Original Article

Systematic review and meta-analysis of the efficacy and pregnancy outcomes of levothyroxine sodium tablet administration in pregnant women complicated with hypothyroidism

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Background: In recent years, the detection rate of pregnancy complicated with hypothyroidism [subclinical hypothyroidism (SCH) during pregnancy] has increased significantly. Levothyroxine sodium tablet is the main drug for the treatment of SCH during pregnancy, but its effect on the treatment of SCH during pregnancy and the effect of pregnancy outcome are still controversial.

Methods: PubMed, Web of Science, Medline, and Embase databases were screened to retrieve clinical studies on levothyroxine sodium tablets in the treatment of pregnancy complicated with hypothyroidism from the date of establishment to June 2021. Meta-analysis was performed with RevMan5.3 software. The differences in the incidence of preterm birth, miscarriage, gestational hypertension, postpartum hemorrhage, placental abruption, and abnormal neonatal weight were compared between the observation group and the control group. Heterogeneity of results was assessed with chi-square test and I^2 in RevMan5.3 software.

Results: Nine articles with a total of 2,873 pregnant women were included. The Cochrane assessments were all grade B and above, and the Jadad scale scores were all >3 points. The incidences of preterm birth, abortion, postpartum hemorrhage, and low birth weight infants in the pregnant women treated with levothyroxine sodium were lower than those in the control group [odds ratio (OR) =0.42, 0.34, 0.40, and 0.08, respectively; 95% confidence interval (CI): 0.30–0.58, 0.23–0.52, 0.22–0.74, and 0.01–0.51, respectively; Z=5.23, 5.08, 2.97, and 2.70, respectively; P<0.00001, <0.00001, =0.003, and =0.007, respectively].

Discussion: Levothyroxine sodium in the treatment of SCH can significantly reduce the incidence of premature birth, miscarriage, postpartum hemorrhage, and low birth weight infants. Due to the limited number of included studies, it remained to be further verified whether levothyroxine sodium treatment in SCH patients would affect the incidence of gestational hypertension.

Keywords: Levothyroxine sodium; ultrasonic examination; subclinical hypothyroidism during pregnancy (SCH during pregnancy); meta-analysis

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Introduction

To satisfy the physical demands of pregnancy, certain changes occur to the mother's thyroid, including increased thyroid volume, increased secretion of thyroid hormones, and elevated thyroid blood flow (1). When the body cannot adapt to this change, hypothyroidism may develop (2-4). According to statistics, the incidence of subclinical

hypothyroidism (SCH) is about 2–3%, and it is increasing year by year (5). The occurrence of SCH can significantly affect the outcome of pregnancy, resulting in a significant increase in the incidence of spontaneous abortion, stillbirth, premature birth, macrosomia, low birth weight, placental abruption, gestational diabetes, gestational hypertension, and preeclampsia. It also affects the development of fetal neurological intelligence, especially in early pregnancy (6). The incidence of SCH in pregnancy is high, but the treatment rate is low. According to statistics, only 16% of pregnant women with SCH in the United States receive treatment (7). It can be seen that there is still a need to strengthen the understanding and increase the attention of patients with SCH during pregnancy.

Levothyroxine sodium tablet is currently the first-choice drug for the clinical treatment of SCH. It has the effect of gradually increasing the levels of triiodothyronine and free thyroxine and decreasing the level of thyroid stimulating hormone (TSH) (8). The results of Ding *et al.* [2021] pointed out that levothyroxine sodium tablets can promote human metabolism, maintain human growth and development, and strengthen the sympathetic-adrenal system sensitivity. It can improve the metabolic disorder caused by subclinical hypothyroidism during pregnancy, and promote the return of thyroid function-related hormones to normal (9). The timely and appropriate application and adjustment of levothyroxine sodium tablets during pregnancy can promote the normalization of thyroid function, reduce the occurrence of corresponding complications, and achieve satisfactory pregnancy outcomes (10). A study of SCH patients treated with levothyroxine sodium tablets until delivery found that the incidence of adverse maternal and infant outcomes was significantly lower in patients treated with levothyroxine sodium tablets (11). In addition, Yu *et al.* [2021] used levothyroxine sodium tablets and thyroxine tablets to treat patients with hypothyroidism in late pregnancy; the results found that the incidence of adverse pregnancy in pregnant women treated with levothyroxine sodium tablets was significantly lower than that in pregnant women treated with thyroxine tablets (12). However, the current evidence for levothyroxine sodium tablets for the treatment of SCH is still insufficient (13). The American Thyroid Association recommends that patients with hypothyroidism and thyroid peroxidase antibodies in pregnancy should be treated with levothyroxine sodium tablets. The American Endocrine Society and the European Thyroid Association recommend levothyroxine sodium tablets for SCH women during pregnancy (14). Moreover, whether levothyroxine sodium tablets can improve the harm caused by SCH to pregnant women and their offspring has not yet formed a clear conclusion (15). Therefore, there is still controversy about the scope of use of levothyroxine sodium tablets and its effect on SCH and pregnancy outcomes.

