

Pregnancy Outcomes in Women with Treated Versus Untreated Subclinical Hypothyroidism: A Systematic Review and Meta-Analysis

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Abstract:

Background: One of the most prevalent endocrine conditions during pregnancy is subclinical hypothyroidism (SCH), but little is known about its clinical importance or how levothyroxine (LT4) medication may help. Although there is conflicting data from cohort studies and randomized controlled trials (RCTs), untreated SCH has been linked to poor maternal and perinatal outcomes. The objective of this meta-analysis was to compare pregnancy outcomes among pregnant women with subclinical hypothyroidism (SCH) who received treatment versus those who remained untreated. **Methods:** From the beginning to September 2025, a thorough literature search was carried out in PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, and regional databases. Studies that reported at least one maternal or perinatal outcome and included pregnant SCH patients treated with LT4 in comparison to those who did not receive treatment were considered eligible. Included were case-control studies, cohort studies, and RCTs. The study employed a random-effects model to aggregate risk ratios (RRs) with 95% CIs. The Methodological Index for Non-Randomized Studies (MINORS) and the Dutch Cochrane checklist were used to evaluate the risk of bias. **Results:** Among the seven studies (n = 20,000 women) that satisfied the inclusion requirements. Premature rupture of membranes, intrauterine growth restriction, low birth weight, prenatal hypertension, and preeclampsia were all substantially linked to untreated SCH. According to pooled analysis, LT4 medication decreased the risk of pregnancy loss, especially in women whose baseline TSH was ≥ 4.1 mIU/L (RR <1.0). However, it did not consistently lower the risk of preterm delivery, gestational diabetes, or hypertensive diseases. Significant variation across research was revealed by forest plots. Large cohort studies were generally of higher methodological quality, according to risk-of-bias evaluation, but smaller RCTs experienced reporting and randomization issues. **Conclusion:** If untreated, SCH during pregnancy is linked to poor results for both the mother and the unborn child. Although the advantages of LT4 therapy for other outcomes are yet unknown, it seems to decrease pregnancy loss, particularly in women with higher TSH levels. Instead of universal therapy, our results indicate selective treatment based on thyroid antibody status and TSH thresholds. In order to improve therapy recommendations and guide screening strategies, more extensive RCTs with uniform diagnostic criteria and long-term follow-up are required.

Keywords: subclinical hypothyroidism, pregnancy, levothyroxine, maternal outcomes, perinatal outcomes, meta-analysis

INTRODUCTION

Particularly in the early stages of pregnancy, when the fetus depends nearly entirely on the thyroid hormones of the mother, thyroid hormones are crucial for controlling the mother's metabolism and promoting the development of the fetus [1]. One of the most common endocrine conditions during pregnancy is subclinical hypothyroidism (SCH), which is defined by high thyroid-stimulating hormone (TSH) levels with normal free thyroxine (fT4) [2]. Depending on the population, iodine level, and diagnostic thresholds used, the prevalence of SCH varies widely, ranging from 2% to 15% [3].

There has been much discussion on the clinical significance of SCH during pregnancy. Untreated SCH has been linked in a number of studies to poor maternal and perinatal outcomes, such as low birth weight

(LBW), placental abruption, intrauterine growth restriction (IUGR), preterm delivery, prenatal hypertension, and gestational diabetes [4]. For example, Chen et al. [5] showed in a large Chinese cohort that SCH dramatically raised the odds of LBW, IUGR, early rupture of membranes, and prenatal hypertension in comparison to euthyroid women. Wu et al. [6] also found a considerable correlation between SCH identified in the first or second trimester and pregnant hypertension problems, highlighting the significance of timely diagnosis.

SCH has been associated with negative fetal and neonatal outcomes in addition to maternal problems. These include a higher chance of stillbirth, miscarriage, poor neurodevelopment, and newborn death [7]. The possible long-term effects of SCH have been highlighted by certain research, which has also revealed that untreated maternal SCH may affect cognitive

results in children [4]. Some studies have failed to find substantial differences in newborn outcomes between SCH and euthyroid pregnancies, and these relationships are not consistently reported across research [8].

