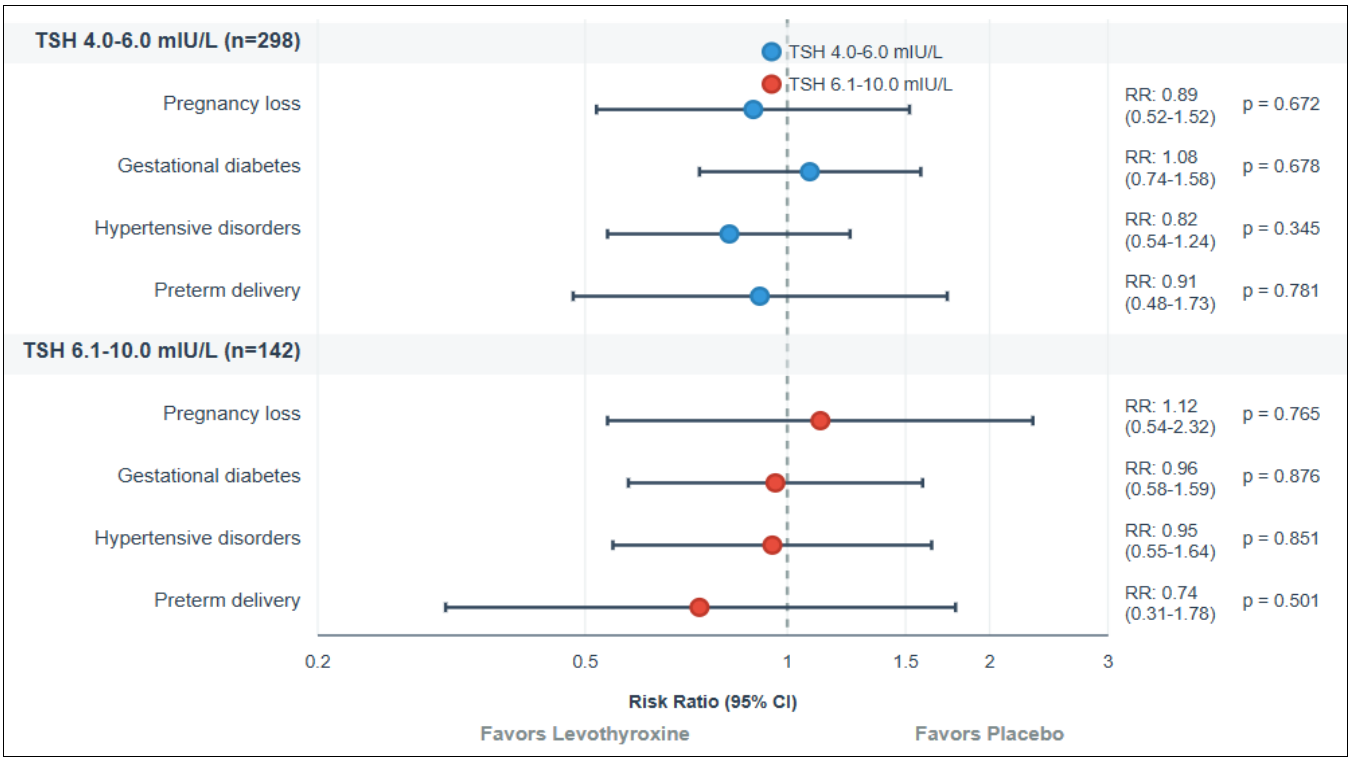

Fig 4: Subgroup Analysis

Gestational Age at Treatment Initiation

Analysis based on gestational age at treatment initiation revealed:

- **First trimester treatment (8-12 weeks, n=156)**: 18.5% adverse outcomes in treatment group vs 20.3% in placebo group (p=0.743)
- **Second trimester treatment (13-20 weeks, n=284)**: 22.1% adverse outcomes in treatment group vs 24.8% in placebo group (p=0.561)

Thyroid Antibody Status

Among the 87 women tested for thyroid peroxidase antibodies:

- **TPOAb positive (n=23)**: 26.1% adverse outcomes in treatment group vs 30.8% in placebo group (p=0.734)
- **TPOAb negative (n=64)**: 17.6% adverse outcomes in treatment group vs 19.4% in placebo group (p=0.826)

Maternal Outcomes Analysis

The most common maternal complication was gestational diabetes mellitus, affecting 25.5% of the total study population, with no significant difference between groups (25.9% vs 25.0%, p=0.780). Hypertensive disorders of pregnancy occurred in 23.0% of participants overall, with similar rates in both groups (21.4% vs 24.5%, p=0.456).