To systematically evaluate the efficacy of levothyroxine sodium tablets in the treatment of SCH and its effect on pregnancy outcomes, used meta-analysis was adopted in this work to evaluate the differences in pregnancy outcomes between thyroxine sodium tablets and conventional interventions in SCH, aiming to provide reference evidence-based medical evidence for the clinical treatment of patients with SCH. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-269/rc).

Methods

Literature retrieval strategy

Registers and online databases such as the National Center for Biotechnology Information, the Cochrane Library, PubMed, Medline, and Embase were searched for related keywords and medical subject heading terms for SCH. Relevant literatures published from the establishment of the database to June 2021 were retrieved. The descriptive terms included SCH, levothyroxine, spontaneous abortion, stillbirth, premature delivery, macrosomia, low birth weight, placental abruption, gestational diabetes, gestational hypertension, and preeclampsia. Key words were freely combined with "or" and "and" for joint search, and were input into each database to search the target literature. The language was not limited during the search. Full text articles were retrieved and manual screening was conducted.

Criteria for inclusion and exclusion of literature

The following inclusion criteria were applied: (I) the diagnostic criteria of hypothyroidism during pregnancy was in accordance with the *Guidelines for Diagnosis and Treatment of Pregnancy and Postpartum Thyroid Diseases*; (II) the two indicators were thyroid stimulating hormone (TSH) >2.5 mIU/L in patients with early pregnancy and >3.0 mIU/L in patients with middle or late, and positive autoantibodies to thyroid peroxidase (TPOAb; >9.0 IU/mL) (12); and (III) randomized controlled trials (RCTs) involving singleton pregnancies in women >18 years of age.

The following exclusion criteria were applied: (I) articles with high similarity to the original text; (II) literatures that did not report the required indicators; (III) non-clinical trials; (IV) patients with simple hypothyroxinemia [free thyroxine (FT4) <12 pmol/L], simple elevated TSH, or simple positive thyroid peroxidase antibody (TPOAb); (V) patients with other reproductive diseases; (VI) individual case reports and literature reviews, etc.; (VII) meta-analyses as references rather than included in the literature; and (VIII) publications in which the results were not clear, or the patient data was incomplete.

Literature screening and quality assessment

Based on the Cochrane system, two reviewers independently evaluated the quality of the included literature and extracted the literature data, so as to exclude the literatures that did not meet the requirements and were of low quality. When there was inconsistency in the review results, two reviewers needed to decide whether the article was included through discussion, or a third reviewer was introduced for final evaluation.

The bias of the included literature was evaluated according to 4.2.6 of the Cochrane Evaluation Manual. The evaluation criteria included: (I) whether the research method was correct and clear; (II) whether the method for generating random sequences was clearly explained in the text; (III) whether the research results were clear and clear, whether the data was complete, and whether there was a problem of selective reporting; (IV) whether there was a problem of selective reporting of the results, whether the results were processed by the intention-to-treat analysis method; and (V) whether there was a blinded controlled study of participants and personnel in the article. According to the standard, the literatures included were divided into 3 levels (low bias, moderate bias, and high bias). The literature was initially screened by reading the title, and the lack of data was attempted to be supplemented by contacting the original author. The abstract and full text were further read, and then combined with the Jadad scale to evaluate the quality of the included literature. Finally, the literature with a Jadad scale score of more than 3 was selected for inclusion in this meta-analysis. For selected studies, information on all available variables was extracted and entered into a Microsoft Excel database.

Data extraction

The included literature was extracted by two reviewers. The main contents extracted included: (I) basic information: article title, first author, publication year, publication journal, research type, and research start and deadline; (II) research objects: the number, the age, gestational age, and intervention methods of the research subjects; (III) evaluation method: statistics and analysis of the main indicators of the experimental group and the control group; and (IV) observation indicators: the incidence of premature birth, miscarriage, gestational hypertension, postpartum hemorrhage, placental abruption, and abnormal neonatal weight.