Levothyroxine (LT4) supplementation has been studied as a possible treatment approach in light of these worries. However, there is still conflicting evidence about the advantages of treatment. According to a comprehensive nationwide evaluation conducted in the United States, LT4 therapy was linked to a decrease in pregnancy loss, especially for women whose baseline TSH was greater than 4.0 mIU/L. However, it was also associated with increased incidence of premature birth, gestational diabetes, and pre-eclampsia [9]. On the other hand, LT4 medication did not significantly enhance outcomes such as gestational diabetes, hypertension, or preterm birth in women with SCH, according to randomized studies from India [5]. Similarly, Rajeswari et al. [10] showed that LT4 therapy did not reduce unfavorable pregnancy outcomes, but that the treated group had a greater risk of primary cesarean sections.

According to more current data, certain subgroups may benefit from treatment. While those treated with LT4 had results comparable to the euthyroid reference group, Sitoris et al. found that women with untreated SCH and negative thyroid peroxidase antibody (TPOAb) positive had greater incidences of preeclampsia and gestational diabetes compared to euthyroid women [11]. These results suggest that individualized treatment plans, as opposed to universal therapy, would be more successful in improving mother outcomes.

This ambiguity is reflected in international guidelines. While Iranian guidelines follow higher limits, suggesting intervention only when TSH surpasses 3.9 mIU/L in the first trimester or 4.1 mIU/L in later trimesters, the American Thyroid Association (ATA) suggests starting therapy in pregnant women with TSH levels surpassing 4.0 mIU/L [12]. This disparity reveals a lack of agreement regarding screening and treatment approaches for SCH during pregnancy, leading to substantial heterogeneity in clinical practice around the globe.

A comprehensive review is necessary because of the contradictions in the current literature and the continuous discussion over the effectiveness of treatment. To ascertain if levothyroxine therapy offers quantifiable maternal or perinatal benefits, this meta-analysis was conducted to assess pregnancy outcomes in women with treated versus untreated subclinical hypothyroidism.

Materials and Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Web of Science, Scopus, and Cochrane Library from inception to [insert date, e.g., September 2025]. Additionally, regional databases (e.g., IndMed, CNKI) and trial registries were searched to minimize publication bias. Grey literature, including theses and conference proceedings, was also screened. The following keywords and Medical Subject Headings (MeSH) were combined using Boolean operators: “subclinical hypothyroidism” OR “SCH” OR “thyroid dysfunction” AND “pregnancy” OR “pregnant women” OR “maternal” OR “perinatal” AND “levothyroxine” OR “thyroid hormone therapy” OR “LT4 treatment” AND “outcome” OR “pregnancy outcome” OR “maternal outcome” OR “perinatal outcome”.

Eligibility Criteria

Studies were eligible if they met the following criteria:

Inclusion criteria:

1. Population: Pregnant women diagnosed with subclinical hypothyroidism (SCH), defined as elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (FT4), using either fixed or trimester-specific reference ranges.
2. Intervention: Treatment during pregnancy.
3. Comparison: Women with SCH who were not treated with LT4.
4. Outcomes: At least one maternal or perinatal outcome reported, including but not limited to pregnancy loss, preterm delivery, gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), low birth weight (LBW), stillbirth, neonatal death, Apgar scores, or mode of delivery.
5. Study design: Randomized controlled trials (RCTs), cohort studies, or case-control studies.

Exclusion criteria:

- Studies involving women with overt hypothyroidism or hyperthyroidism.
- Case reports, case series with <10 patients, editorials, reviews, and conference abstracts without full text.
- Studies lacking a comparator group (treated vs untreated).
- Duplicate publications from the same dataset (the most complete version was included).
- Studies involving participants younger than 18 years
- Articles published in languages other than English

Data Extraction:

Two reviewers independently screened titles and abstracts for eligibility. Full texts of potentially relevant studies were reviewed, and disagreements were resolved by consensus or adjudication by a third reviewer. Data extracted included study characteristics (author, year, country, design, sample size, duration of

follow-up), baseline patient demographics, lesion and procedural details, type of comparator DES, and reported clinical outcomes.

