Review Article

A Meta-Analysis Examining the Impact of Levothyroxine Supplementation on Gestational Weight Gain in Women with Overt Hypothyroidism

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Abstract

Background: Overt Hypothyroidism (OH) is commonly treated with Levothyroxine (LT4), typically at a dose of 50 to 100 mg per day. Hypothyroidism is associated with excessive weight gain; therefore, we meta-analyzed the effect of *LT4* on Gestational Weight Gain (GWG) in women treated for OH compared to control subjects. **Materials and Methods:** We conducted a comprehensive review of several databases, including Medline, Science Direct, ProQuest, Scopus, Web of Science, and the Cochrane Library, as well as Google Scholar. Our goal was to identify English-language Randomized Controlled Trials (RCTs) and observational studies assessing the impact of LT4 on GWG and Body Mass Index (BMI) in pregnant women with OH, between August 4 and January 30, 2023. Additionally, we explored Persian databases such as Magiran, Islamic World Science Citation (ISC), and Scientific Information Database (SID). Because the studies reviewed included participants with Subclinical Hypothyroidism (SCH) as well, the meta-analysis also incorporated data from individuals with both OH and SCH. **Results:** The random-effects model indicated that after LT4 therapy, the GWG was not significantly different between the treated and control groups in studies involving women with OH [mean = 0.04, 95% CI: (−0.64, 0.72), $p = 0.908$, $I^2 = 57.13\%$]. Similarly, in studies comprising women with both OH and SCH, the difference in GWG was negligible [mean = −0.02, 95% CI: (−0.40, 0.35), $p = 0.909$, $I^2 = 22.93\%$]. **Conclusions:** Following LT4 treatment in pregnant women diagnosed with hypothyroidism, there was no significant difference in total GWG between the treated and control counterparts.

Keywords: *Gestational weight gain, hypothyroidism, levothyroxine, pregnancy, thyroxine*

Introduction

Overt Hypothyroidism (OH) is defined by a thyroid-stimulating hormone (TSH) level above the 97.5th percentile and a Free Thyroxine (FT4) level below the 2.5th percentile. This condition occurs in approximately 2%–3% of pregnant women. The reference ranges for TSH levels vary according to the trimester: in the first trimester, the range is 0.1–4.0 milli-international units per milliliter (mIU/ml); in the second trimester, it is 0.2–4.5 mIU/ml; and in the third trimester, it is 0.3–5.0 mIU/ml. Normal values for Free Triiodothyronine (FT3) and FT4 during pregnancy have been reported to be 1.7 to 4.2 pg/mL and 0.7 to 1.8 ng/dL, respectively.[1] Levothyroxine (LT4), typically prescribed at daily doses ranging from 50 to 100 mg, is one of the most frequently recommended medications during pregnancy. It is used by approximately 2 to 15 percent of women of reproductive age.[2] In one cohort of 16,364 hypothyroid women who were at risk for pregnancy complications, consistent LT4 therapy was shown to potentially reduce many of these risks.[3] One of the most important outcomes of pregnancy is achieving appropriate Gestational Weight Gain (GWG). The standard ranges for GWG are advised by the Institute of Medicine (2009) and are determined by taking the difference between the weight recorded immediately before pregnancy and the weight measured between 37 and 40 weeks of gestation.[4] In this regard, a particular study indicated that normal TSH levels during the first trimester correlate with weight gain in that same trimester.[5] Also, Pop *et al*.[6] reported that thyroid function parameters are linked to maternal weight gain throughout pregnancy. In addition, Collares *et al*.[7] found that elevated TSH levels and decreased FT4 levels in early gestation were associated with greater GWG, which positively correlates