Statistical analysis

Excel 2016 software was used to organize the data in the included literature, and the Cochrane Reviewer' Handbook and Jadad scale were used to evaluate the quality of the literature. RevMan5.3 software was used for meta-analysis of the included literature.

First, the chi-square test was used to conduct a preliminary test of literature heterogeneity, and the significance level of the test was set to $\alpha=0.05$, and $P<0.05$. Then, I^2 in RevMan5.3 software was used to quantitatively evaluate the heterogeneity results. It was considered that when $I^2<25\%$, the literature had low degree of heterogeneity; when $25\%<I^2<50\%$, the literature had moderate heterogeneity; and when $I^2>50\%$, there was substantial heterogeneity in the literature. Based on this, when $I^2<50\%$, a fixed effects model was used for meta-analysis; while when $I^2>50\%$, a random effects model was used for meta-analysis.

Pooled effects statistical model: dichotomous variables were described by relative risk (RR), odds ratio (OR), or risk difference (RD); and continuous variables were described by weighted mean difference (WMD) or standard mean difference (SMD). The RevMan5.3 software was used to output the forest plot to evaluate the bias of the included literature, and the Z value and P value in the results were extracted to judge the results of the meta-analysis. In addition, each effect size was expressed by 95% confidence interval (CI). When $P<0.05$, the difference between groups was considered statistically significant.

Results

Results of the literature search

In this study, a total of 389 articles were retrieved,

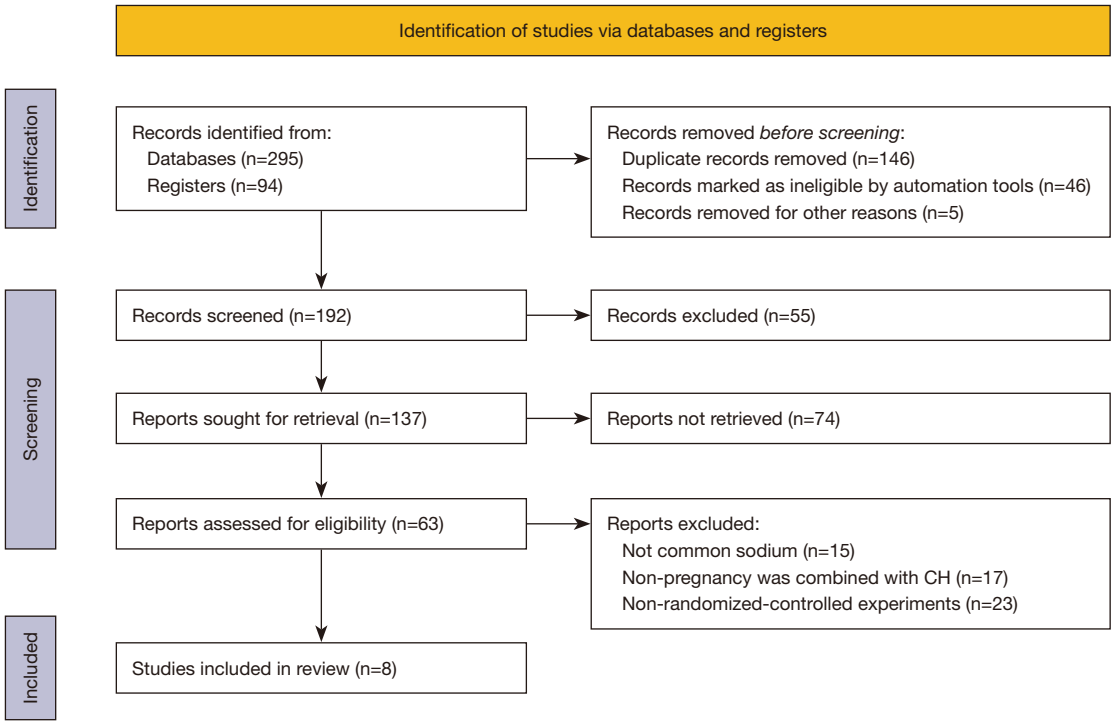

Figure 1 A flow chart showing the literature retrieval process.

including 295 articles from the PubMed and Embase database, and 94 articles from registers. After excluding the literatures that did not meet the inclusion criteria, 192 articles were obtained. Then, through the literature titles, article abstracts, and research content, literatures such as reviews, conference papers, case analysis, and risk factor assessment were excluded, and a total of 63 literatures were initially screened and met the inclusion criteria. After further intensive reading of the included studies, 17 non-SCH literatures, 23 non-RCTs, and 15 unconventional hypothyroid drug treatment studies were excluded. Finally, 8 articles (16-23) that satisfied the inclusion criteria were included. *Figure 1* shows the details of the literature screening process. The basic characteristics of the included literatures are shown in *Table 1*.