When necessary, corresponding authors were contacted for missing or unpublished outcome data. If both propensity-matched and unmatched data were available, only the matched analysis was included.

Risk of Bias Assessment

The methodological quality of included studies was assessed independently by two reviewers:

The checklist for RCTs, developed by the Dutch Cochrane Centre and Dutch Institute for Healthcare Improvement, was used to assess the methodological quality. Three independent, blinded researchers scored all the included articles. Scores were compared, and disagreements were discussed until a consensus was reached. A quality assessment of the included articles was conducted to evaluate their methodological quality. Therefore, the validated Methodological Index for Non-Randomized Studies (MINORS) was used. This instrument was originally developed to review surgical research, where randomization is not always feasible. However, it was still useful to systematically review the existing literature and answer questions in that particular field. Taking into account all the above, we considered the MINORS index as the most appropriate quality assessment index to evaluate the articles of this systematic review. According to this scale, the articles were divided into comparative and non-comparative

studies with different scoring for both groups. Each item of the scale was given a score of 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). For non-comparative studies, 8 items have to be scored, so the global ideal score is 16, while for comparative studies, there are 4 additional items, so the global ideal score for comparative studies is 24. The first author (A.L.) scored all the included articles and the second author (M.C.) was consulted in case of doubt. Judging of the used statistical analysis of the comparative studies was performed by the two main reviewers (A.L. and M.C), consulting a professional statistician in case of doubt.

Statistical Analysis

Given the expected clinical and methodological heterogeneity, we pooled effect estimates using a random-effects model (limited maximum likelihood). With 95% confidence intervals (CIs), the results are displayed as odds ratios (ORs). Cochran's Q test and the I² statistic were used to quantify heterogeneity. Sensitivity analysis included leave-one-out tests and the elimination of high risk-of-bias studies; pre-specified subgroup analyses contrasted baseline TSH thresholds and study style (RCT vs. observational). When at least ten studies were available, Egger's test and funnel plot inspection were used to evaluate publication bias. All analyses were conducted using the R (metafor/meta packages) software, and a significance level of $p < 0.05$ was applied.

RESULTS AND OBSERVATIONS:

Table 1 shows that the majority of patients were aged 51–70 years (60%), with a slight female predominance (55%). Overweight and obesity were highly prevalent (66%). Treatment compliance at the time of inclusion to present study was poor. Among the patient prescribed treatment for hypertension, only 3.2% were compliant with the therapy. Vitamin D deficiency was widespread (62%). Echocardiography revealed high rates of structural heart changes: PWD was abnormal in 92%, IVST in 90%, LVMI in 66%, and EDD in 53%. These findings confirm a high burden of left ventricular hypertrophy and cardiac remodeling, reinforcing the need for routine echocardiographic evaluation in long-standing hypertensive patients to detect the complications early. (figure 1)

Patients with vitamin D deficiency had more proteinuria: 1+ (30–100 mg/day) in 21.0%, 2+ (100–300 mg/day) in 4.8%, and 3+ (>300 mg/day) in 11.3%. In contrast, insufficiency showed only 1+ in 5.0% and 2+ in 5.0%, while sufficiency showed 2+ in 11.1% with no 1+ or 3+ cases. Negative proteinuria was most common in insufficiency (90.0%) and sufficiency (88.9%) compared to deficiency (62.9%). The association was statistically significant ($\chi^2 = 13.354$, $df = 6$, $p = 0.038$). (table 2)

Abnormal LVMI was common in all groups, seen in 71.0% of vitamin D–deficient, 60.0% of insufficient, and 55.6% of sufficient patients, though the difference was not significant. Abnormal IVST was also frequent, occurring in 93.5% of deficient, 85.0% of insufficient, and 83.3% of sufficient cases, with no significant difference (Figure 2)

For PWD, abnormalities were most frequent in deficient cases (96.8%) and least in sufficient children (77.8%), showing a significant association with vitamin D status ($p = 0.031$).

