Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Effect of levothyroxine on gestational hypertension and pre-eclampsia in subclinical hypothyroidism, hypothyroidism, and thyroid autoimmunity: a systematic review and meta-analysis

Masoomeh Goodarzi-Khoigani
Isfahan University of Medical Sciences
Ashraf Aminorroaya
Isfahan University of Medical Sciences
Raziyeh Mohammadi (razieh.mohammadi@alumni.iut.ac.ir)
Isfahan University of Technology

Article

Keywords: Hypothyroidism, Levothyroxine Sodium, Preeclampsia, Hypertension, Pregnancy-Induced, Anti-thyroid autoantibodies

Posted Date: November 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2234840/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

We assessed the effect of levothyroxine (LT4) therapy on gestational hypertension (GH) and preeclampsia (PE) in subclinical hypothyroidism (SCH), overt hypothyroidism (OH), or thyroperoxidase antibody (TPOAb) positivity.

Methods

Scopus, Medline, Science Direct, ProQuest, Google Scholar, and Cochrane library were scientifically searched for randomized controlled trials (RCTs), cohorts, and case-control studies assessing the effect of levothyroxine on incidences of GH or/and PE compared to control or placebo up to November 2022.

Results

After LT4 therapy in women with SCH, the ORs of GH and PE were not significantly different from compared groups; also, in OH, and studies recruited both SCH or OH subjects. LT4 reduced GH in TPOAb + women compared with a non-treated group, while after treatment in TPOAb + versus TPOAb- women, the ORs of GH and PE did not change significantly.

Conclusion

After LT4 therapy, the ORs of GH and PE did not significantly change in SCH, OH, SCH or OH participants compared to controls; also, in TPOAb + compared to TPOAb- equivalents. Reduction of GH in treated TPOAb + versus non-treated TPOAb + women refers to the importance of TPOAb determination. Insignificant changes of both ORs in treated SCH compared to untreated indicates whether SCH increases the incidence of GH and PE.

Introduction

Thyroid hypofunction, including subclinical hypothyroidism (SCH), overt hypothyroidism (OH), and autoimmune thyroid disease, are present in 3%, 0.4%, and 5.6–22.1% of pregnant women, respectively (1, 2). SCH refers to TSH of the 97.5th percentile or more and free T4 between the 2.5th and 97.5th percentiles, and OH refers to TSH between the 2.5th and 97.5th percentiles and a free T4 less than the 2.5th percentile. Thyroid autoimmunity refers to the presence of antibodies to thyroperoxidase or thyroglobulin, or thyroid-stimulating hormone receptor antibodies, or a combination of these, and is expressed by thyroperoxidase antibody (TPOAb) positivity > 15 to 143 IU/L (2, 3, 4). Levothyroxine (LT4), with the usual dosage ranging between 50 and 100 µg/day, is one of the most widely prescribed drugs in pregnancy, and two to fifteen percent of women in the reproductive ages use it (5).

On the other hand, gestational hypertension (GH) and preeclampsia (PE) are the most widespread hypertensive disorders of pregnancy (HDPs), which cause nearly 30% of maternal deaths per annum. Also, the HDPs cause approximately eight early neonatal deaths and three late neonatal deaths of 1000 live birth (6). Researchers stated that the risk of PE enhances in SCH, OH, or thyroid autoimmune disease (7, 8). Also, a U-shaped correlation between TSH and preeclampsia has been reported, which refers to determining the optimal treatment goal in pregnant women treated with LT4 (9). In this field, one study demonstrated that LT4 therapy enhances the risk of PE by 1.5 times, but this risk is also associated with other co-morbid agents (10). One meta-analysis by using four studies showed that LT4 supplementation significantly decreased the risk of GH in pregnant women with SCH (11). In another meta-analysis on infertile women with SCH or positive TPO-Ab, LT4 significantly reduced the incidence of GH but not PE (12). Others supported the treatment of OH with LT4 but stated that there was insufficient evidence to recommend treatment for SCH and thyroid autoimmunity (13). Because of the insufficient number and sample size of available meta-analyses and lack of sufficient evidence, we meta-analyzed the effect of LT4 on GH and PE in women with SCH, OH, and thyroid autoimmunity. Also, age, pre-pregnancy body mass index (BMI), serum levels of thyroid-stimulating hormone (TSH), thyroperoxidase antibodies (TPOAb) status, study design, the trimester of study entry (first, second, or third), and time to start treatment (before or during pregnancy) were extracted for subgroup meta-analysis and meta-regression.

Methods

Search strategy:

This registered meta-analysis by the PROSPERO team (CRD42021237175) was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and PICO. A comprehensive search was carried out using electronic databases such as Scopus, Medline, Science Direct, ProQuest, Google Scholar, and Cochrane library between 4 April and 1 November 2022. RCTs, cohorts, and case-control studies and related meta-analyses with the following search terms in the titles, abstracts, or keywords were involved: ((“levothyroxine” OR “LT4” OR “thyroxine supplementation”) AND (“subclinical hypothyroidism” OR “SCH”) AND (“ thyroid peroxidase antibodies” OR “autoimmune thyroid disease”) AND (“pregnancy outcomes” OR “preeclampsia” OR “gestational hypertension” OR “PIH”)). Then, the first author assessed the selected articles and reference lists of those to find trials or hypotheses that surveyed the effect of levothyroxine on PE or GH. Next, the full text of the specified papers was evaluated to determine the studies that met the inclusion criteria. Endnote software (Thomas Reuters, Philadelphia, PA) was used to control the search findings identified by the stated strategies.

Inclusion And Exclusion Criteria:

1-RCTs, cohorts, and case–controls that assessed the effect of LT4 on GH or/and PE in pregnant women with SCH, OH, or thyroid autoimmunity.

2-Studies in which treatment with levothyroxine has been compared to placebo or no treatment in euthyroid (EU, $0.2 \leq TSH < 4.0$ mIU/L), control, or untreated women.

3-Studies whose subjects were healthy, non-smoking women with a singleton pregnancy. Also, they were free of alcohol, acute and chronic medical problems, and usage of drugs, including prescriptions affecting thyroid function.

4-Published in Persian and English language until 2022.

Exclusion Criteria For The Studies

Animal studies.

Review Question

The PICO (population, intervention, comparator, outcomes) question was expressed to best use the review's yield and significance. Thus, the population was pregnant women with SCH, OH, or thyroid autoimmunity. The intervention was treatment with levothyroxine compared to placebo or no treatment in euthyroid, control, or untreated women, and the outcomes were GH or/and PE (Table 1).

Data Extraction And Study Quality Assessment

Studies were selected in two stages by the first author and confirmed by the corresponding author. The PROSPERO registration number was CRD42021259200. Endnote software (Thomas Reuters, Philadelphia, PA) was used to control the search findings. The first author name, publication year, study design, sample size, rate of GH or/and PE (with and without LT4), trimester of study entry, age, BMI, TSH levels, TPOAb status, and time to start treatment were extracted by the first author and confirmed by the corresponding author (Table 1). Also, they scrutinized the study with the Cochrane risk of bias tool (Table 2a), and NIH (the national institutes of health) quality assessment tool (Table 2b and 2c).

Statistical analysis:

We used Stata 17 to perform the statistical analysis. The random-effects meta-analysis with inverse variance weighting was conducted for each outcome to compare the included studies. The pooled odds ratios (OR) and corresponding 95% intervals were computed to indicate the pooled results. Forest plots were used to display the weighted OR of outcomes. I-squared estimators were utilized to investigate the heterogeneity issue. The sensitivity analysis was performed to extract the potential influence studies. The publication bias was checked by utilizing Egger's test. In the case of significant publication bias, the trim and fill method is used for adjustment. To survey the impact of LT4 on the OR of both outcomes in SCH studies, PE outcome in SCH or OH studies, also PE outcome in TPOAb + and TPOAb- studies, the subgroup meta-analysis was conducted according to the study design (RCT, cohort, or case-control).

Because the type of compared groups was different [(treated vs. untreated, euthyroid, placebo, and control in SCH), (treated vs. placebo, euthyroid, untreated, control in OH), (treated vs. control and uncontrolled in SCH or OH), (treated vs. untreated in TPOAb + versus TPOAb+), and (treated vs. control and untreated, treated and untreated vs. treated and untreated, treated and placebo vs. treated and placebo in TPOAb + versus TPOAb-)], the subgroup meta-analysis was applied for both outcomes in SCH, SCH or OH, and TPOAb + versus TPOAb-. Moreover, the trimester of study entry (first, second, or third trimester) was surveyed by subgroup meta-analysis for both outcomes in SCH studies, OH studies, and also GH outcome in TPOAb + versus TPOAb- studies. Meta-regression analysis investigated the association between the effect size of age, BMI, TSH levels, and TPOAb status as covariates for both outcomes in SCH studies, also age and BMI for OH.

Results

Study selection process:

We showed the search results and the selection process in Fig. 1.

Description of included trials:

After considering duplicates (182), 1044 articles were screened between 4 April and 1 November 2021 from the database searches. The full text of 81 articles was recovered, while fifteen did not have inclusion criteria, eighteen did not have data for PE or GH, and in fifteen, data was insufficient. Twenty-seven articles were eligible, but six papers were not acceptable after a detailed survey by statistician (Fig. 1). The present meta-analysis was performed on fifteen studies that their participants were pregnant women with SCH, including eighteen hypotheses (comparisons) (5117 vs. 49457 participants) on GH (14–20, 22–23, 25–28) and eleven hypotheses (2162 vs. 26401) on PE (14–17, 21–24, 26) (Table 1). It should be noted that some involved studies included two or more hypotheses with different sample sizes or other conditions of the survey. Therefore, we first referred to the number of these hypotheses (comparisons) and then mentioned preliminary studies in parentheses. Seventeen hypotheses were cohorts (14–15, 17–18, 20, 22–28), and three were RCTs (16, 19, 21). Eight hypotheses compared treated with euthyroid (15, 18, 24, 26), and two with control (19, 28), one of them compared SCH with participants who their TSH levels were equal or lesser than 2.5 without treatment, but may be TPOAb+ (28). Two hypotheses compared SCH with placebo in RCT (16) and cohort (25) studies. Eight hypotheses (14, 17, 20–23, 27) compared treated SCH with untreated SCH. The trimester of study entry in ten was first, five was second, one was third, three were first or second, and in one was first, second, or third trimesters. For GH outcome, the time to start treatment was during gestation except for one that was unknown (25) and another (27) that was before or during pregnancy; and for PE outcome, in all was during pregnancy.