Risk assessment of bias in the included literatures

The Cochrane Handbook 5.3 version of the systematic review manual was used to evaluate the risk of bias in 8 articles included in this study. The risk map of bias is shown in *Figures 2,3*. The Review Manager 5.3 software was used to evaluate the risk of bias in literature quality. The risk of case selection bias was mainly due to the lack of emphasis on the continuity of the included patients. There were 8 articles (16-23) with partial risk of bias to be tested. With the exception of 2 publications (21,23), the other 6 articles were all found to have low risk bias. The risk of gold standard bias was mainly due to the interpretation of undefined gold standard results in 5 articles (17,18,20,22,23), and 3 articles (16,19,21) used ultrasound-assisted biopsy as gold standard. The risk of case process bias was mainly due to two articles (18,19) that did not specify whether there was a suitable interval between the test and the interpretation of the gold standard. Clinical applicability was good with the exception of one publication (20). The risk assessment is illustrated in *Figures 2,3*.

Premature birth

Figure 4 shows a forest map of the incidence of premature birth in patients with outcome indicators. A total of 8 articles met the requirements. The results showed that I^2=0% and P=0.70, and the fixed effects model was selected. Meta-analysis demonstrated that levothyroxine sodium reduced the incidence of premature delivery in pregnant women with hypothyroidism (OR =0.42; 95%

Table 1 General information of the included literatures

First author	Year	Country	Inspection methods	Number of research cases	Intervention measures	The experimental group	The control group
Abdel (16)	2010	Egypt	Ultrasound	70	Levothyroxine sodium a + routine	35	35
Costantine (17)	2020	USA	Ultrasound	245	Levothyroxine sodium a + routine	124	121
Kim (18)	2011	Korea	Ultrasound	64	Levothyroxine sodium a + routine	32	32
Li (19)	2020	China	Ultrasound	1,556	Levothyroxine sodium a + routine	585	971
Ma (20)	2016	China	Ultrasound	1,671	Levothyroxine sodium a + routine	675	996
Maraka (21)	2016	USA	Ultrasound	366	Levothyroxine sodium a + routine	82	284
Nazarpour (22)	2017	Italy	Ultrasound	1,746	Levothyroxine sodium a + routine	65	66
Negro (23)	2006	Italy	Ultrasound	984	Levothyroxine sodium a + routine	57	58

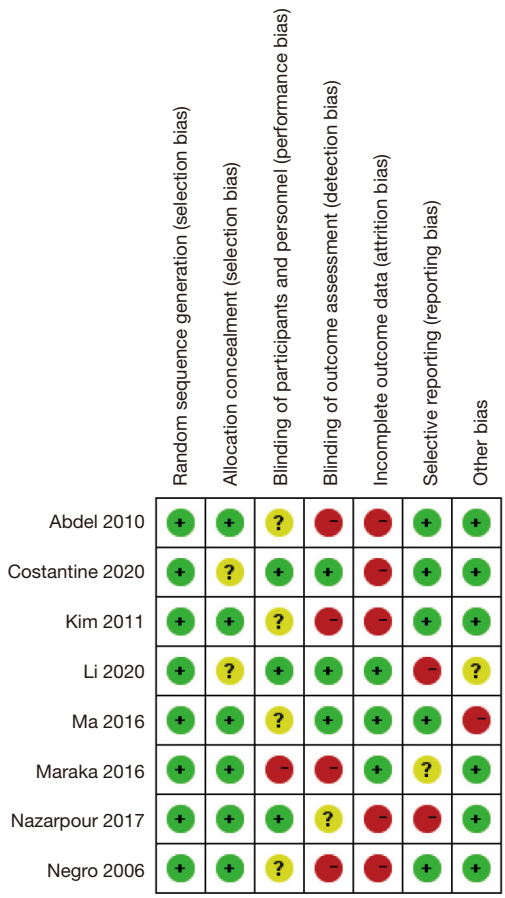

Figure 2 Risk bias risk assessment of the included literatures.

CI: 0.30 to 0.58; Z=5.23; P<0.00001). The funnel plot is basically symmetrical (*Figure 5*), and most of the data are on both sides of the central axis, suggesting that publication bias was effective.