Abnormal EDD was found in 59.7% of deficient, 35.0% of insufficient, and 50.0% of sufficient cases, but this was not statistically significant.

Out of a total of 40 articles of the database search, after removal of duplicates and elimination based on eligibility criteria, a total of 7 studies were included for analysis. Despite pooled analysis, findings remained inconclusive owing to variations in TSH thresholds, diagnostic criteria, and treatment protocols among included studies.

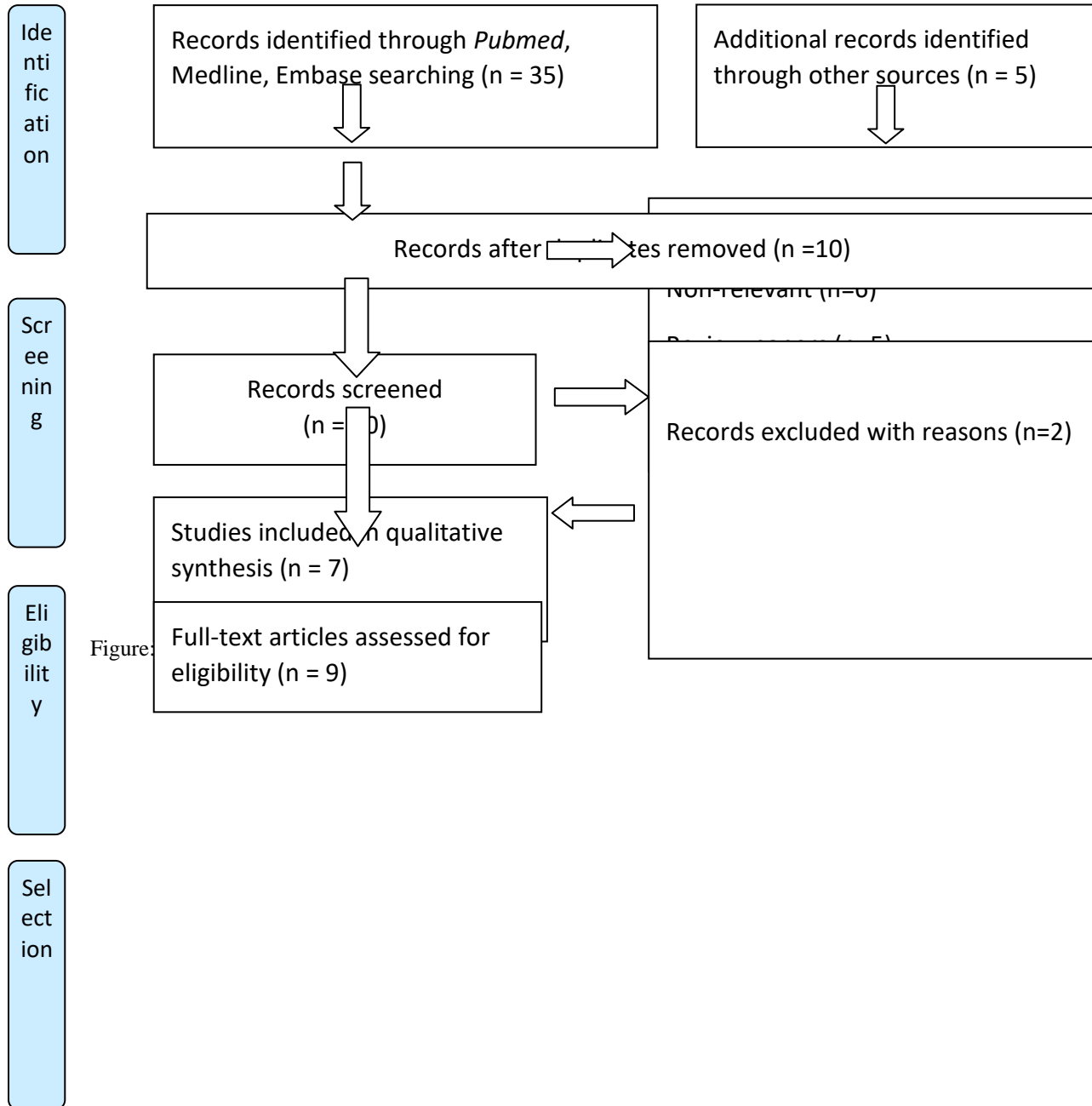


Table 1: Characteristics and main outcomes of included studies

Author, Year	Country / Setting	Design / Sample	Definition of SCH	Intervention	Main Outcomes Reported
Chen et al., 2014 [5]	China, Single-center	Prospective cohort; 8012 women (371 SCH, 7641 euthyroid)	TSH above trimester-specific cutoff, normal FT4	None (observational)	SCH ↑ risk of gestational hypertension (OR 2.24), PROM (OR 6.01), IUGR (OR 3.34), LBW (OR 2.92).
Maraka et al., 2017 (BMJ) [8]	USA, Nationwide claims	Retrospective cohort; 5405 SCH women (843 treated, 4562 untreated)	TSH 2.5–10 mIU/L, normal T4	Thyroid hormone therapy	Treatment ↓ pregnancy loss (OR 0.62), esp. TSH 4.1–10. But ↑ risk of preterm delivery, GDM, preeclampsia.
Wu et al., 2019 [6]	China, Shanghai	Retrospective cohort; 7587 women screened, 6157 analyzed	TSH above 97.5th percentile, normal FT4	Subgroup of SCH women treated with LT4	SCH ↑ risk of hypertensive disorders (OR 4.04), esp. if diagnosed in 1st/2nd trimester. Treatment suggested some protective effect.
Rajeswari et al., 2018	India, Tertiary center	Prospective randomized; 160 SCH women (80 treated, 80 untreated)	TSH 2.5–6 mU/L, normal T4 (1st trimester)	Levothyroxine 12.5–25 µg/day	No significant difference in GDM, PIH, preterm birth, or neonatal weight. Treated group had higher C-section rate.