Results of five studies were summarized for OH, in which ten hypotheses (1165 vs. 27829) evaluated the effect of levothyroxine on GH (16, 26, 29–30) and eight (866 vs. 24994) on PE (16, 24, 26, 30). In seven hypotheses, the trimester of study entry was first, in three was second, and in Casey et al.' study was first or second. The time to start treatment in all was during gestation. One hypothesis was RCT (16), and

others were cohorts (24, 26, 29–30). Seven compared treated women with euthyroid (24, 26, 30), two with controls (29), and one with placebo (16). One compared treated and untreated women with OH in the first trimester (29).

Participants in five studies had OH or SCH in which four hypotheses reported GH rates (17068 vs. 554508) (31, 32, 35), while five stated PE rates (17074 vs. 553716) (31, 33–35). The trimester of study entry was different among involved studies, while treatment in all except one (33) started before or during pregnancy. Four hypotheses were cohorts (31–32, 35) and two case controls (33–34) which compared treated participants with controls. Two hypotheses compared participants whose TSH levels were controlled and uncontrolled (35).

Three studies, including three hypotheses (1127 vs. 306), estimated the effect of levothyroxine on OR of GH in treated TPOAb + women versus untreated (20, 36–37). The trimester of study entry was first except one (36), which was first or second, and treatment in all started during pregnancy. Two studies were cohorts (20, 37), and one was RCT (37).

Seven studies were met-analyzed in which eight hypotheses (1633 vs. 5341) compared the ORs of GH (20, 28, 36–39), and five (404 vs. 2693) the ORs of PE (36–37, 40) in TPOAb + compared to TPOAb-. The trimester of study entry was first, second, or third in one study (39), first in four studies, first or second in other four, and finally, second trimester in one. The time of starting trimester in all except one (39) was during pregnancy. Three hypotheses compared treated TPOAb + with control TPOAb- (20, 36–37). Also, two treated TPOAb + with treated TPOAb- (38–39) and one treated and untreated TPOAb + with treated and untreated TPOAb- (28), which we performed a subgroup meta-analysis on all three (Fig. 11). Two hypotheses compared treated and placebo TPOAb + with treated and placebo TPOAb- (40). One compared untreated TPOAb + with untreated TPOAb- (28), and another untreated with control (36).

Two hypotheses (430 vs.2065) compared the OR of GH in TPOAb- with TPOAb- (20).

Quality of the included studies:

The quality of the included RCTs, cohorts, and case controls have been shown in Tables 2a, 2b, and 2c.

Bias Assessment:

We provided the risk of bias assessment in Table 2a, and deficiency cases were classified as not written (NR). In all studies, RCTs have been developed by a numerical list created by a computer system. The sequence generation was observed in all except one study (36). Allocation concealment from researchers and participants and also implementations were not observed in most studies. The blinding of participants, personnel, outcome assessor and analysis approach were not written in all studies. Baseline variables were statistically similar in all studies; also, incomplete outcomes and reporting bias were not observed in all. Quality in cohort studies was rated as good in eleven studies, and as fair in ten studies

(Table 2b). Quality in case-control studies was good in two studies considering that one item (non-response rate) has not been reported (Table 2c).

Meta-analysis Results For Studies Included Pregnant Women With SCH

Random-effects model in SCH showed that ORs of GH (18 comparisons) and PE (11 comparisons) after LT4 therapy were not significant between compared groups [OR = 1.03, 95% CI: (0.85, 1.25), I^2 = 35.25%, P = 0.78, OR = 1.02, 95% CI: (0.66,1.58), I^2 = 46.86%, P = 0.94, respectively] (Figs. 2, 3). For both analyses, the heterogeneity was not significant. Also, Egger's test did not indicate any evidence of publication bias for GH outcome (P = 0.69), whereas, for PE, the publication bias was seen (P = 0.04). According to the fill and trim method, the value of the adjusted OR of PE was 1.37 with 95% CI (0.86, 2.18). Therefore, based on 11 observed hypotheses, the overall effect size may be smaller than that in the absence of publication bias. The sensitivity analysis results indicated that after excluding each study, the total effect size did not change.

Subgroup meta-analysis based on the design study to analyze its effect on the association between levothyroxine treatment and two outcomes did not demonstrate significant effects (Figs. 1–2 supplementary file). Also, the type of two compared groups (treated versus control, placebo, euthyroid, or untreated) were not significantly effective on obtained results for the two outcomes (Figs. 4–5). Furthermore, the subgroup meta-analysis based on the trimester of study entry did not show significant effects between subgroups for both outcomes (Figs. 3–4 supplementary file). For both outcomes, age, BMI, TSH levels, and TPOAb status were insignificant by meta-regression (P > 0.05).

OH

Meta-analysis indicated that the ORs of GH (10 comparisons) and PE (8 comparisons) after levothyroxine therapy were not significantly different between compared groups [OR = 1.23, 95% CI: (0.86,1.78), I^2 = 34.29%, P = 0.26, OR = 1.32, 95% CI: (0.83, 2.09), I^2 = 0.00%, P = 0.24, respectively] (Figs. 6–7). The heterogeneity was not significant for both models. Egger's test demonstrated no publication bias for both models (for GH: P = 0.44 and PE: P = 0.62). The sensitivity analysis results indicated that after excluding each study, the total effect size did not change. For both outcomes, all studies were cohort except one (16) was RCT. For GH outcome, the comparison was conducted between treated versus euthyroid or control, except one (16) that compared treated versus placebo and also another (29) that compared treated versus untreated in the first trimester. For PE outcome, all comparisons were made between treated versus euthyroid except in one (16) that compared treated with placebo. Therefore, subgroup meta-analysis based on study design and compared groups were not needed. We performed a subgroup meta-analysis for both outcomes based on the trimester of study entry, considering that one study (16) was deleted due to its trimester that was first or second. For GH outcome, subgroup meta-analysis showed significant heterogeneity between two subgroups of first, also second trimesters (Fig. 5

supplementary file). The overall effect size of each group showed that in the second-trimester subgroup, the levothyroxine treatment was associated with an increased risk of GH [OR = 1.97, 95% CI: (1.34, 2.90)], whereas there was no significant effect in the first-trimester subgroup [OR = 0.95, 95% CI: (0.62, 1.47)]. The test of group differences demonstrated that the group-specific overall effect sizes were statistically different (Q_b=6.04, P = 0.01). For PE outcome, the subgroup meta-analysis did not show any significant heterogeneity between subgroups (Fig. 6 supplementary file). Meta-regression did not show any significant effect of age and BMI.

Sch Or Oh

Random-effects model on four hypotheses for GH and five for PE in women with SCH or OH revealed that the ORs of GH and PE were not significantly different [OR = 1.22, 95% CI: (0.56, 2.66), I^2 = 94.71%, P = 0.62, OR = 0.56, 95% CI: (0.13, 2.31), I^2 = 98.13%, P = 0.42, respectively] (Figs. 8–9). For both analyses, the heterogeneity was significant. Also, Egger's test did not indicate any publication bias (for GH: P = 0.42 and for PE: P = 0.19). The sensitivity analysis results for GH showed that after excluding each study, the total effect size did not change. However, for PE outcome, after omitting the Das, et al.' study, the overall effect size will be significant without heterogeneity (OR = 1.36, 95% CI: (1.24, 1.49), P = 0. 00) due to the Turunen et al.' study that has the highest effect. For GH outcome, all hypotheses were cohort. For PE, three hypotheses were cohort, and two hypotheses were case-control. Therefore, we conducted a subgroup meta-analysis based on the design study. However, there was no significant difference between the two subgroups (Fig. 7 supplementary file). The overall effect size of each group determined by subgroup meta-analysis based on the type of compared groups for GH outcome indicated that participants whose TSH levels were controlled (less than 2.5) had lesser OR of GH compared to uncontrolled [OR = 0.63, 95% CI: (0.42, 0.95)], whereas there was no significant effect for the subgroup that compared treated with controlled participants [OR = 2.17, 95% CI: (0.94, 5.04)]. The test of group differences demonstrated that the group-specific overall effect sizes were statistically different (Q_b=6.68, P = 0.01) (Fig. 8 supplementary file). However, for PE outcome, there was no evidence of significant heterogeneity between the two subgroups (Fig. 9 supplementary file). For both outcomes, the trimester of study entry was different among studies, so the information was not enough for subgroup meta-analysis.

Antibody +&+

Meta-analysis on three hypotheses to estimate the OR of GH in TPOAb + women showed that levothyroxine treatment decreased the risk of GH compared with untreated (OR = 0.43, 95% CI: (0.30, 0.62), I^2 = 0.00%, P = 0.00) (Fig. 10). The heterogeneity was insignificant, and publication bias was not seen (P = 0.56). The sensitivity meta-analysis indicated that after excluding Yang et al.' study, the OR of GH will not be significant (OR = 0.65, 95% CI: (0.22, 1.91)), I^2 = 0.00%, P = 0.43), whereas after excluding two other studies (36, 37), the overall total effect will stay significant.

Two studies were cohort (20, 36), and one was RCT (37). The trimester of study entry was the first, except one that was the first or second (37), and the time to start treatment was during pregnancy for all studies. For PE, the studies were not enough to conduct a mate-analysis.