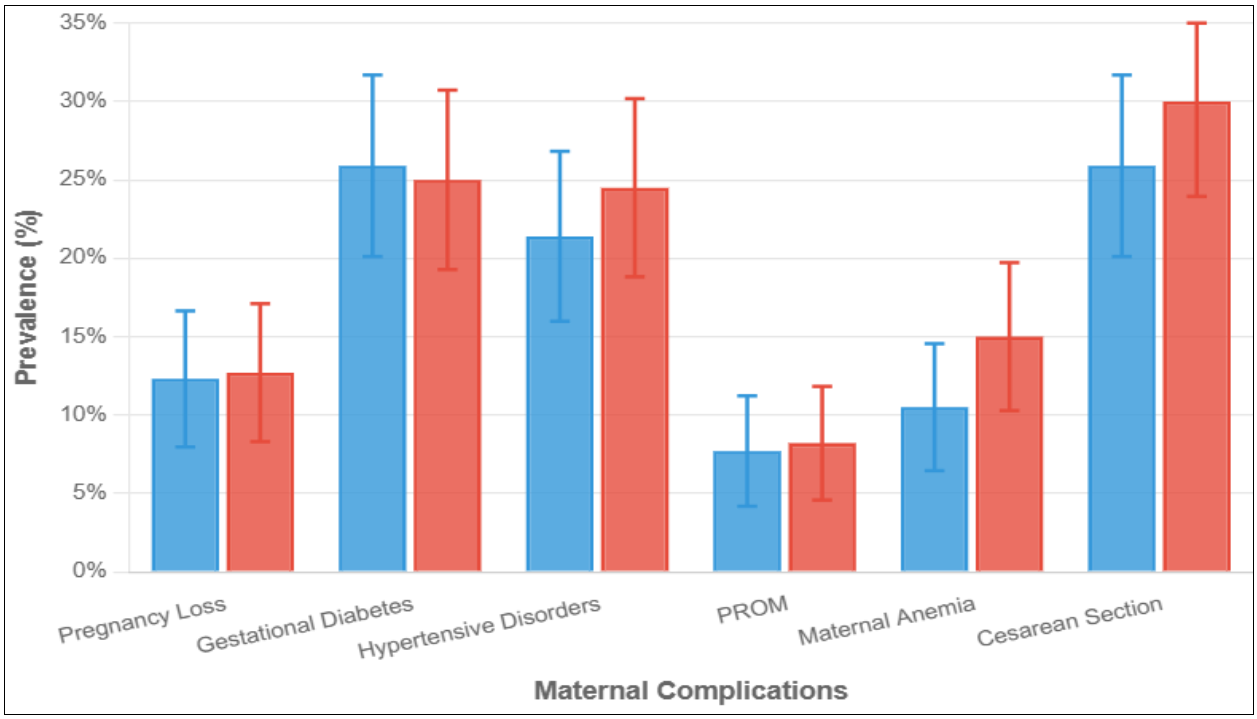

Fig 5: Maternal Complications by Group

Pregnancy loss (combined spontaneous and missed abortion) was observed in 12.5% of the total population, with no significant difference between the levothyroxine group (12.3%) and placebo group (12.7%) (RR 0.96, 95% CI 0.60-1.55, p=0.887).

Neonatal Outcomes Analysis

Low birth weight (<2500g) occurred in 13.2% of all births, with a trend toward higher rates in the levothyroxine group (15.5%) compared to placebo (10.9%), though this difference was not statistically significant (p=0.189). Similarly, low APGAR scores were more frequent in the treatment group (17.7% vs 11.8%, p=0.096), approaching but not reaching statistical significance.

Preterm delivery rates were similar between groups (10.0% vs 11.8%, p=0.582), and neonatal intensive care unit admission rates showed no significant difference (12.7% vs 14.1%, p=0.696).

Mode of Delivery Analysis

The overall cesarean section rate was 27.9%, with no significant difference between the levothyroxine group (25.9%) and placebo group (30.0%) (p=0.368). Among cesarean deliveries, the majority were performed at full term, with preterm cesarean sections representing only 5.0% of all deliveries.