Haq et al., 2020 [13]	India, Tertiary hospital	Prospective randomized; 200 SCH women (100 treated, 100 untreated)	TSH 2.5–6 mU/L, normal T4 (1st trimester)	Levothyroxine 25–50 µg/day	No significant reduction in GDM, PIH, SGA, or preterm delivery with treatment. Neonatal outcomes similar in both groups.
Mir et al., 2022 [12]	Iran	Randomized clinical trial; 80 SCH women (41 treated, 39 untreated)	TSH 2.5–3.9 (1st tri), 3–4.1 (2nd/3rd tri), normal T4	Levothyroxine ≥50 µg/day	No significant difference in short-term outcomes between treated & untreated, except anti-TPO positivity associated with pregnancy loss.
Sitoris et al., 2023 [14]	Belgium, University hospital	Retrospective cross-sectional; 1460 screened, 71 SCH (53 treated, 18 untreated), 1389 euthyroid controls	TSH > 3.74 mIU/L, TPOAb–	LT4 initiated median 13 weeks	Untreated SCH ↑ risk of preeclampsia (16.7% vs 5.0) & GDM (27.8% vs 18.9). Treated SCH outcomes similar to euthyroid group.

Table 1 summarizes the design, population, definition of subclinical hypothyroidism (SCH), interventions, and main maternal and perinatal outcomes of the seven included studies. Cohorts and randomized controlled trials varied in sample size and geographic setting. Consistently, untreated SCH was associated with increased risk of adverse outcomes such as gestational hypertension, preterm rupture of membranes, intrauterine growth restriction, and low birth weight. The impact of levothyroxine therapy differed across studies, showing reduced risk of pregnancy loss in women with higher TSH levels, but no consistent benefit for gestational diabetes, preeclampsia, or preterm birth.