Antibody + versus -

Using eight hypotheses that compared TPOAb + women with TPOAb- women, the random-effects model revealed that the ORs of GH was not significantly different from compared groups (OR = 0.99, 95% CI: (0.8, 1.24), I^2 = 0.00%, P = 0.96) (Fig. 11). Also, using five hypotheses that compared the ORs of PE, there was not seen any significant association (OR = 1.13, 95% CI: (0.67, 1.92), I^2 = 0.00%, P = 0.65) (Fig. 12). For both analyses, the heterogeneity was not significant. Also, there was no publication bias for both outcomes (GH: P = 0.73 and PE: P = 0.78). The sensitivity analysis results indicated that after excluding each study, the total effect size did not change. For GH, all studies were cohort except one, which was RCT (27). For PE, two studies were cohort, and three studies were RCT. However, the subgroup meta-analysis based on the study design did not show any significant differences between the two subgroups (Fig. 10 supplementary file). The effect of the type of compared groups for both outcomes was surveyed by subgroup meta-analysis, which did not demonstrate effects between subgroups (Figs. 11–12 supplementary file).

For GH, the trimester of study entry in four hypotheses was the first, one was the second (38), two hypotheses were first or second (36), and one was the first, second, or third trimester (39). However, a considerable difference didn't show between subgroups by subgroup meta-analysis (Fig. 13 supplementary file). For PE outcome, the trimester of study entry in four hypotheses was the first or second trimester, except one which was the first. For both outcomes, the time to start treatment in all studies was during pregnancy.

Discussion

The present meta-analysis showed that after LT4 therapy, the ORs of GH and PE were not different between compared groups. Similarly, Nazarpour et al. did not show significant differences in pooled ORs of GH and PE between treated SCH women and the placebo group (41). Also, Han et al.'s meta-analysis indicated that SCH in each trimester enhanced the risk of developing HDP, but receiving LT4 did not decrease this risk (42). Oppositely, Geng et al.'s and Ding et al.' meta-analyses demonstrated that LT4 therapy reduced the PIH rate in pregnant women with SCH, but the sample size is small (43, 44). Also, Li et al.' meta-analysis on 14 RCTs, including 1918 infertile participants with SCH or anti-TPO antibody positivity, reported that LT4 supplementation decreased GH but not PE (45). Kexin et al.'s meta-analysis based on 14 literature showed that LT4 reduced the incidence of adverse pregnancy outcomes such as GH and PE (46).

As the sample size of our meta-analysis is much more than the previously mentioned studies, their results need to be interpreted with caution. However, more clinical trials with enough sample size are required to

confirm our results. Li et al. concluded that LT4 decreased GH in infertile women with SCH or TPO antibody positivity (45), similar to our finding in TPOAb + women, which will be discussed in the next fifth paragraph. As if thyroid autoimmunity may enhance the risk of GH via TSH and non-TSH-dependent mechanisms; however, most of our included studies in SCH women did not report the TPOA-b status.

The TSH cut-off levels may be related with the effect of levothyroxine on HDPs, considering that when those are ≥ 4 m IU/l, the risk of HDPs increases (47); and this is in line of ATA guidelines (48). However, our meta-regression results for both outcomes did not show a significant effect of TSH levels obtained from some studies. The time of levothyroxine administration is also effective in reducing HDPs after LT4 (23), but we did not observe any significant effect by subgroup analysis.

Insignificant ORs of GH and PE in treated SCH compared with untreated (3035 vs. 11953) by subgroup meta-analysis raise the question of whether SCH increases the incidence of HDPs in SCH women, which has been reported by others (41). However, adequately powered RCTs are needed. Our meta-analysis on pregnant women with overt hypothyroidism indicated that the ORs of GH and PE after treatment were not different from euthyroid or control equivalents. Likewise, Chen et al.'s meta-analysis on patients with hypothyroidism showed that compared with L-T4, L-T4 plus L-T3 significantly reduced TSH amounts and enhanced FT3 levels without affecting SBP (49). Oppositely, Lintula et al.' study showed that LT4 use increased the risk of PE by 1.5-times (OR 1.48, 95th CI 1.06–2.07; $p \leq 0.022$), which has been due to other comorbid risk factors and not because of LT4 or OH per se (50). Of course, they stated that their participants were older, more obese, and initiated LT4 treatment during pregnancy compared to before gestation. However, we did not observe any significant effect of age and BMI. But, treatment starting in the second trimester compared to the first trimester increased the risk of GH, which is similar to Lintula et al.'s finding and Turunen et al.'s study that emphasized longer and consistent usage of levothyroxine (50, 31).

Perhaps OH increases the risk of GH and PE to the extent that after LT4 therapy, these ORs reach euthyroid or control equivalents. Thyroid hypofunction is associated with endothelial cell dysfunction, possibly due to decreased production of nitric oxide and vasoactive compounds that lead to declined vasorelaxation, enhanced sympathetic tone, vascular resistance, and, finally, hypertension (51). Important processes, including decidual cell migration and angiogenesis, are adjusted by inflammatory mediators and, to some extent, influenced by thyroid hormones (52). Subsequently, low thyroid hormone accessibility might end in an insufficient anti-inflammatory setting which develops placental vascularity disorders, and, consequently, preeclampsia and miscarriage (53). We also found that the OR of both outcomes after LT4 therapy was not different from the control in studies that recruited women with SCH or OH, confirming our previous findings. Moreover, a subgroup meta-analysis on two hypotheses in Kiran et al.' study (35) showed that the OR of GH was significantly lesser in participants who their TSH levels were controlled (less than 2.5) compared with uncontrolled; however, the sample size is small, and further studies with enough sample size is needed.

LT4 therapy in TPOAb + pregnant women decreased the risk of GH compared with untreated. Similarly, Li et al.'s meta-analysis, including 14 RCTs on 1918 infertile pregnant women with SCH or TPOAb positivity, reported that LT4 supplementation decreased GH but not PE (45). In Di Girolamo et al.' s meta-analysis, levothyroxine therapy in euthyroid anti- TPO + women was not associated with reduced risk of GH and PE (54). Also, Lau et al.' systematic review showed that LT4 supplementation in women with thyroid autoimmunity without SCH or OH was not beneficial on pregnancy outcome (55). One reason for our finding is the higher elementary TSH values in TPO antibody positivity compared to TPOAb- subjects which may worsen during pregnancy. Also, TPOAb-positive women may not be able to adapt themselves sufficiently to the enhanced request for the synthesis of thyroid hormones during pregnancy (56, 57). RCTs showed that LT4 in these women might be useful, especially in cases with higher TSH levels (58, 59). Perhaps this is why meta-analyses in treated euthyroid subjects were not associated with a reduction in the risk of HDPs, as well we showed that treatment in the SCH subgroup and not in the EU group reduced the risk of GH. Another reason is the instabilities of the local inflammatory process in TPOAb + pregnant women that may change the regulation of cytokine networks inside the local placental–decidual setting or fetal development (60, 61); which in turn could be correlated with adverse pregnancy outcomes (62). As researchers stated that adverse pregnancy outcomes were positively associated with TPOAb status (63, 64).

Other findings are insignificant ORs of both outcomes in treated TPOAb + compared to TPOAb- groups, which supports the mentioned results. It is likely that TPOAb + increases the risk of both outcomes to the extent that after LT4 therapy, these ORs reach euthyroid women. Oppositely, in Blumenthal et al.' study, the risk of GH in untreated TPOAb + versus untreated TPOAb- was not significantly different, but the sample size (191 vs. 742) was small.

Strengths and limitations:

A large number of included studies is one strength that paved the way for meta-analyzes on SCH, OH, and autoimmune thyroid disease, and meta-regression on age, pre-gravid BMI, TSH level, and TPOAb status to consider covariates. Moreover, it became possible to use subgroup analysis on the trimester of study entry (first, second, or third), time to start treatment (before or during pregnancy), study design, and type of compared groups to have matched control groups for the stated reasons. Additionally, the results of the effects of LT4 on both outcomes were polled in women with OH, which has been rarely done. The first limitation was the small number of studies assessing the effect of levothyroxine on both outcomes in TPOAb + against TPOAb-. The Second was data obtained from observational studies in most studies.

Declarations

Data Availability

All the data supporting this systematic review are from previously reported studies and data sets, which have been cited. The processed data are available from the corresponding author upon request.

References

1. Krassas G., Karras SN. &Pontikides N. Thyroid diseases during pregnancy: A number of important issues. *Hormones*. **14**(1), 59–69 (2015).
2. Korevaar TI. et al. Dose dependency and a functional cutoff for TPO-antibody positivity during pregnancy. *J. Clin. Endocrinol. Metab*. **103**(2), 778 – 89 (2018).
3. Cleary-Goldman J. et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet. Gynecol*. **112**(1), 85 (2008).
4. Mardanian F. et al. The association between serum TSH concentration whithin the normal range and nutritional status in euthyroid pregnant women at the first trimester of gestation. *J Res Med Sci: The Official Journal of Isfahan University of Medical Sciences.* **26**, (2021).
5. Ghaderian S., Rashidi H. & Etessaminia S. Levothyroxine dosage requirement during pregnancy. Drug Invention Today. 10, (2018).
6. Von Dadelszen P., Magee LA. Preventing deaths due to the hypertensive disorders of pregnancy. *Best Pract. Res. Clin. Obstet. Gynaecol*. **36**, 83–102 (2016).
7. Devi PU. & Vanaja G. Maternal and perinatal outcome in antenatal women with hypothyroidism. *International Archives of Integrated Medicine*. **4**(12), 199–207 (2017).
8. van den Boogaard E. et al. Significance of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum. Reprod. Update*. **17**(5), 605 – 19 (2011).
9. Toloza FJ. et al. Association between maternal thyroid function and risk of gestational hypertension and pre-eclampsia: a systematic review and individual-participant data meta-analysis. *Lancet Diabetes Endocrinol*. (2022).
10. Lintula A., Keski-Nisula L. & Sahlman H. Hypothyroidism and the increased risk of preeclampsia–interpretative factors? *Hypertens Pregnancy*. **39**(4), 411-7 (2020).
11. Ding Z. et al. Pregnancy and neonatal outcomes with levothyroxine treatment in women with subclinical hypothyroidism based on new diagnostic criteria: A systematic review and meta-analysis. *Front. Endocrinol*. **12**, (2021).
12. Li J., Shen J. & Qin L. Effects of Levothyroxine on Pregnancy Outcomes in Women With Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. *Altern. Ther. Health Med.* **23**(2), (2017)
13. Shan Z. & Teng W. Thyroid hormone therapy of hypothyroidism in pregnancy. *Endocrine*. **66**(1), 35–42 (2019).
14. Maraka S. et al. Coddington III CC, Montori VM, Stan MN. Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. *Thyroid*. **26**(7), 980-6 (2016).
15. Han L., Ma Y., Liang Z. & Chen D. Laboratory characteristics analysis of the efficacy of levothyroxine on subclinical hypothyroidism during pregnancy: a single-center retrospective study. *Bioengineered*. **12**(1), 4183-90 (2021).