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with pregnancy complications.[8,9] Now the question arises, whether levothyroxine is effective on GWG in women with thyroid hypofunction, while it is well known that hypothyroidism is associated with excessive weight gain.[10] In a study by Wang *et al*.,[11] women with OH who received treatment experienced greater gestational weight gain compared to the control group. In contrast, Chen *et al*.[12] found that pregnancy weight gain in women undergoing LT4 therapy was lower than that in non-hypothyroid women. On the other hand, researchers have shown that total weight gain at the end of pregnancy did not differ between participants with Subclinical Hypothyroidism (SCH) and OH who did not take levothyroxine.[13,14] Due to the insufficient and conflicting evidence available, along with our previously published articles,[15-17] We made the decision to perform a meta-analysis aimed at comparing the average weight gain during pregnancy and the maternal Body Mass Index (BMI) at the conclusion of pregnancy in women diagnosed with OH, as well as those with SCH and OH, who underwent treatment with levothyroxine, in contrast to individuals who did not receive any treatment or were given a placebo. Our search revealed that there is no prior meta-analysis addressing this subject.

Materials and Methods

The PROSPERO team has officially registered this systematic review and meta-analysis (CRD42022355697), which was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic review was conducted by searching through published articles, supplemented by manual searching. In our search for articles, we explored multiple databases, such as Medline, Science Direct, ProQuest, Scopus, Web of Science, Cochrane Library, and Google Scholar, to identify English-language studies published from August 4 to January 30, 2023. Additionally, we also explored Persian databases such as Magiran, Islamic World Science Citation (ISC), and Scientific Information Database (SID) during the same period. The search line used in the keywords, titles, abstracts was: ((“levothyroxine” OR “LT4” OR “thyroxine supplementation”) AND (“pregnancy outcomes” OR “ gestational weight gain” OR “preeclampsia” OR “gestational hypertension” OR “PIH” OR “gestational diabetes” OR “GDM” OR “hemorrhage” OR “postpartum hemorrhage” OR “PPH” OR “placenta abruption” OR “placenta previa” OR “preterm” OR “prematurity” OR “premature rupture of membrane” OR “PROM” OR “intrauterine growth restriction” OR “IUGR” OR “small for gestational age” OR “low birth weight” OR “LBW” OR “apgar” OR “fetal distress” OR “neonatal distress” OR “RDS” OR “neonatal admission” OR “NICU admission”)). For the hand searches, we examined the reference lists of selected studies and meta-analyses that were not identified through literature searches. Specifically, we focused on studies that assessed the impact of levothyroxine on maternal GWG and/or body mass index (BMI). Full-text articles were then evaluated to identify studies that met our inclusion criteria; animal studies were excluded from consideration. The first author (M G-KH) selected the papers, while another author (R M) confirmed the selections. We used EndNote software (Thomson Reuters, Philadelphia, PA) to manage the articles identified through these strategies. We conducted a meta-analysis encompassing four observational studies, since we identified only one RCT that satisfied our inclusion criteria.

The PECO (population, exposure, comparison, and outcome) question was designed to optimize the efficiency and significance of the review. The study population consisted of pregnant women diagnosed with OH, or OH and SCH. The exposure of interest was the use of levothyroxine compared to either a placebo or no treatment in control, Euthyroid (EU), or untreated subjects. The desired outcomes were gestational weight gain and/or maternal body mass index at the end of pregnancy. Participants in the study were women with hypothyroidism, who were pregnant with a single fetus and did not have any acute or chronic medical conditions. They were also non-smokers, free from substance abuse, and not taking any medications during their pregnancy, except for LT4 or prenatal supplements. Additionally, the subjects did not have high-risk pregnancies and delivered at 37 weeks of gestation or later.

We included trials and observational studies, including cohort, case-control, and cross-sectional studies, that evaluated the impact of levothyroxine on GWG and/or BMI at the end of pregnancy in participants with OH, or SCH and OH. Also, trials and hypotheses assessing levothyroxine therapy compared to placebo or no treatment in control, euthyroid, or untreated subjects. Furthermore, we included articles published in both English and Persian from August 4 to January 30, 2023. It should be noted that the present meta-analysis was conducted on four observational studies, since we identified only one RCT that met the desired inclusion criteria. Finally, we excluded animal studies.

