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REVIEW

Levothyroxine for subclinical hypothyroidism during pregnancy: an updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose We aimed to perform a systematic review and meta-analysis addressing the efficacy of levothyroxine therapy in pregnant women with subclinical hypothyroidism considering most recent evidence and subgroups of interest for clinical practice.

Methods PubMed, Embase, and Cochrane Central were searched from inception for randomized controlled trials (RCTs) comparing levothyroxine with placebo or no intervention in pregnant women with subclinical hypothyroidism. We used a random-effects model and conducted subgroup analyses based on thyroid peroxidase antibody status, thyroid stimulating hormone levels, fertility treatment, and recurrent miscarriage.

Results We included 11 RCTs comprising 2,749 pregnant women with subclinical hypothyroidism. Patients treated with levothyroxine (1,439; 52.3%) had significantly lower risk of pregnancy loss (risk ratio 0.69; 95% confidence interval 0.52–0.91; $p < 0.01$; 6 studies). However, there was no significant association between levothyroxine and live birth (risk ratio 1.01; 95% confidence interval 0.99–1.03; $p = 0.29$; 8 studies). No statistically significant interaction was observed across subgroups ($p > 0.05$).

Conclusion Levothyroxine replacement therapy for subclinical hypothyroidism during pregnancy may decrease pregnancy loss when early prescribed. Nevertheless, further investigation is needed in patients with thyroid stimulating hormone above four milliunits per liter, especially when associated with recurrent miscarriage or infertility.

Keywords Subclinical hypothyroidism · Pregnancy · Thyroid peroxidase antibody · Thyroid autoimmunity · Recurrent miscarriage

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What does this study adds to the clinical work?

This study investigated the potential benefit of levothyroxine in patients with subclinical hypothyroidism during pregnancy considering different subgroups of clinical interest. While levothyroxine may decrease the risk of pregnancy loss, additional studies are required to investigate this treatment effect in patients with a history of recurrent miscarriage or infertility, particularly in cases where thyroid-stimulating hormone levels exceed four milliunits per liter.

Introduction

Subclinical hypothyroidism (SCH) is a condition characterized by elevated serum thyroid-stimulating hormone (TSH) levels in the setting of normal serum thyroid hormone levels and the presence or absence of symptoms [1]. SCH is considered the most common thyroid disorder in pregnant women, with an estimated prevalence between 2.3 and 13.5% [2–6]. Despite its substantial prevalence and several studies suggesting an association with adverse maternal–fetal outcomes [7, 8], there is still controversy on whether medically managing pregnant women with SCH is appropriate. This can be attributed to the fact that the diagnostic criteria for SCH in pregnancy has evolved over time, and consequently, the literature contains divergent findings due to the un-uniformity of TSH cutoff values used for the diagnosis of SCH.

Given the geographic and ethnic variability in normal TSH concentrations during pregnancy, a reference limit of 4 milliunits per liter (mU/L) has been recommended by the 2017 American Thyroid Association (ATA) guidelines as a diagnostic criteria for SCH in the first trimester [9], which updated a previous recommendation of a limit of 2.5 mU/L from the 2011 guidelines [10]. At present, only two meta-analyses adopted the new 2017 ATA criteria and have shown no significant improvement with the use of levothyroxine therapy for pregnant women when analyzing only randomized controlled trials (RCTs) [11, 12]. However, these meta-analyses applied only one TSH levels criteria and had an overly narrow eligibility criteria, which may have led to less statistically powered conclusions. Moreover, additional RCTs have recently been published ever since, significantly increasing the pooled population and the statistical power that may result from further analyses.