Abortion

Figure 6 shows the forest map of the incidence of abortion as the outcome indicator. A total of 6 articles satisfied the requirements. The results showed that I^2=0% and P=0.60, and the fixed effects model was selected. Meta-analysis revealed that levothyroxine sodium administration in pregnant females with hypothyroidism resulted in reduced incidence of abortions (OR =0.34; 95% CI: 0.23 to 0.52; Z=5.08; P<0.00001). The funnel plot is basically symmetrical (*Figure 7*) and most of the data are on both sides of the central axis, suggesting that publication bias was effective.

Pregnancy-induced hypertension

Figure 8 shows the forest map of the incidence of pregnancy-induced hypertension. A total of 6 articles met the requirement. The results demonstrated that I^2=42% and P=0.13, and the fix effects model was used. Meta-analysis revealed that the incidence of pregnancy-induced hypertension was low in pregnant females with hypothyroidism who were treated with levothyroxine sodium (OR =0.63; 95% CI: 0.4 to 1.00; Z=1.97; P=0.05). The funnel plot is basically symmetrical (*Figure 9*), and most of the data are on both sides of the central axis, suggesting that publication bias was effective.

Postpartum hemorrhage

Figure 10 shows the forest map of the incidence of postpartum

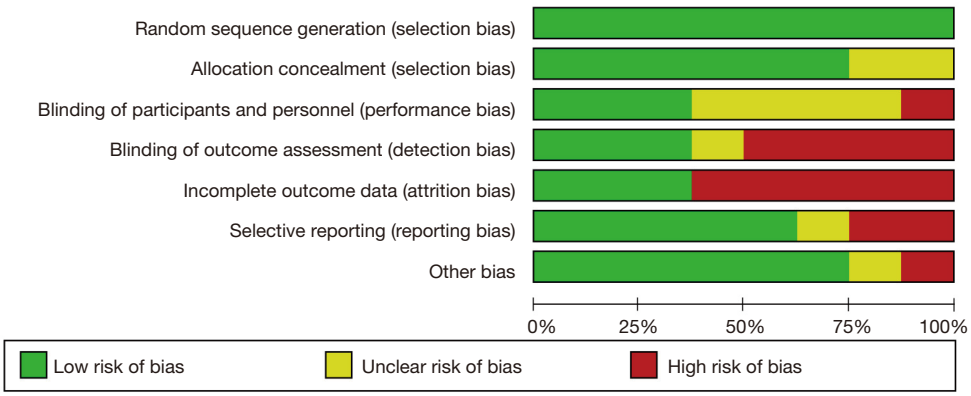

Figure 3 A bar chart showing the bias risk assessment of the included literatures.

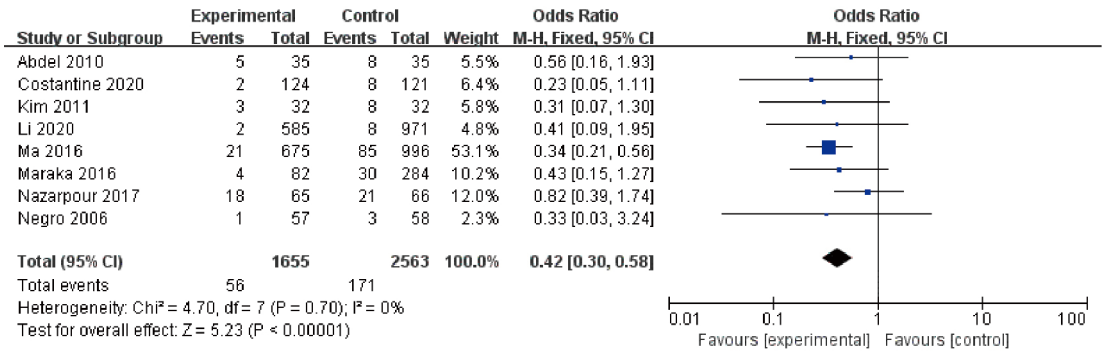

Figure 4 A forest map analyzing the effects of levothyroxine sodium on premature delivery in pregnant women with hypothyroidism. CI, confidence interval.