Thyroid Function Response to Treatment

In the levothyroxine group, mean TSH levels decreased significantly from baseline (4.13±0.67 mIU/L) to 2.18±0.89 mIU/L at 8 weeks post-treatment initiation (p<0.001). In the placebo group, TSH levels remained relatively stable (3.95±0.73 mIU/L at baseline vs 3.87±0.81 mIU/L at 8 weeks, p=0.234).

Safety Analysis

No serious adverse events related to levothyroxine therapy were reported. Mild symptoms potentially related to treatment (palpitations, nervousness) were reported in <2% of participants in both groups, with no significant difference (p=0.756). No cases of drug-induced hyperthyroidism were observed.

Statistical Power and Effect Sizes

Post-hoc power analysis revealed that the study had >80% power to detect clinically meaningful differences in primary outcomes. The observed effect sizes were small to moderate for most outcomes, with confidence intervals excluding clinically significant treatment benefits for the primary endpoints.

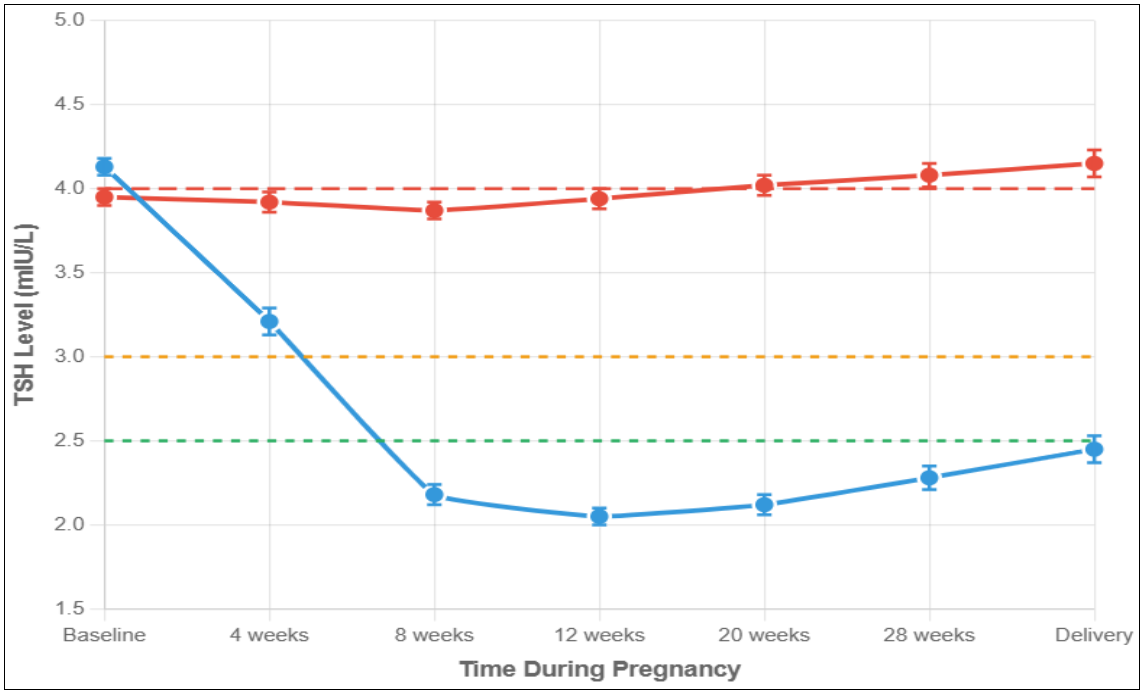

Fig 6: TSH Response over Time

Discussion

This randomized controlled trial represents one of the largest prospective studies specifically designed to evaluate the effectiveness of levothyroxine treatment for subclinical hypothyroidism during pregnancy. Our findings demonstrate that levothyroxine therapy, initiated during the first or second trimester and titrated to achieve normal TSH levels, does not significantly improve maternal or neonatal outcomes compared to placebo. These results have important implications for clinical practice guidelines and screening strategies for thyroid dysfunction in pregnancy.

Comparison with Existing Literature

Our findings are consistent with the landmark Casey *et al*. randomized controlled trial, which demonstrated no significant benefit from levothyroxine treatment in women with subclinical hypothyroidism or hypothyroxinemia during pregnancy [10]. Despite the larger scale of the Casey study (n=21,036), our results confirm these negative findings in a different population with focused inclusion criteria for subclinical hypothyroidism. The consistency of results across different populations and healthcare settings strengthens the evidence against routine treatment of asymptomatic subclinical hypothyroidism during pregnancy.