Therefore, we performed an updated systematic review and meta-analysis of RCTs evaluating the role of levothyroxine in the treatment for SCH during pregnancy. Of note, we aimed to carry out a more inclusive analysis using both definition of SCH, and to explore the role of baseline characteristics on the efficacy of levothyroxine therapy in this population.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we aimed to assess pregnant women diagnosed with SCH (population) who were allocated to levothyroxine (intervention) or no levothyroxine (placebo or no intervention—control) and evaluate the results of pregnancy loss, live birth, and preterm birth before 37 weeks (outcomes) among RCTs (type of study) that followed patients until delivery (time). We included studies regardless of the selected ATA definition or ethnicity. Trials composed by euthyroid control, patients with thyroid diseases other than SCH, or overlapping populations, defined as studies recruiting from the same institution over an overlapping period, and screening studies, defined as trials that allocated patients to thyroid screening versus no screening and treated only those who presented with abnormal TSH levels, were excluded.

Two authors (H.P. and H.C.M.) systematically searched PubMed, Embase, and Cochrane Central from inception to February 1, 2023. The following terms with their respective mesh terms were used without filters, publication date, or language restrictions: (levothyroxine OR LT4 OR "thyroxine supplementation") AND ("subclinical hypothyroidism" OR SCH) AND (pregnancy OR pregnant). The references from all included studies, previous systematic reviews and meta-analyses were also searched manually for any additional studies. Eventual conflicts were resolved by consensus among the authors. Two authors (G.R.N. and H.C.M.) independently extracted data from selected RCTs. Baseline data included: (1) maternal age; (2) gestational age; (3) TSH levels; thyroid peroxidase antibody (TPOAb) status, fertility treatment, and recurrent miscarriage. Individual patient-level data was not requested.

Our study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement [13] and recommendations from Cochrane Collaboration Handbook for Systematic Reviews of Interventions [14]. We prospectively registered our research protocol in the International Prospective Register of Systematic Reviews (PROSPERO) on February 8, 2023 (ID CRD42023395160).

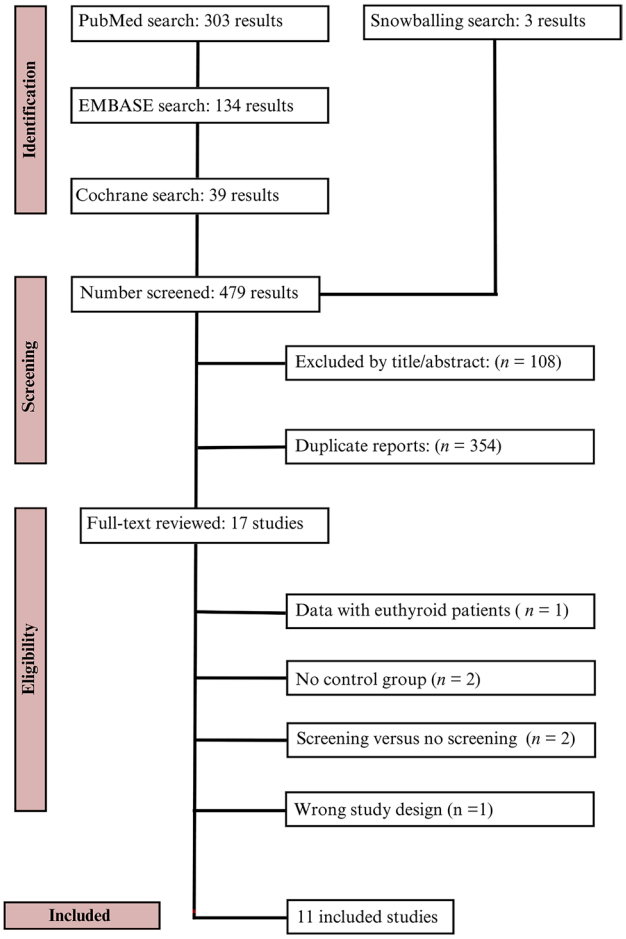

Fig. 1 PRISMA flow diagram

Data analysis

Outcomes evaluated were (1) pregnancy loss, defined as a composite of miscarriage and stillbirth; (2) live birth; and (3) preterm birth before 37 weeks. We also conducted subgroup analyses for live birth based on TPOAb status (positive or negative), TSH levels (2.5–4 or 4–10 mU/L), fertility treatment (with or without fertility treatment), and recurrent miscarriage (with or without recurrent miscarriage).