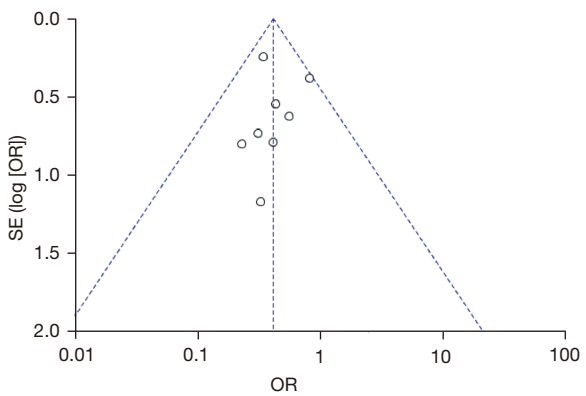

Figure 5 A funnel plot of premature delivery affected by levothyroxine sodium in pregnancy complicated with hypothyroidism. SE, standard error; OR, odds ratio.

hemorrhage in pregnant patients with hypothyroidism. A total of 5 articles satisfied the requirements. The results revealed that I^2=0% and P=0.93, and the fixed effects model was selected. Meta-analysis demonstrated that the incidence of postpartum hemorrhage was low in pregnant women with hypothyroidism who were treated with levothyroxine sodium (OR =0.40; 95% CI: 0.22 to 0.74; Z=2.97; P=0.003). The funnel plot is basically symmetrical (*Figure 11*), and most of the data are on both sides of the central axis, suggesting that publication bias was effective.

Placental abruption

Figure 12 shows the forest map of the incidence of placental

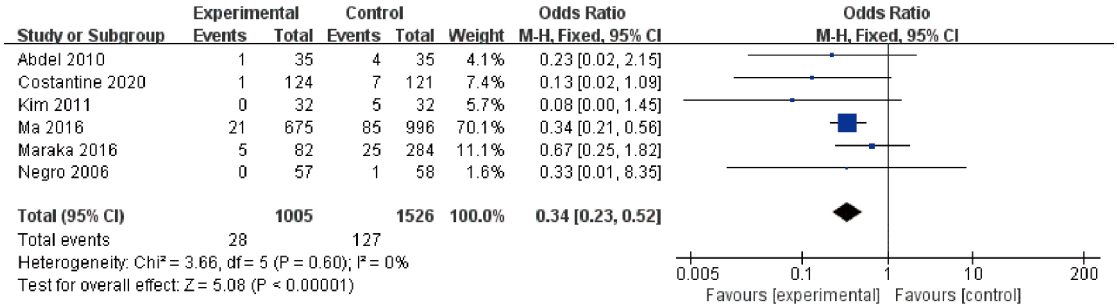

Figure 6 A forest map of the effects of levothyroxine sodium on the incidence of abortion in pregnant women with hypothyroidism. CI, confidence interval.

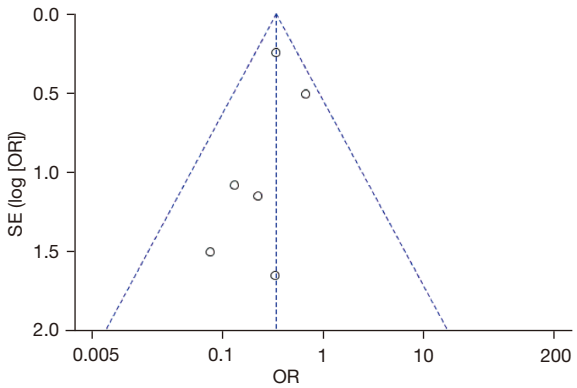

Figure 7 A funnel plot of the effects of levothyroxine sodium on the incidence of abortion in pregnant women with hypothyroidism. SE, standard error; OR, odds ratio.

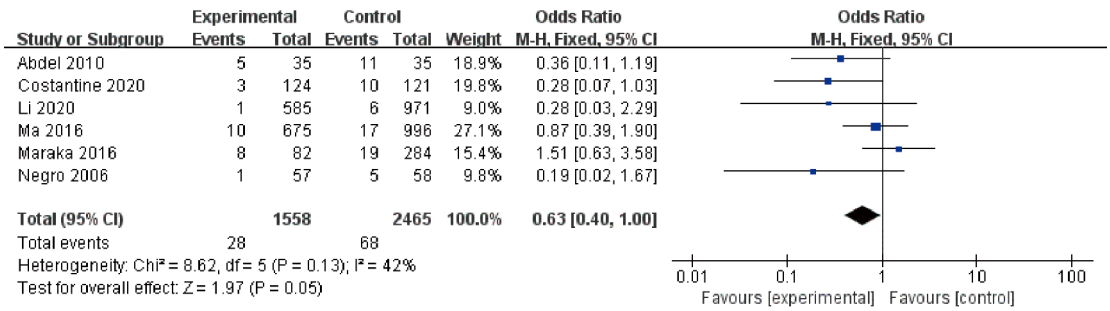

Figure 8 A forest map of the effects of levothyroxine sodium on the incidence of gestational hypertension in pregnant women with hypothyroidism. CI, confidence interval.