16. Casey BM. et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N. Engl. J. Med*. **376**(9), 815 – 25 (2017).
17. Maraka S. et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *Bmj*. **25**, 356 (2017).
18. Chen LM. et al. Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: a single-center cohort study of a Chinese population. *PloS one*. **9**(10), e109364 (2014).
19. Ju R., Lin L., Long Y., Zhang J. & Huang J. Clinical efficacy of therapeutic intervention for subclinical hypothyroidism during pregnancy. *Genet Mol Res*. **15**(4), 4–8 (2016).
20. Yang J., Guo H., Ding S., Tao B. & Zhang X. Effect of the treatment acceptance on the perinatal outcomes in women with subclinical hypothyroidism, positive thyroid gland peroxidase antibody in early pregnancy. *Zhonghua Fu Chan Ke Za Zhi*. **50**(9), 652-7 (2015).
21. Lotfalizadeh M., Ghomian N. & Mohammad Nezhad M. Prevalence and complications of hypothyroidism in pregnancy. *Iran. J. Obstet. Gynecol. Infertil*. **20**(8), 1–5 (2017).
22. Mathuriya G. & Panday S. Levothyroxine replacement in subclinical hypothyroidism during pregnancy and its effect on fetomaternal outcome.
23. Zhao L. et al. Initiation timing effect of levothyroxine treatment on subclinical hypothyroidism in pregnancy. *Gynecol. Endocrinol*. **34**(10), 845-8 (2018).
24. Ajmani SN. et al. Prevalence of overt and subclinical thyroid dysfunction among pregnant women and its effect on maternal and fetal outcome. *J. Obstet. Gynecol. India*. **64**(2), 105 – 10 (2014).
25. Ye W., Guo Y., Chen S., Mai H. & Fan L. Prog Obstet Gynecol. Clinical Observation of L-T4 Treatment in Subclinical Hypothyroidism in Pregnancy with Autoantibody Negative. **28**, 920–2 (2019).
26. Cleary-Goldman J. et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet. Gynecol*. **112**(1), 85 (2008).
27. Yu YH. et al. Use of levothyroxine among pregnant women with subclinical hypothyroidism in the United Kingdom: A population-based assessment. *Pharmacol. Res. Perspect*. **9**(5), e00848 (2021).
28. Blumenthal NJ. & Eastman CJ. Beneficial effects on pregnancy outcomes of thyroid hormone replacement for subclinical hypothyroidism. *Thyroid. Res*. 2017, (2017).
29. Gong X. et al. The impact of isolated maternal hypothyroxinemia during the first and second trimester of gestation on pregnancy outcomes: an intervention and prospective cohort study in China. *J. Endocrinol. Invest*. **42**(5), 599–607 (2019).
30. Negro R. et al. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J. Clin. Endocrinol. Metab*. **95**(4), 1699 – 707 (2010).
31. Turunen S. et al. Pregnancy and perinatal outcome among hypothyroid mothers: a population-based cohort study. Thyroid. **29**(1), 135 – 41 (2019).
32. Sahu M., Das S., Panigrahi PK. & Nanda S. A Prospective Study of Routine Screening of Hypothyroidism in Antenatal Patients and their Outcome with Levothyroxine Treatment. *J. Clin. Diagn. Res*. **11**(10), (2017).

33. Das S., Sahu M., Pattanaik T. & Panigrahi PK. Association of Thyroid Status with Pregnancy Induced Hypertension and Impact of Levothyroxine Treatment. ID: sea-187681, (2018).
34. Lintula A., Keski-Nisula L. & Sahlman H. Hypothyroidism and the increased risk of preeclampsia–interpretative factors? Hypertens Pregnancy. **39**(4), 411-7 (2020).
35. Kiran Z. et al. Maternal characteristics and outcomes affected by hypothyroidism during pregnancy (maternal hypothyroidism on pregnancy outcomes, MHPO-1). *BMC Pregnancy Childbirth*. **19**(1), 1–2 (2019).
36. Lepoutre T., Debiève F., Gruson D. & Daumerie C. Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. *Gynecol. Obstet. Invest*. **74**(4), 265 – 73 (2012).
37. Negro R. et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J. Clin. Endocrinol. Metab*. **91**(7), 2587-91 (2012).
38. Jayaraman M., Verma A., Harikumar KV., Ugale M. & Modi K. Pregnancy outcomes with thyroxine replacement for subclinical hypothyroidism: Role of thyroid autoimmunity. *Indian J. Endocrinol. Metab*. **17**(2), 294 (2013).
39. Vijayasree M. Pregnancy and Thyroid Dysfunction: Need for Universal Screening-A Pilot Study. Bangladesh J. Med. Sci. **13**(1), 49–52 (2014).
40. Casey B. 65: Thyroid peroxidase antibodies in women with subclinical hypothyroidism or hypothyroxinemia. *Am. J. Obstet. Gynecol*. **216**(1), S47 (2017).
41. Nazarpour S. et al. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. *Arch. Gynecol. Obstet*. **300**(4), 805 – 19 (2019).
42. Han Y., Wang J., Wang X., Ouyang L. & Li Y. Relationship between subclinical hypothyroidism in pregnancy and hypertensive disorder of pregnancy: a systematic review and meta-analysis. Front. Endocrinol. **13**, (2022).
43. Geng X. et al. Systematic review and meta-analysis of the efficacy and pregnancy outcomes of levothyroxine sodium tablet administration in pregnant women complicated with hypothyroidism. *Ann. palliat. med*. **11**(4), 1441-52 (2022).
44. Ding Z. et al. Pregnancy and neonatal outcomes with levothyroxine treatment in women with subclinical hypothyroidism based on new diagnostic criteria: a systematic review and meta-analysis. Front. Endocrinol. **12**, (2021).
45. Li J., Shen J. & Qin L. Effects of Levothyroxine on Pregnancy Outcomes in Women With Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. *Altern. Ther. Health Med*. **23**(2), (2017).
46. Kexin C., Hongju G., Shuxia Y. & Lirong C. Effect of levothyroxine for pregnancy outcomes due to subclinical hypothyroidism during pregnancy: A meta-analysis. *Clinical Focus*. **36**(9), 773 (2021).
47. Han Y., Wang J., Wang X., Ouyang L. & Li Y. Relationship between subclinical hypothyroidism in pregnancy and hypertensive disorder of pregnancy: a systematic review and meta-analysis. Front.

Endocrinol. **13**, (2022).

48. Alexander EK. et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. **27**(3), 315–89 (2017). doi:10.1089/thy.2016.0457.
49. Chen Y. & Tai HY. Levothyroxine in the treatment of overt or subclinical hypothyroidism: a systematic review and meta-analysis. *Endocr. J.* EJ19-0583 (2020).
50. Lintula A., Keski-Nisula L. & Sahlman H. Hypothyroidism and the increased risk of preeclampsia–interpretative factors? *Pregnancy Hypertens*. **39**(4), 411-7 (2020).
51. Danzi S. & Klein I. Thyroid disease and the cardiovascular system. *Endocrinol. Metab. Clin. N. Am*. **43**(2), 517 – 28 (2014).
52. Vasilopoulou E. et al. Triiodothyronine regulates angiogenic 682 growth factor and cytokine secretion by isolated human decidual cells in a cell-type specific and 683 gestational age-dependent manner. *Hum. Reprod*. **29**(6), 1161-72 (2014).
53. Adu-Gyamfi EA., Wang YX. & Ding YB. The interplay between thyroid hormones and the 618 placenta: a comprehensive review. *Biol. Reprod*. **102**(1), 8–17 (2020).
54. Di Girolamo R., Liberati M., Silvi C. & D'Antonio F. Levothyroxine Supplementation in Euthyroid Pregnant Women with Positive Autoantibodies: A Systematic Review and Meta-Analysis. *Front. Endocrinol*. **13**, (2022).
55. Lau L., Benham JL., Lemieux P., Yamamoto J. & Donovan LE. Impact of levothyroxine in women with positive thyroid antibodies on pregnancy outcomes: a systematic review and meta-analysis of randomised controlled trials. *BMJ open*. **11**(2), e043751 (2021).
56. Pearce EN. et al. Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. *Endocr. Pract*. **14**(1), 33 – 9 (2008).
57. Banerjee S. Thyroid disorders in pregnancy. *J. Assoc. Physicians India*. **59**(Suppl), 32 – 4 (2011).
58. Negro R. et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J. Clin. Endocrinol. Metab.* **91**(7), 2587-91 (2006).
59. Nazarpour S. et al. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol. **176**(2), 253 – 65 (2017).
60. Weetman AP. Immunity, thyroid function and pregnancy: molecular mechanisms. *Nat. Rev. Endocrinol*. **6**(6), 311–318 (2010).
61. Sailakshmi M., Rekha B. & Akash SS. Autoimmune thyroid disease in pregnancy. *Int. J. Reprod. Contracept. Obstet. Gynecol*. **3**(2), 321–324 (2014).
62. Karakosta P. et al. Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J. Clin. Endocrinol. Metab*. **97**(12), 4464-72 (2012).
63. Nazarpour S. et al. Effects of Levothyroxine on Pregnant Women With Subclinical Hypothyroidism, Negative for Thyroid Peroxidase Antibodies. *J. Clin. Endocrinol. Metab*. **103**, 926–35 (2018).