Quality assessment

We evaluated the risk of bias using version 2 of the Cochrane Risk of Bias Assessment Tool (RoB-2) for RCTs, where each study scored as high, moderate, or low risk of bias. The assessment was performed and documented by two independent authors (L.F.R and M.V.BM.). Disagreements were resolved through consensus after discussing reasons for discrepancy. Publication bias was assessed through the generation of funnel plots.

Statistical analysis

We considered p values of less than 0.05 to be statistically significant and computed risk ratios (RR) using the Inverse Variance test for dichotomous outcomes with 95% confidence intervals (CI) as a measure of effect size. To assess heterogeneity, Cochran's Q test and I^2 statistics were utilized. We classified I^2 values of <25%, 25–75%, and >75%

Table 1 Characteristics of included trials

Study	Country	Sample size[a]	Levothyroxine initiation	TSH range	TPOAb status	Fertility treatment	Recurrent miscarriage
Casey 2017	USA	339×338	Until 20 weeks of pregnancy	4–10 mU/L	Both	Both	Both
Dhillon-Smith et al. [19]	UK	145×143	Before pregnancy	2.5–3.6 mU/L	Positive	Both	No data
Kim et al. [15]	South Korea	17×12	Before pregnancy	4.5–10 mU/L	Both	Yes	Not specified
Lazaro 2019	Spain	181×182	Not specified	2.5–4.9 mU/L	Both	Not specified	No
Leng 2022	China	243×251	First trimester	2.5–10 mU/L	Negative	Not specified	Both
Nazarpour et al. [20]	Iran	38×34	First trimester	4–10 mU/L	Positive	No infertility	Not specified
Nazarpour 2018	Iran	183×183	First trimester	2.5–10 mU/L	Negative	Yes	Not specified
Rahman et al. [16]	Egypt	12×9	Before pregnancy	4–10 mU/L	Not specified	Yes	Not specified
Van-Dijk et al. [17]	Netherlands	39×30	Before pregnancy	2.5–4 mU/L	Positive	Both	Yes
Wang e al. [18]	China	180×97	Before pregnancy	2.5–4.78 mU/L	Positive	Yes	Yes
Zhao 2018	China	62×31	Until second trimester	2.5–10 mU/L	Both	Not specified	No

mU/L milliunits per liter, *TPOAb* thyroid peroxidase antibody, *TSH* thyroid stimulating hormone, *USA* United States of America, *UK* United Kingdom