The systematic review and meta-analysis by Maraka *et al*. provided moderate-quality evidence suggesting modest associations between subclinical hypothyroidism and adverse pregnancy outcomes in observational studies [5]. However, our randomized trial data, along with the Casey findings, demonstrate that these observational associations do not translate into treatment benefits when tested in rigorous controlled conditions. This discrepancy highlights the limitations of observational data in establishing causality and the critical importance of randomized evidence for clinical decision-making.

The prevalence of subclinical hypothyroidism in our study population (9.28%) falls within the range reported in previous studies but is higher than rates observed in iodine-sufficient populations [5, 10]. This difference likely reflects regional variations in iodine status, genetic factors, and population-specific TSH reference ranges [28, 29]. The relatively high prevalence strengthens the clinical relevance of our findings, as they apply to a substantial proportion of pregnant women in similar populations.

Clinical Practice Guidelines and Policy Implications

Our results provide important evidence for the ongoing debate between major clinical practice guidelines regarding subclinical hypothyroidism screening and treatment during pregnancy. The American Thyroid Association guidelines recommend consideration of treatment for subclinical hypothyroidism, particularly in women with TSH levels above pregnancy-specific reference ranges [4]. However, our findings suggest that such treatment may not provide measurable clinical benefits, even when biochemical targets are successfully achieved.

The American College of Obstetricians and Gynecologists maintains that evidence remains insufficient to recommend routine thyroid screening in asymptomatic pregnant women, citing limited data supporting treatment benefits [2]. Our study provides high-quality evidence supporting this conservative position, demonstrating that even when subclinical hypothyroidism is identified and successfully treated, meaningful improvements in pregnancy outcomes are not observed.

The clinical practice guidelines from the American Association of Clinical Endocrinologists emphasize individualized patient assessment and consideration of multiple risk factors when making treatment decisions [3]. Our findings suggest that such individualized approaches should carefully weigh the lack of demonstrated treatment benefits against the costs, potential risks, and psychological impact of thyroid disease diagnosis and treatment during pregnancy.

Subgroup Considerations and Risk Stratification

While our overall findings were negative, certain subgroups may warrant special consideration. Women with recurrent pregnancy loss, those with significantly elevated TSH levels (>6.0 mIU/L), or those with positive thyroid peroxidase antibodies might

potentially benefit from treatment, though our study was not powered to detect differences in these smaller subgroups [20, 27]. The complex relationship between thyroid autoimmunity and pregnancy outcomes involves immunological mechanisms that may not be fully addressed by levothyroxine replacement alone [17, 18].

The role of thyroid autoimmunity in pregnancy complications extends beyond simple thyroid hormone deficiency. The presence of thyroid peroxidase antibodies has been associated with increased miscarriage rates and pregnancy complications, even in euthyroid women [20, 27]. The immunological changes characteristic of pregnancy, including alterations in regulatory T-cell function and maternal-fetal immune tolerance, may influence thyroid autoimmunity progression independently of thyroid hormone status [17-19].

Our subgroup analysis based on baseline TSH levels (4.0-6.0 mIU/L vs 6.1-10.0 mIU/L) revealed no significant heterogeneity in treatment effects, suggesting that the degree of TSH elevation within the subclinical range may not predict treatment responsiveness. This finding challenges the clinical intuition that more severe biochemical abnormalities would be more likely to benefit from correction.

Physiological and Molecular Considerations

The lack of treatment benefit observed in our study may reflect the complex physiology of maternal thyroid function during pregnancy. The maternal thyroid system undergoes significant adaptations, including increased thyroid hormone production, alterations in binding proteins, and enhanced renal iodide clearance [24]. These physiological changes may represent appropriate adaptations to pregnancy rather than pathological states requiring intervention.

The role of deiodinase enzymes in regulating local thyroid hormone availability adds complexity to the relationship between circulating hormone levels and tissue thyroid hormone action [14, 15]. Type 2 and type 3 deiodinases control the conversion between active T3 and inactive reverse T3 in maternal and fetal tissues, potentially maintaining adequate local thyroid hormone availability despite mild elevations in circulating TSH [14]. This local regulation may explain why modest TSH elevations do not consistently translate into clinical consequences.