Data extraction involved collecting the following information: the first author’s name, year of publication, study design type, sample size, GWG, age, TSH levels, TPOAb status, pre-pregnancy BMI, and maternal BMI at the end of pregnancy. This data was extracted by the corresponding author (M.G. KH) and reviewed by the first author (R.M.). Please refer to Table 1 for a detailed overview.

The National Institutes of Health (NIH) quality assessment tool was utilized to evaluate observational studies [Table 2]. One author (M G-KH) conducted the quality assessment while another author (VI) validated it.

This research constitutes a meta-analysis of observational studies; a strong statistical approach employed to integrate and evaluate data from various studies that focus on the shared research inquiry. We utilized Stata 18 to conduct the meta-analysis,

Table 1: Characteristics of the participants

Author, publication year	Study design	Sample size		Age (yrs)	TSH*** levels	TPOAb**** status		Pre-pregnancy BMI***** Kg/m²	Maternal BMI at the end of pregnancy	Explanation	GWG[$] (I vs. C) kg	*p*
		I* (Intervention)	C** (Control)			TPOAb positive, *n* (%)	Antibody TPO level					
Cappelli C, 2015[18]	Retrospective cohort	*n*=8 Women who needed to increase LT4 dosage	*n*=23 Women with no need to increase LT4 dosage	26.1 (3.1) Vs. 28.1 (3.7)	6.8 (2.1) Vs. 6.8 (1.3)	-		-		OH[$$] An increased dosage of LT4	21.11 (2.20) Vs 19.42 (2.53)	*p*=0.102
Kashi Z, 2016[19]	longitudinal cohort study	*n*=68 Needed levothyroxine increase	*n*=13 No need to increase levothyroxine	26.7 (4.8) Vs. 27.85 (5.5)	1.35 (0.79) Vs. 1.21 (0.78)		270.50±288.10 Vs. 35.67±56.24	26.3 (3.85) Vs. 26.3 (3.47)		OH An increased dosage of LT4	10.34 (11.41) Vs. 10.36 (6.02)	*p*=0.3
Chen L, 2018[12]	Cohort study	*n*=8 Gestational hypothyroid	*n*=8 Non gestational hypothyroid	31.5 (4.6) Vs. 31.1 (3.9)				22.9 (3.6) Vs. 21.5 (2.4)	22.9±3.6 Vs. 21.5±2.4	OH	13.33 (5.54) Vs. 17.80 (7.31)	Not written
Alptekin H, 2016[13]	case control	*n*=27	*n*=40	29.2 (5.9) Vs. 27.5 (4.5)	3.6 (2.6) Vs. 1.7 (0.9) *p*<0.001			29.1 (8.9) Vs. 24.4 (4.1)		SCH[$$$] or OH	10.52 (4.21) Vs. 11.10 (4.01)	*p*=0.57

*: Intervention, **: Control, ***: Thyroid-stimulating hormone, *****: Thyroid peroxidase antibody status, *****: Body mass index, [$]: Gestational weight gain, [$$]: Overt Hypothyroidism, [$$$]: Subclinical Hypothyroidism

Table 2: National Institutes of Health quality assessment tool used to evaluate observational studies

National Institutes of Health quality assessment of cohort studies

Studies	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and defined?	Was the participation rate of eligible persons at least 50%?	Were all the subjects selected or recruited from the same or similar populations?	Were a sample size justification, power description, or variance and effect estimates provided?	For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured?	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	For exposures that can vary in amount or level, did the study examine different levels of the exposure?	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the exposure (s) assessed more than once over time?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented? consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure (s) and outcome (s)?	Total score
Cappelli C, 2015[18]	Yes	Yes	NR	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Good
Kashi Z, 2016[19]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Chen L, 2018[12]	Yes	Yes	NR	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Good

Quality was rated as poor,(0–4 out of 14 questions) fair (5–10 out of 14 questions), or good (11–14 out of 14 questions); NA: not applicable, NR: not reported.