[a]Number of patients in intervention and control group respectively

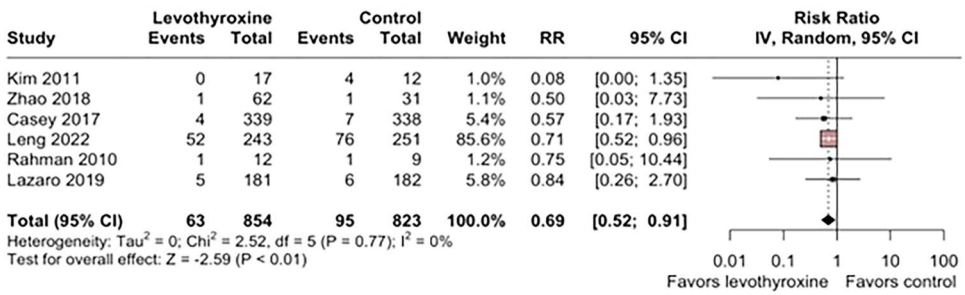

Fig. 2 Forest plot of pregnancy loss

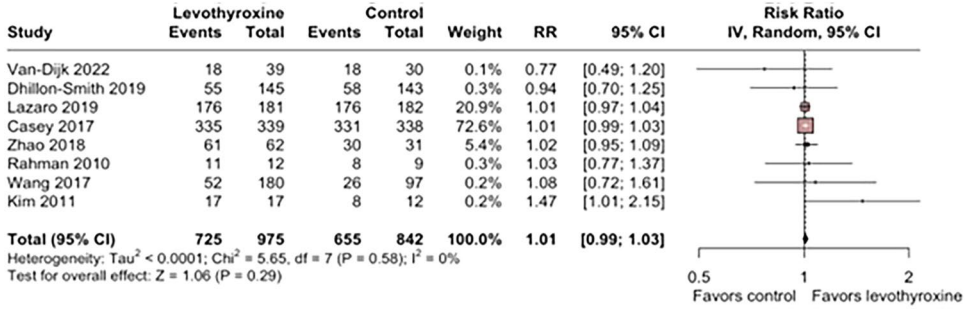

Fig. 3 Forest plot of live birth

as representing low, moderate, and high heterogeneity, respectively. To account for potential disparities in both clinical and methodological aspects across studies, we applied random effects models, and performed subgroup analyses to investigate heterogeneity between study-specific estimates. Our meta-analysis was conducted using the meta package for RStudio version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection and characteristics

The initial search yielded 479 results. After removing duplicate studies, 371 records were identified through database searching and their summaries were screened for eligibility. Of these, 17 remained and were fully reviewed based on the predefined eligibility criteria (Fig. 1). A total of 11 RCTs were included comprising 2,749 patients, of whom 1,439 (52.3%) were in the levothyroxine group. Table 1 summarizes individual studies characteristics. Although five studies allocated participants before pregnancy [15–19], the other trials enrolled patients up to the second trimester. Moreover, only four RCTs encompassed pregnant women with TPOAb positivity [17–20]. The maternal age ranged from 26.9 to 36.1 years.

Pooled analyses

In a pooled analysis of 6 trials, levothyroxine therapy was associated with a significant 31% reduction of the risk of pregnancy loss compared to no therapy (RR 0.69; 95% CI 0.52–0.91; $p < 0.01$; 6 studies; Fig. 2). Out of the 11 studies, 8 provided information on the incidence of live birth, which showed no significant association between levothyroxine and live birth (RR 1.01; 95% CI 0.99–1.03; $p = 0.29$; 8 studies; Fig. 3). Furthermore, when compared with no treatment, levothyroxine was not associated with preterm birth before 37 weeks (RR 0.71; 95% CI 0.49–1.03; $p = 0.07$; 6 studies; Figure S1). There was no significant interaction in live birth across all subgroup analyses ($p > 0.05$) and no subgroup demonstrated an increase in this outcome compared with no treatment (Figs. 4 and 5).

Quality assessment

Individual RCT appraisal is shown in Figure S2. No study was considered to have a high risk of bias. Although the limited number of included studies, there was no evidence of publication bias based on the funnel plots (Figures S3 to S5).

Discussion

In this systematic review and updated meta-analysis of 11 RCTs and 2,749 patients with SCH, we compared levothyroxine with placebo or no treatment, evaluating pregnancy loss, live birth, and preterm birth. Our main findings were:

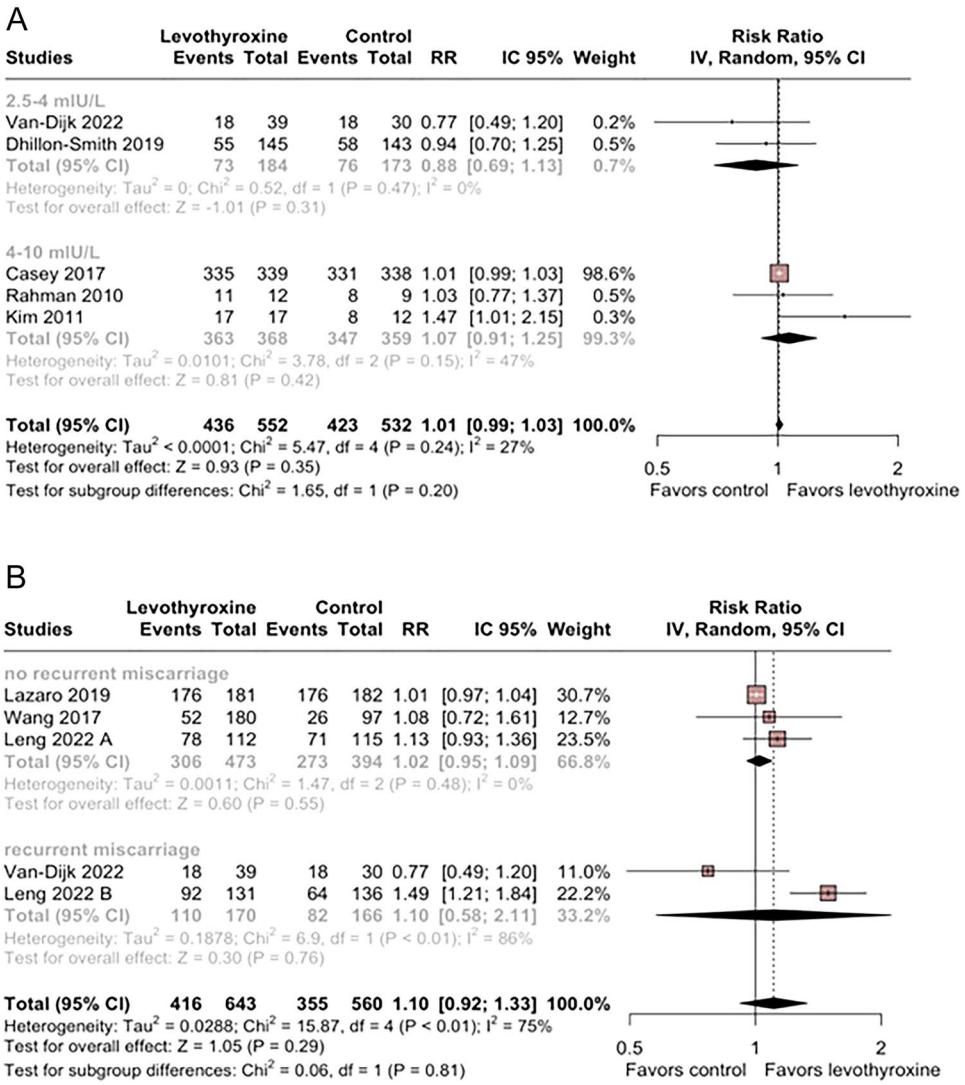

Fig. 4 **A** Subgroup analysis of live birth based on TSH levels. **B** Subgroup analysis of live birth based on recurrent miscarriage

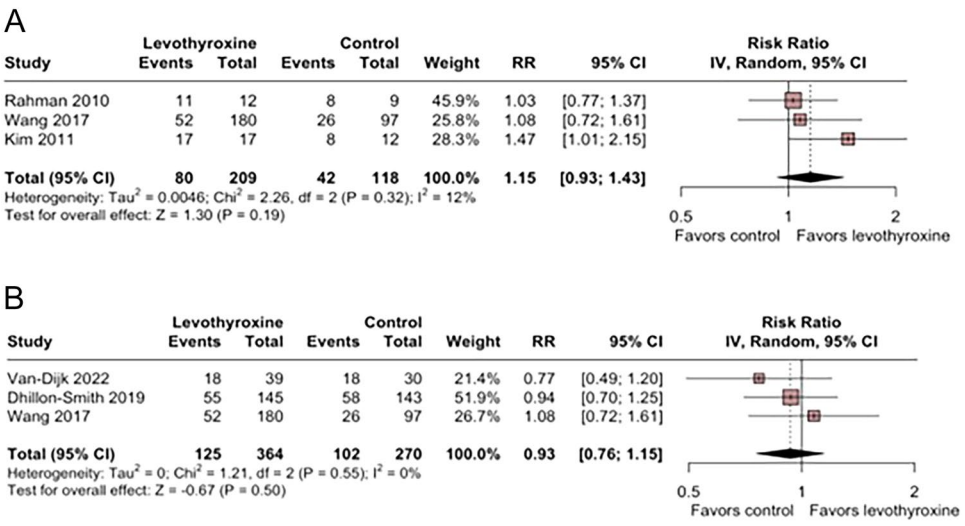

Fig. 5 **A** Subgroup analysis of live birth based on infertility treatment. **B** Subgroup analysis of live birth based on TPOAb positivity