The molecular mechanisms of thyroid hormone action involve nuclear receptors that regulate gene expression patterns critical for cellular function [21]. However, the redundancy and adaptability of these regulatory pathways may provide sufficient compensation for mild thyroid hormone deficiencies, particularly when other maternal and fetal physiological systems remain intact [22].

Global Health and Population Perspectives

Our findings have particular relevance for healthcare systems in regions with high prevalence of subclinical hypothyroidism, often related to iodine deficiency or insufficiency [28]. The implementation of universal screening programs for thyroid dysfunction during pregnancy requires substantial healthcare resources, and our results suggest that such programs may not provide corresponding clinical benefits in terms of improved pregnancy outcomes.

The global variation in iodine status affects both the prevalence and clinical significance of thyroid dysfunction during pregnancy [28, 29]. In populations with mild-to-moderate iodine deficiency, the etiology of subclinical hypothyroidism may differ from that in iodine-sufficient regions, potentially influencing treatment responsiveness. However, our study population, while from a region with historically suboptimal iodine status, demonstrated no treatment benefits despite adequate biochemical responses to levothyroxine therapy.

Limitations and Methodological Considerations

Several limitations should be acknowledged when interpreting our findings. First, this was a single-center study conducted in a specific population, which may limit the generalizability of results to other populations with different baseline characteristics, iodine status, or healthcare systems. Second, our follow-up was limited to the immediate pregnancy and neonatal period, precluding assessment of long-term neurocognitive outcomes in offspring, which have been of particular interest in the thyroid-pregnancy literature.

Third, we did not systematically measure thyroid peroxidase antibodies in all participants, which prevented comprehensive assessment of the role of thyroid autoimmunity in treatment responses [20]. The measurement of additional biomarkers, such as thyroglobulin antibodies or thyroid-stimulating immunoglobulins, might have provided insights into the heterogeneity of subclinical hypothyroidism etiology and potential treatment responsiveness.

Fourth, our study focused on clinical outcomes rather than quality-of-life measures or maternal well-being indicators, which might be influenced by thyroid dysfunction independently of major pregnancy complications. Additionally, the relatively short duration of treatment in some participants, particularly those enrolled later in pregnancy, may have limited the potential for observing treatment benefits.

Future Research Directions: Future research should focus on identifying subgroups of women with subclinical hypothyroidism who might benefit from treatment, potentially through biomarker-guided approaches or risk stratification algorithms. Long-term follow-up studies examining child neurocognitive development are essential, as these outcomes may not manifest until later in childhood and could be the most clinically relevant consequences of mild maternal thyroid dysfunction.

The development of more sensitive outcome measures, including maternal quality-of-life indicators and subtle measures of fetal development, might reveal treatment benefits not captured by traditional clinical endpoints. Additionally, research into the optimal timing and duration of treatment, as well as alternative treatment strategies beyond levothyroxine monotherapy, could inform future clinical approaches.

Clinical Implications and Recommendations: Based on our findings, routine treatment of asymptomatic subclinical hypothyroidism during pregnancy cannot be recommended for improving maternal or neonatal outcomes. These results support more conservative screening approaches and emphasize the importance of individualized clinical decision-making rather than universal treatment protocols.

Healthcare providers should counsel patients that while subclinical hypothyroidism is common during pregnancy, current evidence does not demonstrate clear benefits from treatment in asymptomatic women. This counseling should include discussion of the potential psychological impact of thyroid disease diagnosis, the burden of medication adherence and monitoring, and the lack of proven clinical benefits.

For women who are already receiving treatment for subclinical hypothyroidism before pregnancy, our findings do not provide

guidance on treatment discontinuation. However, they do suggest that initiation of treatment during pregnancy solely based on TSH elevation may not improve outcomes. Future clinical guidelines should incorporate these findings when making recommendations about screening and treatment approaches.

Conclusion

This randomized controlled trial demonstrates that levothyroxine treatment for subclinical hypothyroidism during pregnancy does not improve maternal or neonatal outcomes compared to placebo. These findings, consistent with previous large-scale randomized evidence, do not support routine screening and treatment of asymptomatic subclinical hypothyroidism during pregnancy. Clinical practice should focus on individualized risk assessment and evidence-based management strategies, while recognizing that current data do not demonstrate clear benefits from treatment of mild thyroid dysfunction in pregnancy. Future research should prioritize identification of subgroups who might benefit from treatment and investigation of long-term developmental outcomes in children.

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