National Institutes of Health quality assessment of case-control studies

Study	Was the research question or objective in this paper clearly stated and appropriate?	Was the study population clearly specified and defined?	Did the authors include a sample size justification?	Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Were the cases clearly defined and differentiated from controls?	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	Was there use of concurrent controls?	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time) across all study participants?	Were the assessors of exposure/risk blinded to the case or control status of participants?	Was key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Total score
Alptekin H, 2016[13]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good

comparing group outcomes through mean differences. The results are presented in a forest plot, which visually displays the effect sizes and confidence intervals of individual studies, along with an overall summary estimate. Forest plots also allow us to assess the variability and consistency of findings across the studies, helping to identify patterns or discrepancies.

We utilized Cochran's Q test to measure the strength of the effect and evaluate the heterogeneity among the studies. This test assesses whether the observed differences in effect sizes between the studies are greater than what would be expected by chance alone. Additionally, the I^2 statistic measures the proportion of total variation across studies that arises from heterogeneity rather than random variation. These tests are essential for assessing the robustness and reliability of the meta-analytic findings, providing insights into the generalizability and implications of the pooled results. Additionally, we employed Egger's test to evaluate publication bias, which analyzes the relationship between effect size estimates and their standard errors. A notable intercept in Egger's test indicates a potential asymmetry in the funnel plot, suggesting the possibility of publication bias. For our sensitivity analysis, we used the "leave-one-out" procedure in Stata. This method offers a thorough approach to identifying influential studies and assessing their impact on the overall results, thereby enhancing the credibility and reliability of our meta-analysis. This approach systematically removes one study at a time from the meta-analysis dataset and recalculates the pooled effect estimate to assess the impact of each individual study on the overall results. By iteratively conducting this process for every study in the dataset, we can evaluate the robustness of our meta-analytic findings based on the inclusion or exclusion of specific studies.

Ethical considerations

This article is free from any plagiarism and data fabrication. All methods of this study were conducted in accordance with the PRISMA guidelines and were approved by the Ethics Committee of the Vice Chancellor for Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran (IR.ARI.MUI.REC.1401.285). Also, the results of the meta-analysis are completely honest.

Results

Study identification process

The initial search yielded 4,082 studies. After excluding 509 duplicates, 3,461 studies were discarded based on a review of titles and abstracts. In the following step, out of the remaining 90 studies, 48 articles were eliminated due to not meeting the inclusion criteria, and 30 articles were excluded because of insufficient information. Among the studies that were included, there were three studies involving pregnant women with SCH, four studies on OH, three studies on both SCH and OH, and two studies that evaluated participants' Thyroid Peroxidase Antibody (TPOAb) status. Out of seven cases discarded by the statistician, four observational studies were selected for meta-analysis: three focused on women with OH and four on women with SCH and OH [see Figure 1]. Only one clinical trial was found but excluded from the meta-analyses due to heterogeneity.

Description of included studies

One case-control study[13] involved 27 pregnant women with hypothyroidism who received levothyroxine replacement therapy, along with 40 healthy pregnant women matched for age and parity who did not have hypothyroidism. Among the cases, 11 women (40.74%) had OH, while 16 women (59.26%) had SCH. There was no significant difference in weight gain during pregnancy between the two groups (p = 0.572). In a retrospective cohort study,[18] 31 pregnant women with hypothyroidism underwent replacement therapy. Among them, 14 received liquid levothyroxine, while 17 were on tablet form. There was no significant difference in body weight at delivery between the two groups, with weights recorded as 69.92 (4.21) kg for the liquid LT4 group and 71.11 (3.73) kg for the tablet group (p = 0.433). Additionally, the increase in weight during pregnancy was 21.10 (2.23) kg for the eight women who needed an increase in their LT4 dosage, compared to 19.44 (2.50) kg for the 23 women who did not require a dosage increase. This difference was not statistically significant (p = 0.102). In the third cohort study,[12] eight women with gestational hypothyroidism, who received thyroxine replacement therapy during pregnancy were compared to eight women without gestational hypothyroidism. The weight gain and maternal BMI were statistically similar in both groups. In a longitudinal cohort study conducted from 2007 to 2010,[19] 81 women with hypothyroidism were followed, with their Levothyroxine dosage adjusted based on TSH levels. Among the participants, 54.32% (44 women) had clinical hypothyroidism, while 45.67% (37 women) had subclinical hypothyroidism. The change in weight during pregnancy was measured, showing an average increase of 10.34 (11.4) kg in participants who required an increase in levothyroxine dosage, compared to an average increase of 10.36 (6.0) kg in those who did not need to adjust their dosage (p = 0.314).