(1) a significantly reduced risk of pregnancy loss with the use of levothyroxine; (2) no significant association between levothyroxine and live birth or preterm birth; and (3) no significant interaction between all subgroups analyzed.

Pregnant women diagnosed with SCH are at a higher risk of experiencing adverse outcomes, such as preterm delivery, hypertensive disorders of pregnancy, and preeclampsia. More specifically, women with untreated SCH in early pregnancy show a 1.9-fold risk of miscarriage compared to euthyroid subjects [7]. The condition also has important implications for neonatal outcomes, such as an elevated risk of intellectual disability [21]. However, there is no current consensus on the effectiveness of thyroid hormone replacement therapy in pregnant women with SCH to prevent such adverse outcomes [22]. Observational and randomized data present conflicting conclusions, and as a result, various scientific bodies, including the ATA and the European Thyroid Association report weak or insufficient evidence on the effectiveness of thyroxine treatment in pregnancy and neonatal outcomes [9, 23].

To the best of our knowledge, this is the first meta-analysis to explore the efficacy of levothyroxine in different subgroups of clinical interest. Our finding of pregnancy loss was consistent with prior meta-analyses that were performed adopting the old 2011 ATA criteria, such as those of Rao et al., and Nazarpour et al., which also found a reduced risk of pregnancy loss with the use of levothyroxine [24, 25]. However, more recent meta-analyses based on the 2017 ATA criteria, such as the one performed by Jiao and colleagues [11], found no differences in maternal and neonatal outcomes between groups when restricted to RCT data. This can be attributed to the fact that studies in their analysis did not have enough statistical power to reach firm conclusions, which was confirmed by their trial sequential analysis. In addition to having included studies with both 2011 and 2017 ATA criteria for a higher power in our analyses, we have also included recent RCTs published since prior reviews were conducted, resulting in a larger pooled population and thus, more accurate conclusions on the management of SCH.

This meta-analysis provides an up-to-date synthesis of published RCTs that were not previously included in other systematic reviews and meta-analyses, and the inclusion of only RCTs minimizes the effect of confounding factors. In addition, different subgroup analyses provide data that are applicable in a range of clinical settings. Nonetheless, our findings must be interpreted in the context of our study's limitations. First, it is important to note that some analyzes were considered with significant heterogeneity. However, this finding was expected in view of the variation in starting doses of levothyroxine therapy and mean gestational age. To minimize and interpret such heterogeneities, we conducted subgroup analyses for each ATA criteria, TPOAb status, fertility treatment and recurrent miscarriage. We cannot, however, eliminate the impact of other clinical factors that may have resulted in the observed discrepancy between studies. Furthermore, individual participant-level data was not requested, limiting our ability to further delineate the effect of variables such as race and geographical location which have been suggested to greatly impact the variability of TSH levels [26].

Conclusion

Although our meta-analysis has shown that treatment with levothyroxine led to a significant reduction in the risk of pregnancy loss, this finding contrasts with the results of live birth and preterm birth, in addition to substantial heterogeneity in certain subgroups. Additional analyses are warranted for individuals exhibiting thyroid stimulating hormone levels exceeding four milliunits per liter, particularly when associated with recurrent miscarriage or infertility.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00404-024-07512-3.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Henrique Provinciatto, Marcus Vinicius Barbosa Moreira and Gabriel Rezende Neves. The first draft of the manuscript was written by Henrique Costa Mitsui, Julio Min Fei Zhang and Edward Araujo Júnior and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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