64. Zhang SC., Wang SW., Zhao XD. & Zhang JR. Obstetrical complications of thyroid peroxidase antibody positive during pregnancy and effects of intervention: a meta-analysis. Zhonghua fu Chan ke za zhi. **51**(4), 250-7 (2016).
65. Nazarpour S. et al. Effects of Levothyroxine Treatment on Pregnancy Outcomes in Pregnant Women with Autoimmune Thyroid Disease. *Eur J Endocrinol*. **176**, 253–65 (2017).

Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

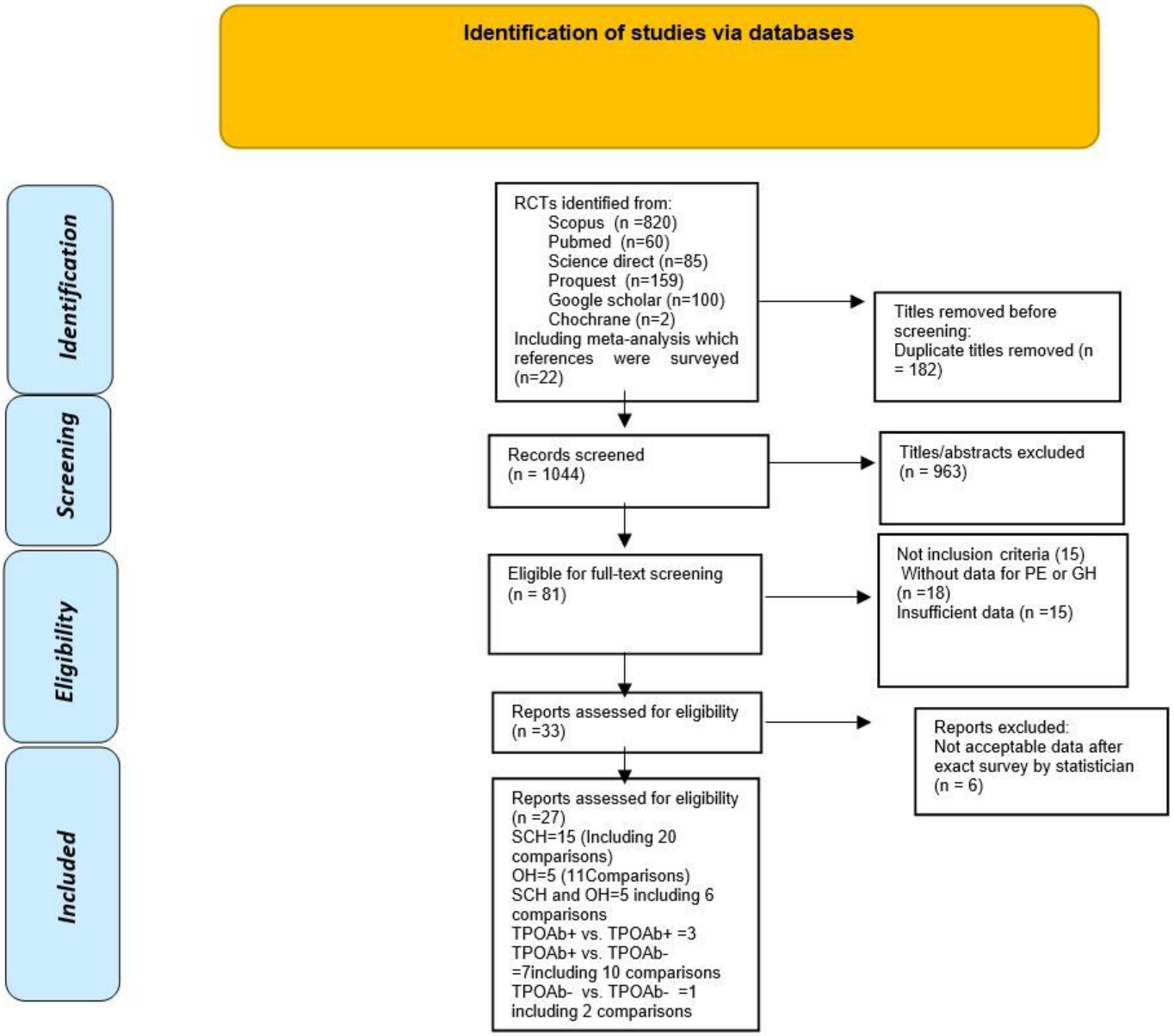

Figure 1

PRISMA flow diagram of included studies.

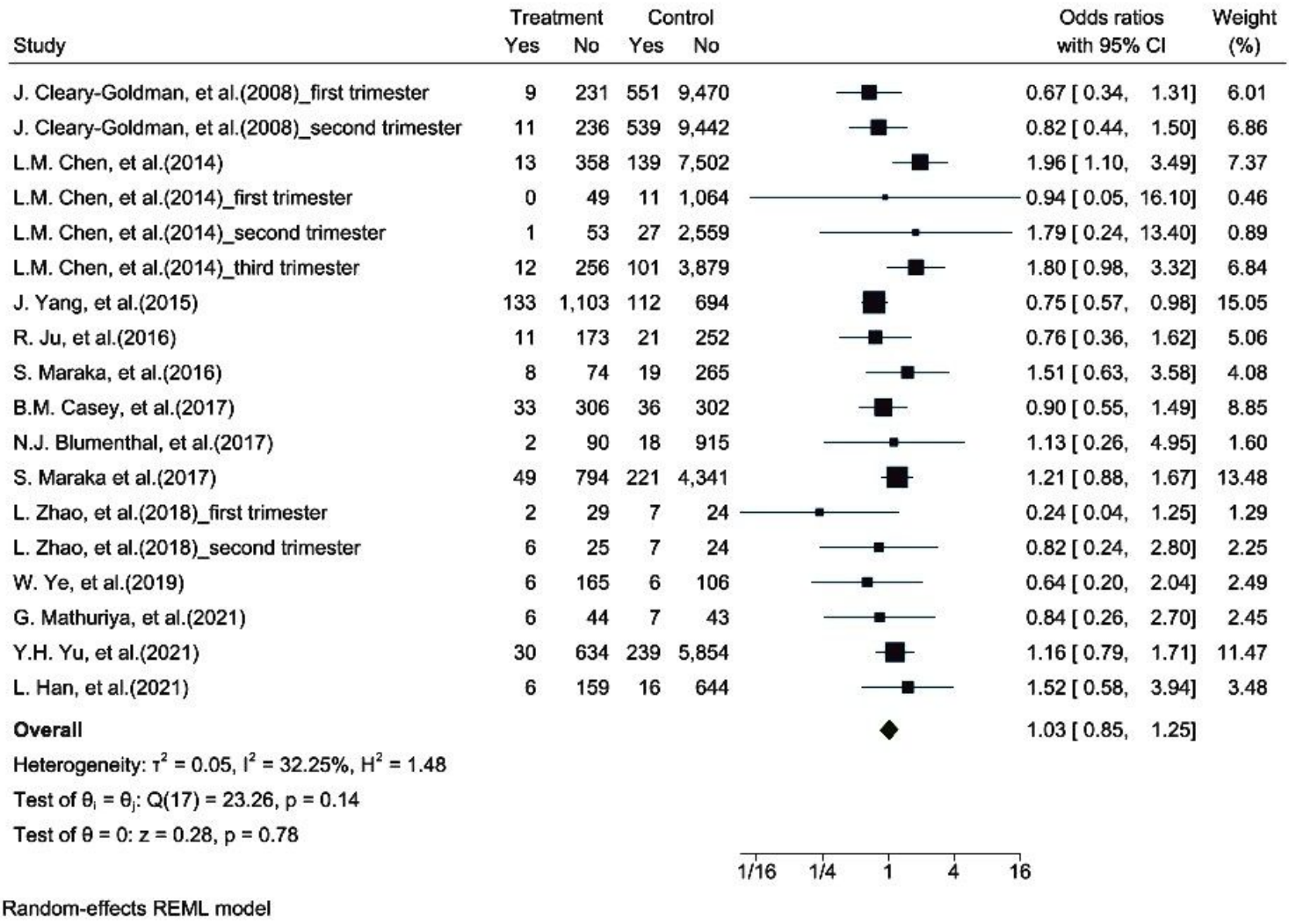

Figure 2

Effect of levothyroxine treatment on GH among SCH (treated versus untreated, euthyroid, placebo, and control).