Meta-analysis results

In this study, we conducted a meta-analysis that included four studies meeting our inclusion criteria. Using a random-effects model, our analysis focused on women with OH from these observational studies. The results showed no significant difference between the treated and control groups (mean = 0.04, 95% CI: -0.64 to 0.72, p = 0.908), as illustrated in the forest plot [Figure 2]. Furthermore, there was no significant heterogeneity among the included studies (I^2 = 57.13%, p = 0.104), and Egger's test revealed no evidence of publication bias (p = 0.695). Our sensitivity analysis revealed that the overall effect size remained consistent even when each study was

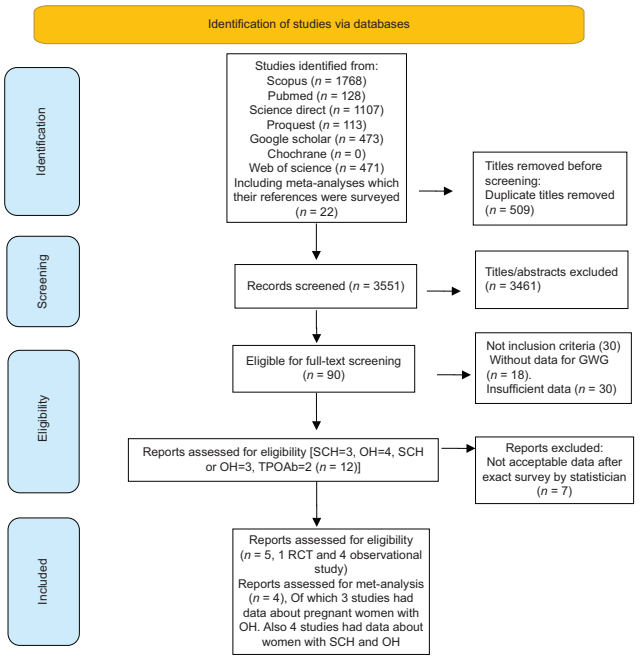

Figure 1: PRISMA flow diagram of included studies

excluded individually [see Figure 3]. Additionally, when we expanded our analysis to include studies of women with both OH and SCH, our meta-analysis resulted in a similar non-significant finding (mean = −0.02, 95% CI: −0.4 to 0.35, p = 0.909), as shown in the forest plot in Figure 4. No significant heterogeneity was found among the studies included (I^2 = 22.93%, p = 0.178), and Egger's test showed no evidence of publication bias (p = 0.900). The sensitivity analysis also yielded consistent results [Figure 5].

Discussion

This meta-analysis indicated that, after treatment with levothyroxine, the average gestational weight gain in participants with OH and those in the control group were not significantly different. This may suggest that OH increases the likelihood of overweight to such an extent that the GWG of individuals with OH aligns with that of the control group following levothyroxine treatment. Furthermore, a research study conducted with 92 pregnant women diagnosed with OH who were receiving levothyroxine treatment revealed that the average GWG did not show a significant difference between pregnancies that resulted in complications and those that were uncomplicated.[20] Also, Gao *et al*.[21] indicated that there were no significant differences in GWG among the four groups of treated pregnant women with SCH and OH. Additionally, GWG greater than 15 kg was not identified as a risk factor for reducing LT4 doses after delivery in cases of overt hypothyroidism.