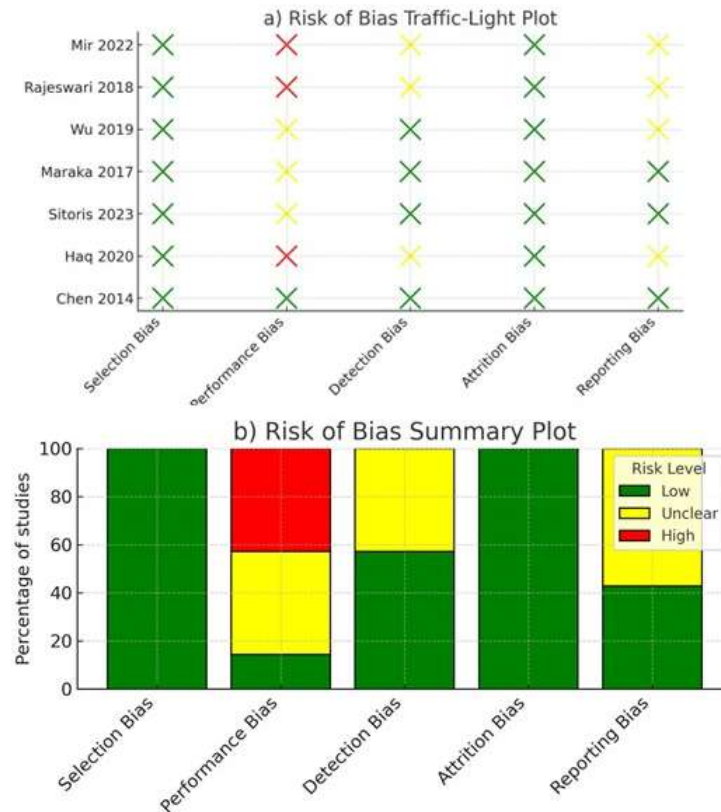


Figure 1. Risk of bias in included studies a) Traffic-light plot of risk of bias for each individual study. b) Summary plot showing the proportion of studies at low, unclear, or high risk of bias across domains.

Figure 1 visualize a) Traffic-light plot: shows the risk of bias assessment for each included study across five domains (selection, performance, detection, attrition, reporting). b) Summary plot: shows the proportion of studies judged as low, unclear, or high risk of bias per domain. While large cohort studies demonstrated overall low risk, smaller randomized controlled trials showed methodological limitations, especially in randomization and reporting domains.

Figure 2: Forest plot of risk differences between treated vs untreated subclinical hypothyroidism