abruption. A total of 5 articles met the requirements. The results showed that I^2=0% and P=0.47, and the fixed effects model was applied. Meta-analysis showed that levothyroxine sodium treatment reduced the incidence of placental abruption in pregnant women with hypothyroidism, however, the decrease was not significantly different compared to patients who did not receive levothyroxine sodium treatment (OR =1.06; 95% CI: 0.42 to 2.64; Z=0.12; P=0.90). The funnel plot is basically symmetrical (*Figure 13*), and most of the data are on both sides of the central axis,

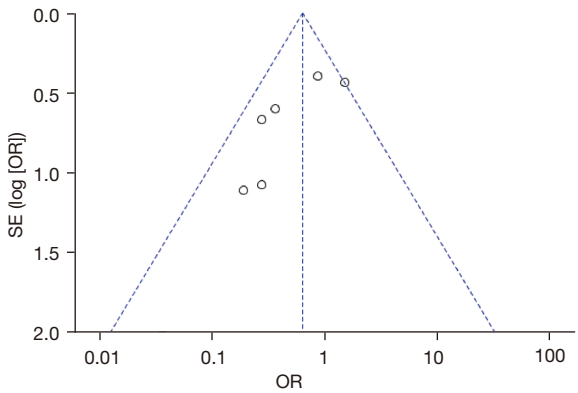

Figure 9 A funnel plot of the effects of levothyroxine sodium on the incidence of gestational hypertension in pregnant women with hypothyroidism. SE, standard error; OR, odds ratio.

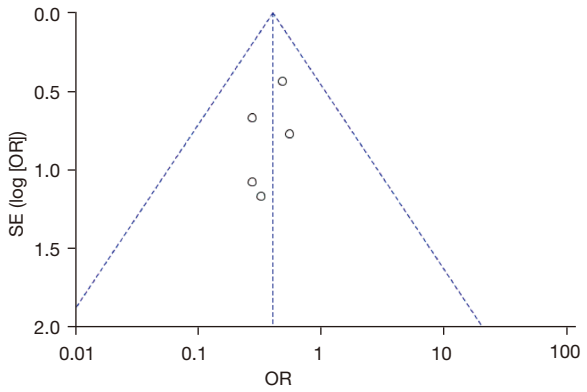

Figure 11 A funnel plot of the effects of levothyroxine sodium on the incidence of postpartum hemorrhage in pregnant women with hypothyroidism. SE, standard error; OR, odds ratio.

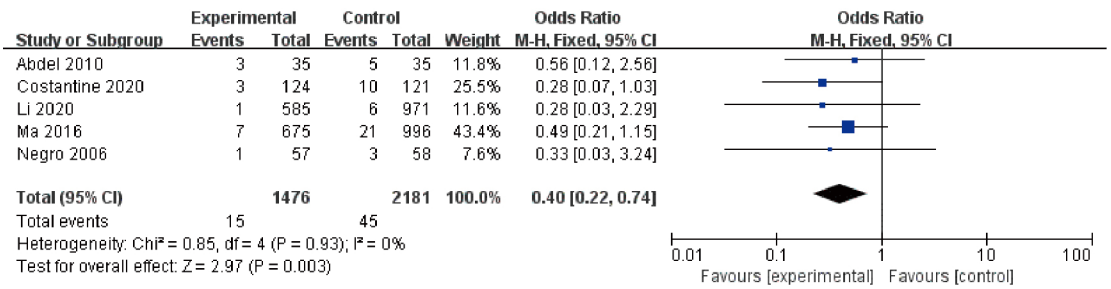

Figure 10 A forest map of the effects of levothyroxine sodium on the incidence of postpartum hemorrhage in pregnant women with hypothyroidism. CI, confidence interval.

suggesting that publication bias was effective.

Abnormal neonatal weight

Figure 14 shows the forest map of the incidence of abnormal neonatal weight. A total of 4 articles satisfied the requirements. The results showed that I^2=76% and P=0.005, and the fixed effects model was selected. Meta-analysis demonstrated levothyroxine sodium reduced the incidence of low birth weight in newborns compared to patients who did not receive treatment (OR =0.08; 95% CI: 0.01 to 0.51; Z=2.70; P=0.007). The funnel plot is basically symmetrical (*Figure 15*), and most of the data are on both sides of the central axis, suggesting that publication bias was effective.