Our results align with published reports regarding thyroid parameters and GWG. For example, Pop *et al*.[6] discovered that women who underwent excessive GWG during all three trimesters exhibited elevated mean TSH levels and reduced mean FT4 levels in comparison to those who maintained normal weight gain. Furthermore, higher free T4 levels during mid-gestation were associated with lower GWG. Collares *et al*.[7] demonstrated that higher concentrations of TSH and lower levels of FT4 during the first half of pregnancy were associated with an increased rate of excessive GWG, independent of other related factors. Additionally, Kahr *et al*.[22] found that excessive GWG was linked to lower FT4 levels compared to inadequate GWG. However, current results indicate that after treatment with levothyroxine and proper management of thyroid function parameters in hypothyroid women, gestational weight gain is comparable to that of women with normal thyroid function. Additionally, two studies have shown that higher levels of FT4 in the second trimester are associated with lower maternal weight in both euthyroid and treated hypothyroid participants.[23,24] Thyroid hormones play a crucial role in regulating appetite, energy availability, and the basal metabolic rate, all of which influence weight.[25,26]

Both diminished fT4 levels and a heightened free triiodothyronine to free thyroxine (fT3/fT4) ratio are linked to maternal obesity. Additionally, lower fT4 concentrations are correlated with excessive GWG. It appears that deiodinase activity regulates the local availability of fT3, which can be inferred from the fT3/fT4 ratio.[22] Also, researchers have reported a bidirectional relationship between thyroid function and basal metabolism, suggesting that changes in thyroid function can influence weight gain, and vice versa.[25,26] This connection may be mediated by alterations in leptin levels, which can affect thyroid function by stimulating the hypothalamus-pituitary-thyroid axis.[6,27,28] For instance, in a study conducted by Samuels *et al*.,[29] increasing the doses of levothyroxine (LT4) in patients with hypothyroidism resulted in a higher Resting Energy Expenditure (REE) relative to lean body mass. They showed that increasing the LT4 dose raised fT4 and fT3 levels (with a stronger association for fT4 than for fT3), and lowered TSH levels across the full range of TSH values (0.12–11.0 mU/L).

In this field, some studies suggest that even small changes in thyroid hormone levels can affect REE.[30] However, other studies have reported opposite findings.[31,32] They argue that lowering TSH levels to less than 2.50 mU/L is unlikely to improve weight or body composition in patients with hypothyroidism.[29] Therefore, a more accurate conclusion can be drawn when assessing the impact of levothyroxine on weight gain alongside measurements of energy expenditure and all indicators of thyroid function.

Our findings are significant because this study demonstrated that after treatment with levothyroxine, the total weight gain of pregnant women was not different from that of the control group. Therefore, it appears that LT4 therapy does not interfere with nutrition education or physical activity interventions aimed at weight control. This is particularly relevant given the unusual increase in LT4 prescriptions over the last decade, with a notable percentage of pregnant women in certain populations taking levothyroxine. Furthermore, we did not identify any

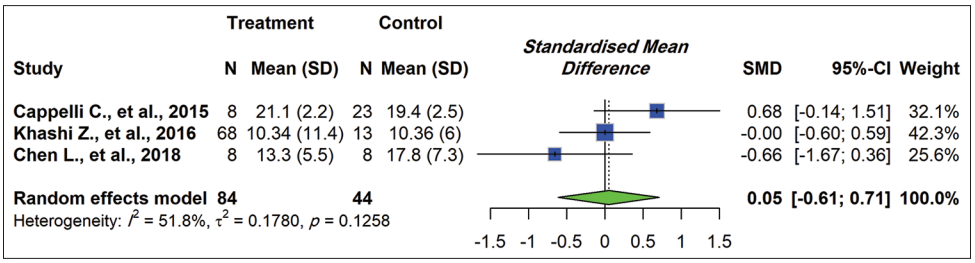

Figure 2: Effect of levothyroxine treatment on gestational weight gain among OH women. N: sample size; CI: confidence interval; SD: standard deviation, SMD: standardized mean difference; OH: overt hypothyroidism