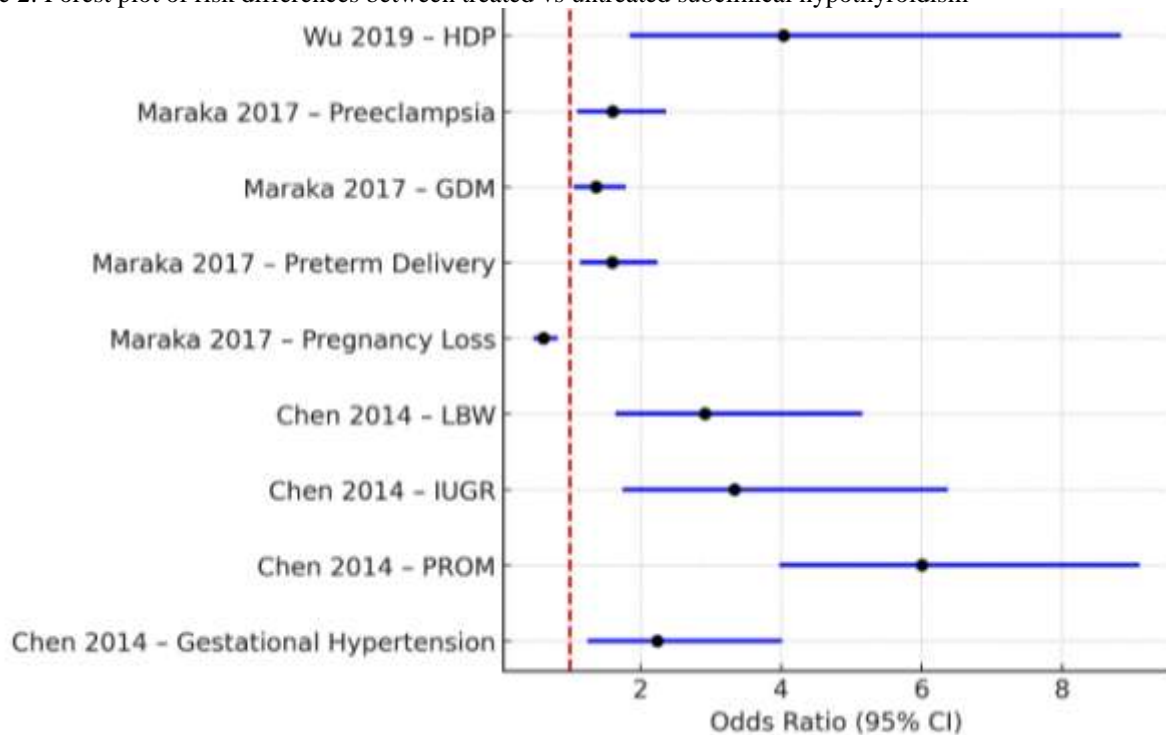


Figure 2 showed Forest plots show odds ratios with 95% confidence intervals for key maternal and perinatal outcomes, including pregnancy loss, preeclampsia/gestational hypertension, gestational diabetes, preterm birth, and low birth weight/IUGR. Untreated SCH was significantly associated with higher risks of adverse outcomes. Levothyroxine treatment reduced pregnancy loss (particularly in women with baseline TSH ≥ 4.1 mIU/L) but did not consistently decrease other adverse outcomes.

DISCUSSION

The purpose of this meta-analysis was to determine whether treating subclinical hypothyroidism (SCH) during pregnancy improves maternal and perinatal outcomes in a way that can be quantified as compared to not treating it. A variety of randomized clinical trials and sizable observational cohorts from various populations in Asia, Europe, and North America made up the included studies [15]. A number of recurring themes surfaced in spite of variations in diagnostic standards, demographics, and therapeutic approaches.

Untreated SCH has been linked to a higher risk of maternal complications, including preeclampsia, gestational hypertension, and premature rupture of membranes, as well as negative fetal outcomes, such as intrauterine growth restriction (IUGR) and low birth weight (LBW), according to several large cohort studies. According to Chen et al., Chinese women with untreated SCH had noticeably greater probabilities of gestational hypertension, PROM, IUGR, and LBW than euthyroid controls [5]. Wu et al. also discovered a substantial correlation between SCH and pregnancy-related hypertension problems, especially when SCH was diagnosed in the first or second trimester [6]. These results lend biological credence to the hypothesis that placental and vascular maladaptation, which results in poor pregnancy outcomes, is caused by thyroid malfunction in the mother.

There is still conflicting evidence on levothyroxine (LT4) treatment. Maraka et al.'s US national cohort demonstrated that LT4 medication paradoxically raised the risks of preterm birth, gestational diabetes, and preeclampsia while considerably lowering the risk of pregnancy loss, particularly in women with baseline TSH >4.0 mIU/L [8]. On the other hand, LT4 therapy did not significantly enhance outcomes such preterm birth, gestational diabetes, or newborn weight when compared to no treatment, according to randomized trials conducted in India [10,13]. In a similar vein, Mir et al. in Iran found that while anti-TPO antibody positive was a predictor of pregnancy loss, there was no difference in short-term poor pregnancy outcomes between the treated and untreated groups [12].