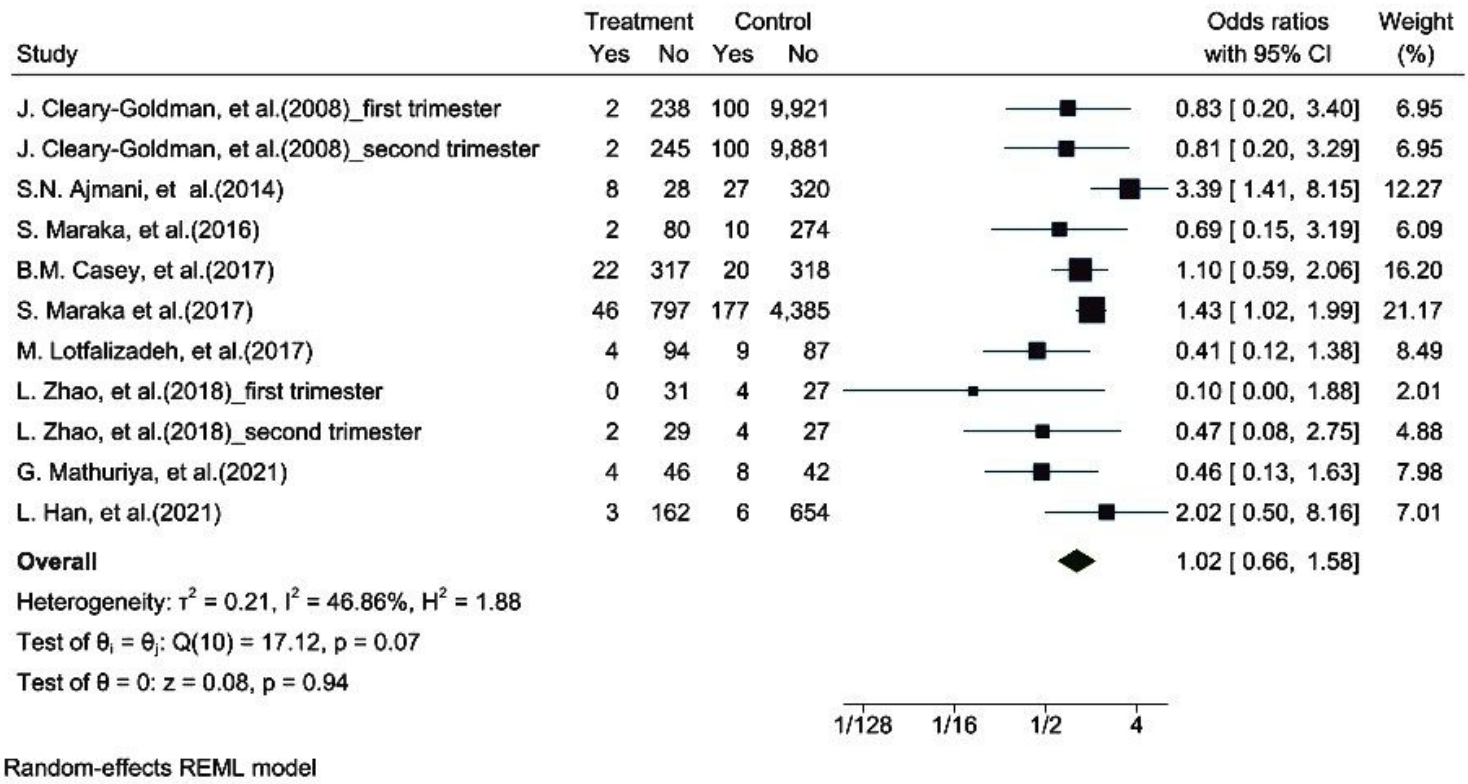

Figure 3

Effect of levothyroxine treatment on PE among SCH (treated versus untreated, euthyroid, and placebo).

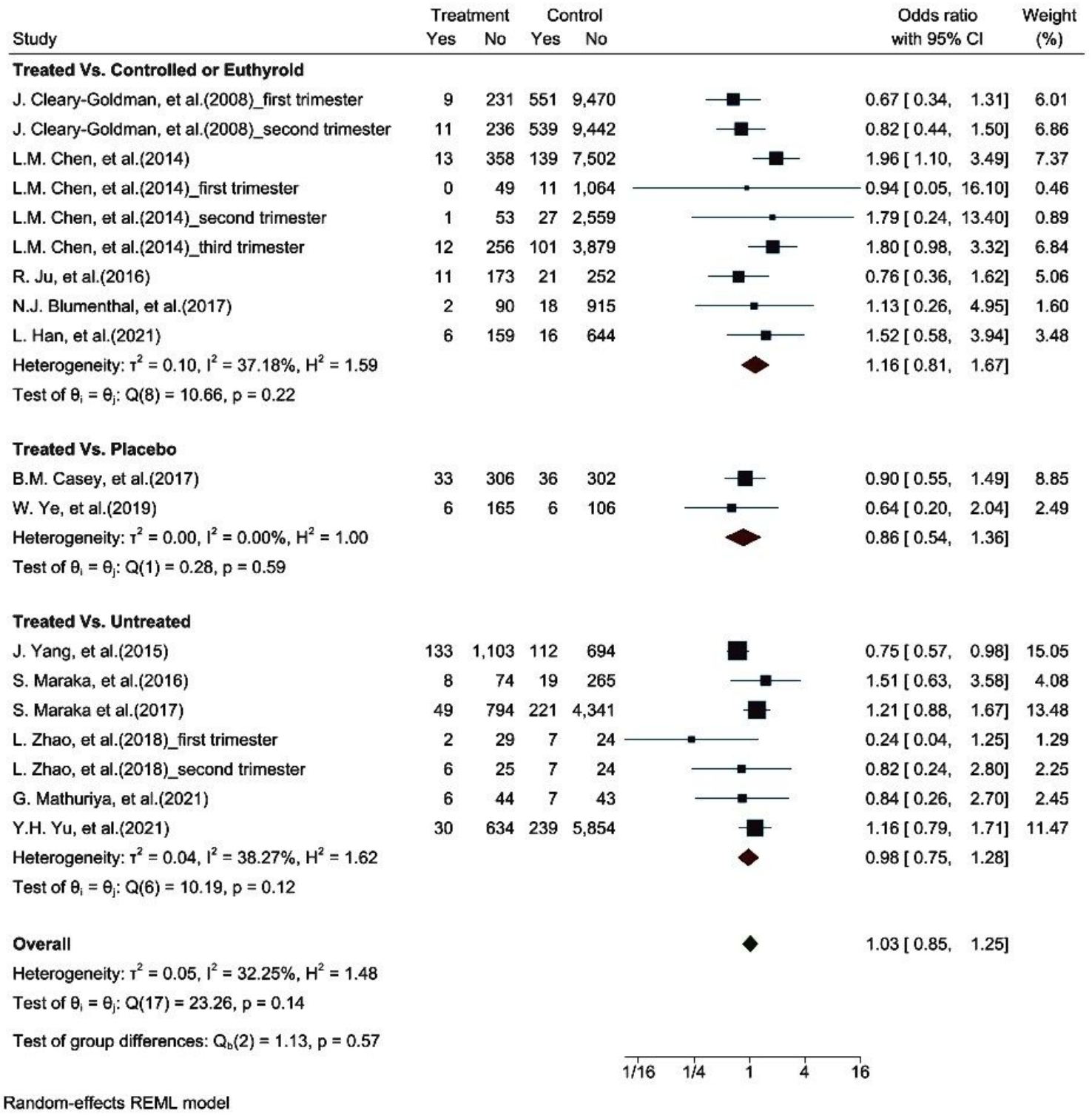

Figure 4

Subgroup meta-analysis to evaluate the effect of levothyroxine treatment on GH among SCH based on type of compared groups.

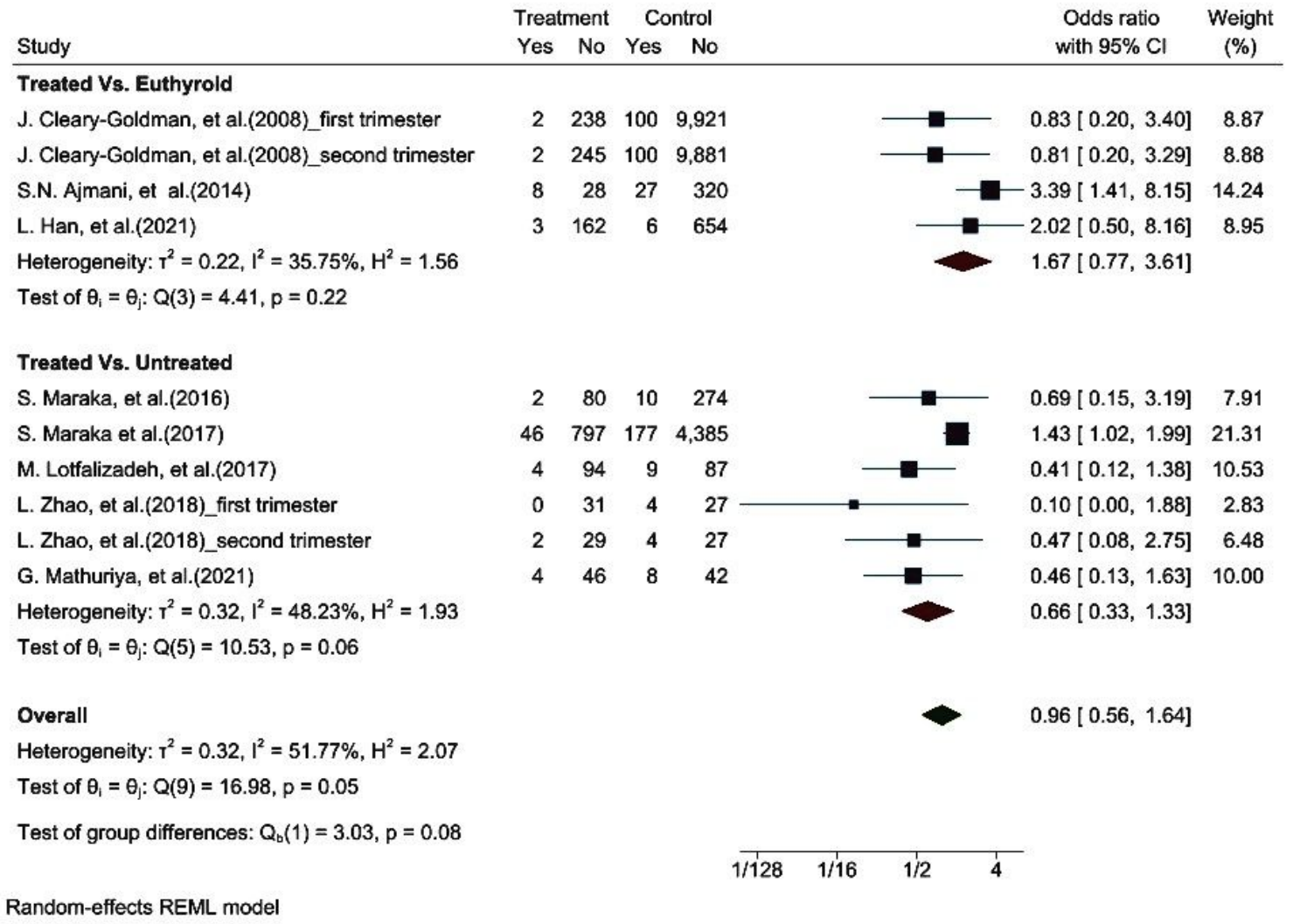

Figure 5

Subgroup meta-analysis to evaluate the effect of levothyroxine treatment on PE among SCH based on type of compared groups.