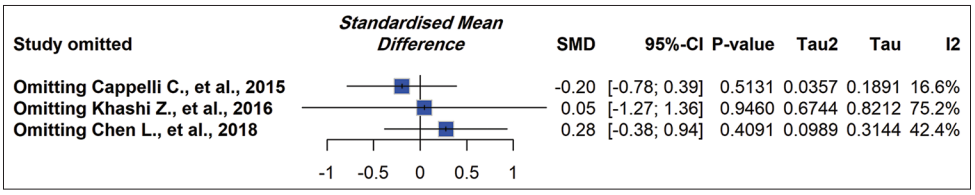

Figure 3: Sensitivity analysis for meta-analysis investigating the effect of levothyroxine treatment on gestational weight gain among OH women. CI: confidence interval; SMD: standardized mean difference; OH: overt hypothyroidism

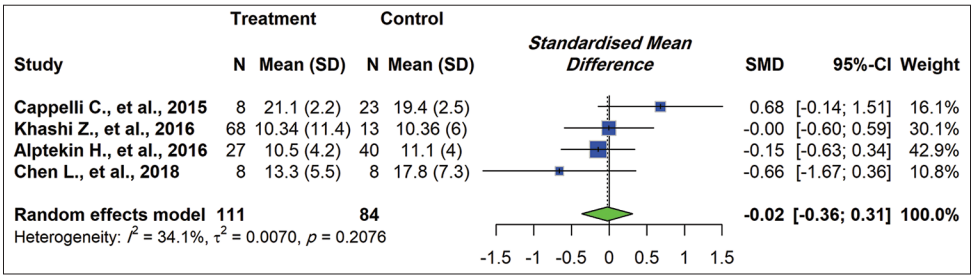

Figure 4: Effect of levothyroxine treatment on the gestational weight gain among OH, and SCH and OH women. N: sample size; CI: confidence interval; SD: standard deviation, SMD: standardized mean difference; OH: overt hypothyroidism; SCH: sub clinical hypothyroidism

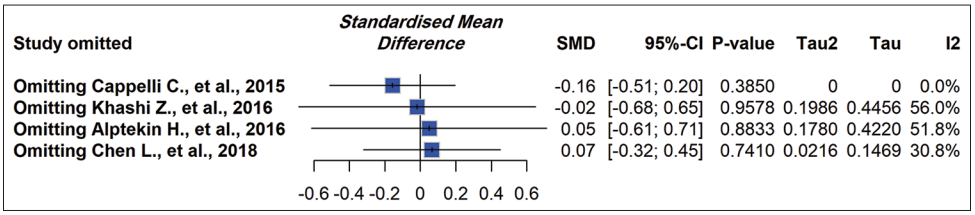

Figure 5: Sensitivity analysis for the meta-analysis investigating the effect of levothyroxine treatment on gestational weight gain among OH, and SCH and OH women. CI: confidence interval; SMD: standardized mean difference; OH: overt hypothyroidism; SCH: sub clinical hypothyroidism

other meta-analysis that has compiled data regarding the impact of levothyroxine on GWG in comparison to control subjects. Thus, this study offers insights for future research on the impact of levothyroxine on total GWG. Although we reviewed over 4,060 manuscripts, the small sample size remains our most significant limitation. Ultimately, it is recommended that additional prospective clinical trials and cohort studies be carried out, incorporating regular evaluations of thyroid function and energy expenditure over time, to offer a more comprehensive insight into this contentious matter.

Conclusion

After administering LT4 therapy to pregnant women with overt hypothyroidism, there was no significant difference in total GWG between those receiving treatment and the control group. However, further research is necessary to assess the impact of levothyroxine on GWG in hypothyroid women compared to healthy controls matched for TSH levels, pre-pregnancy BMI, and other relevant factors. We hope the findings of this study will enhance our understanding of weight gain during pregnancy in women who are taking levothyroxine.

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Conflicts of interest

Nothing to declare.

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