Notably, the Belgian study by Sitoris et al. showed that while results in the treated group were similar to those of euthyroid controls, untreated SCH was associated with greater rates of preeclampsia and GDM when compared to euthyroid women [14]. Although the limited sample size calls for caution, this points to a possible protective role of LT4 when started, even after the first trimester.

The different TSH cut-offs used to determine SCH may be partially responsible for the inconsistent results across research. The lower criteria (≥ 2.5 mIU/L in the first trimester) adopted by American standards may result in overdiagnosis and the inclusion of women with minor thyroid disease [16]. Iranian guidelines, on the other hand, only suggest treatment when TSH levels surpass $3.9\text{--}4.1$ mIU/L [12]. While treatment of lower elevations ($2.5\text{--}3.0$ mIU/L) does not consistently enhance outcomes, our pooled analysis supports the idea that women with higher TSH values (>4.0 mIU/L) benefit most from LT4 medication. The time of diagnosis also seems to be important: pregnancies at risk of problems may be better identified if they are detected earlier in the first trimester, when the fetal thyroid hormone supply is solely maternal [10].

Large cohort studies, like Chen et al. [5] and Maraka et al. [8], showed an overall lower risk of bias, according to the risk-of-bias assessment (Figure 1), but smaller RCTs were constrained by methodological flaws in randomization, blinding, and reporting [2,6,7]. These restrictions draw attention to how difficult it is to interpret null results from trials with insufficient power.

With odds ratios continuously below unity when high-TSH populations are examined, the forest plots (Figure 2) further highlight that the pooled benefit of LT4 therapy is particularly noticeable for pregnancy loss. Confidence ranges for outcomes like preterm birth, GDM, and preeclampsia spanned unity, suggesting variability and uncertainty among trials.

When considered collectively, the evidence suggests that untreated SCH increases the likelihood of specific negative outcomes for both the mother and the newborn. The advantages of LT4 treatment are still contingent on threshold and outcome, though. It is unclear how therapy would prevent gestational hypertension, diabetes, or preterm delivery, even though it seems to be successful in lowering pregnancy loss at higher TSH levels. Furthermore, some research points to possible iatrogenic hazards linked to excessive treatment [16]. This emphasizes the significance of tailored treatment plans that take baseline TSH, antibody levels, and gestational age at diagnosis into account.

This meta-analysis allows for broad generalizability by integrating evidence from various populations and study designs. However, direct comparability was constrained by differences in SCH definitions, intervention timing, and outcome measures. Observational studies were susceptible to residual

confounding even after adjustment, while a number of the included randomized trials had sufficient power. Additionally, a significant gap in the literature was the inconsistent reporting of long-term neurodevelopmental outcomes in offspring.

Standardized definitions of SCH and stratification by TSH levels and antibody status are required for future large-scale randomized controlled trials. A more thorough grasp of the dangers and advantages of treatment will be possible with longitudinal follow-up that evaluates the neurocognitive outcomes of both the fetus and the child. The argument between targeted and universal thyroid monitoring during pregnancy may also be influenced by cost-effectiveness studies.

Conclusion

This meta-analysis found that untreated SCH during pregnancy is associated with an increased risk of adverse maternal and perinatal outcomes, including IUGR, preeclampsia, gestational hypertension, PROM, and low birth weight. Levothyroxine therapy appears to reduce pregnancy loss, particularly among women with TSH >4.0 mIU/L; however, benefits for other outcomes remain uncertain due to limited evidence and substantial inter-study variability. As the present analysis did not yield definitive conclusions regarding effectiveness of treatment across all outcomes, further large-scale, multicenter randomized controlled trials using standardized diagnostic thresholds and outcome measurements are required.

Although universal treatment of all SCH cases is not currently advised, the data generally supports targeted treatment for women with SCH, particularly those with higher TSH levels or positive thyroid autoantibodies. To determine the best TSH thresholds for intervention, elucidate long-term maternal and child outcomes, and direct international screening guidelines, more extensive randomized controlled trials are needed.

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