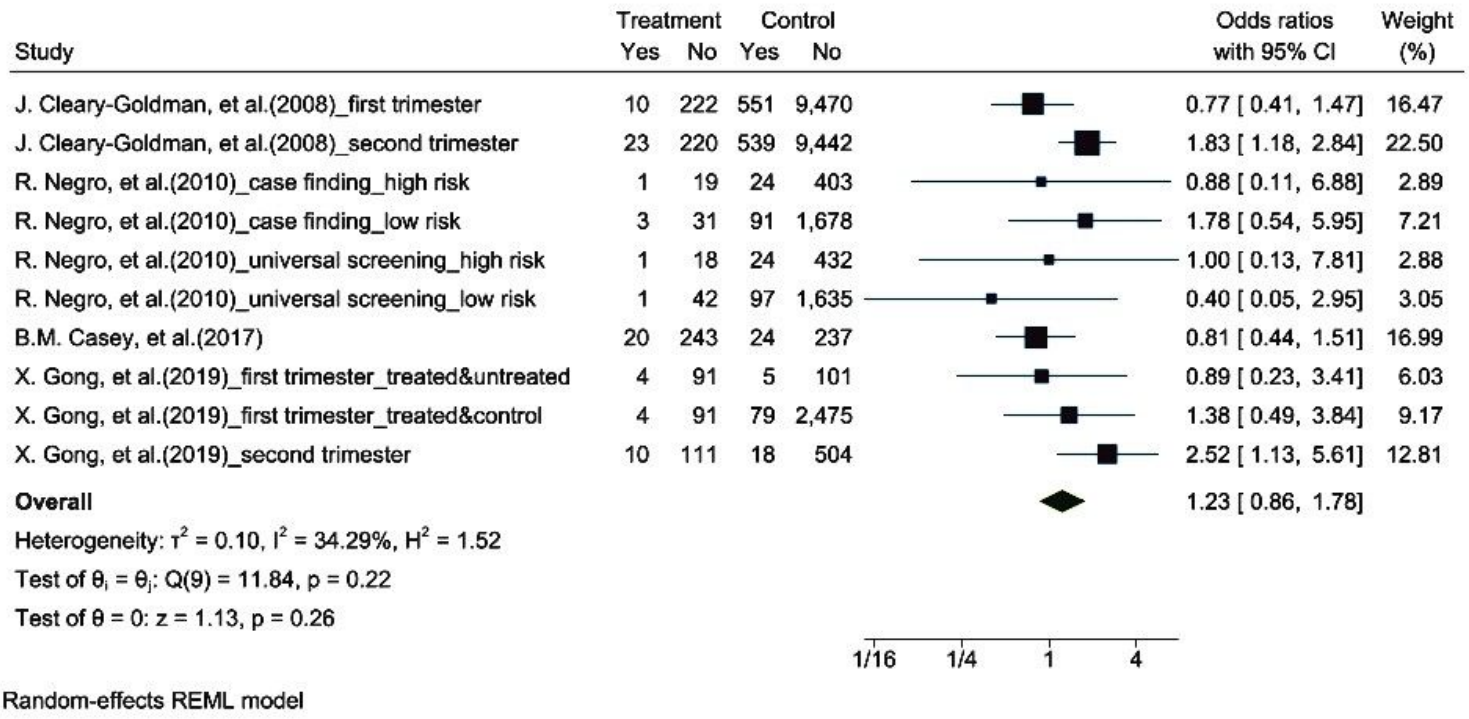

Figure 6

Effect of levothyroxine treatment on GH among OH women (treated versus placebo, euthyroid, untreated, control).

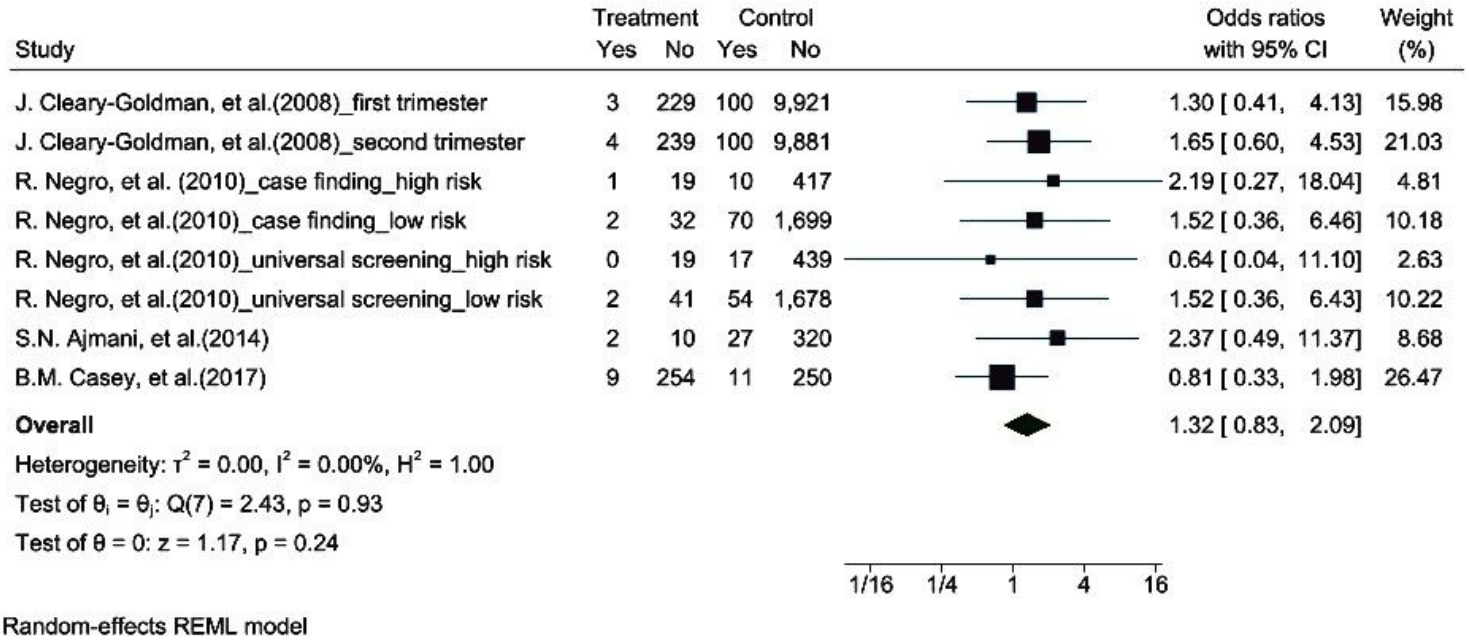

Figure 7

Effect of levothyroxine treatment on PE among OH women (treated versus placebo, euthyroid, control).

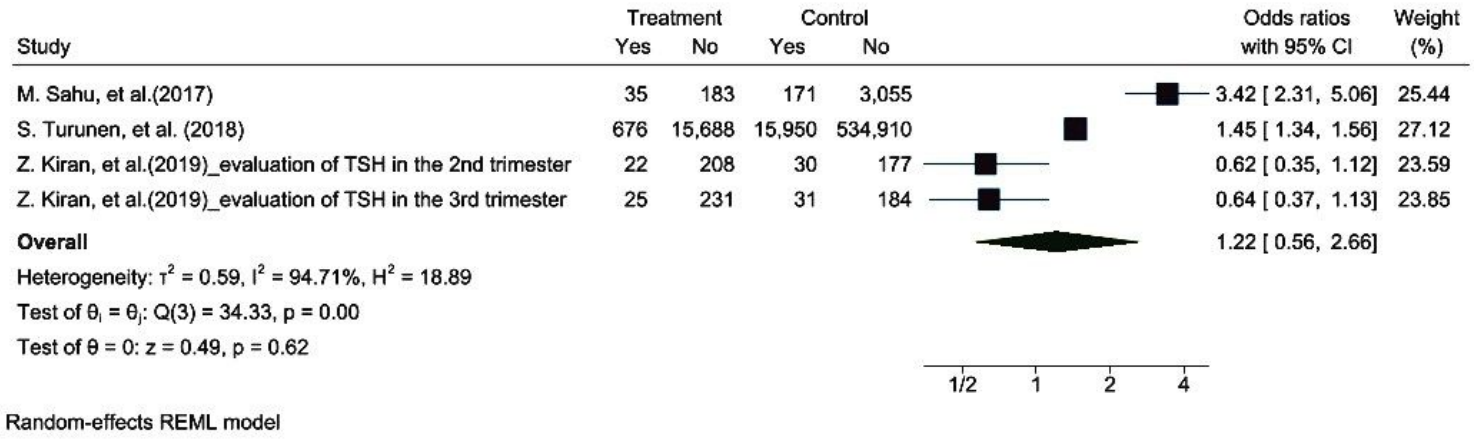

Figure 8

Effect of levothyroxine treatment on GH among SCH or OH women (treated vs. control, controlled vs. uncontrolled).

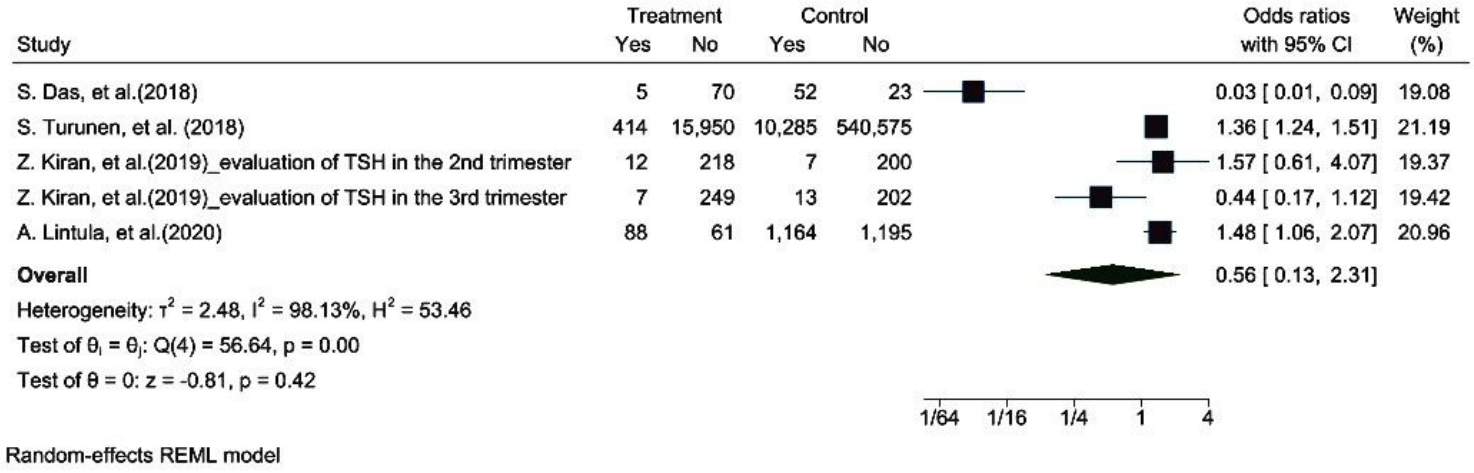

Figure 9

Effect of levothyroxine treatment on PE among SCH or OH women (treated vs. control, controlled vs. uncontrolled).

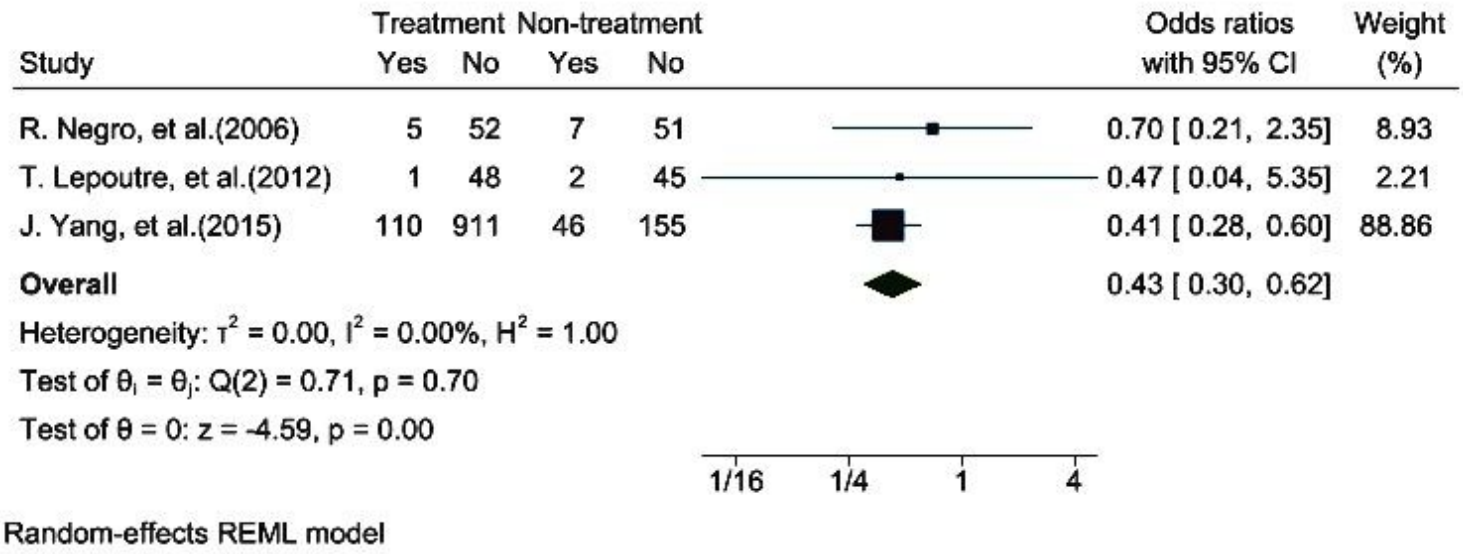

Figure 10

Effect of levothyroxine treatment on GH in TPOAb+ versus TPOAb+ (treated versus untreated).

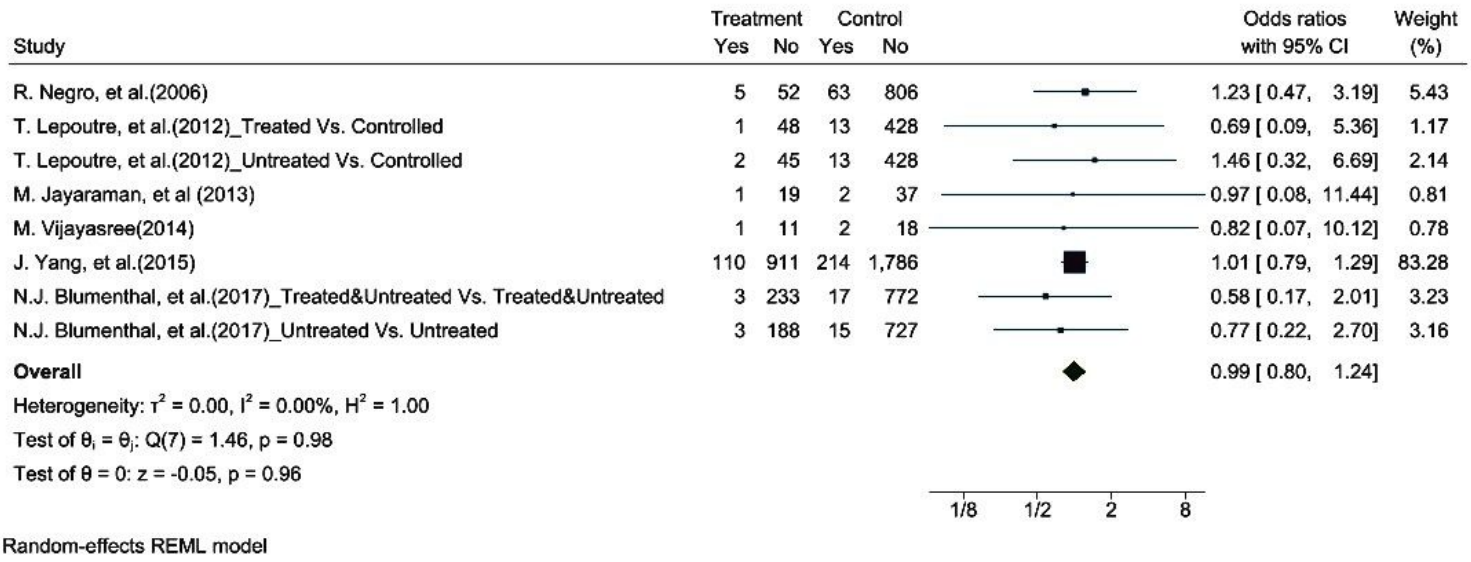

Figure 11

Effect of levothyroxine treatment on GH in TPOAb+ women versus TPOAb- (treated versus control, treated, and treated & untreated versus treated & untreated).

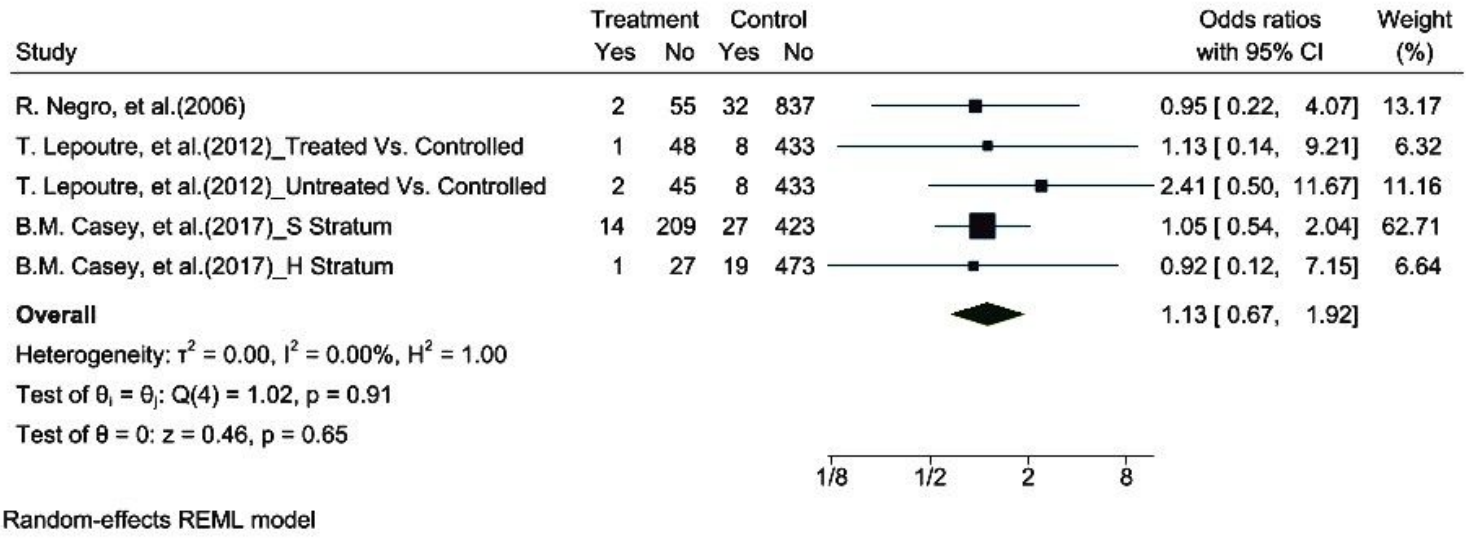

Figure 12

Effect of levothyroxine treatment on PE in TPOAb+ women versus TPOAb- (treated versus control and treated & plasebo versustreated &placebo).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile.doc
- Tables.docx