Discussion

A total of 8 articles (16-23) were included in this meta-analysis. Quality evaluations of the 8 articles revealed that there was 1 grade A article and 8 grade B articles. Premature birth refers to a gestation period of ≥28 weeks to 37 weeks, while abortion refers to a gestation period <28 weeks (24,25). Fluctuations in maternal hormones can causes miscarriage and premature birth of infants. Other factors include chromosomal abnormalities, anatomical abnormalities, as well as genetic and acquired thrombocytopenia (26). Hypothyroidism results from thyroid dysfunction caused by insufficient synthesis and secretion of thyroid hormones (27). Insufficient thyroid hormone can affect the function of the placenta, resulting in ineffective supply of nutrition to the fetus. Therefore, patients with hypothyroidism are prone to adverse events during pregnancy. Levothyroxine sodium is a sodium salt of tetraiodothyronine, which is commonly used for the treatment of hypothyroidism. Its function and application are similar to thyroid tablets and is suitable for thyroid hormone supplementation therapy.

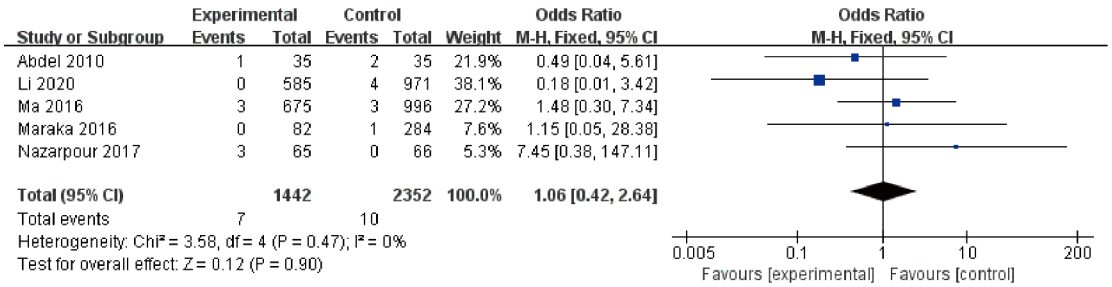

Figure 12 A forest map of the effects of levothyroxine sodium on the incidence of placental abruption in pregnant women with hypothyroidism. CI, confidence interval.

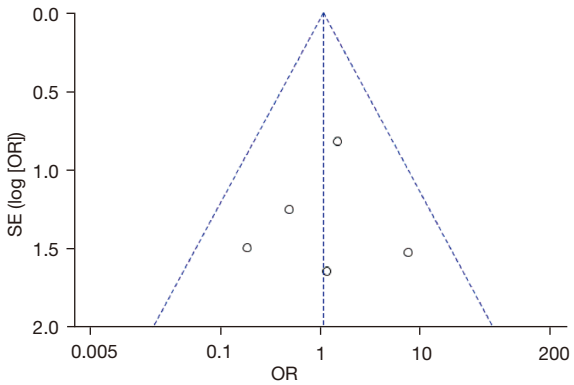

Figure 13 A funnel plot of the effects of levothyroxine sodium on the incidence of placental abruption in pregnant women with hypothyroidism. SE, standard error; OR, odds ratio.

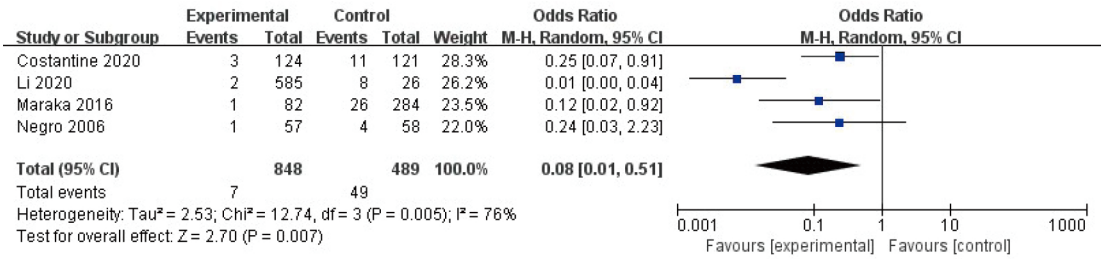

Figure 14 A forest map of the effects of levothyroxine sodium on abnormal low birth weight in pregnant women with hypothyroidism. CI, confidence interval.

This meta-analysis demonstrated that levothyroxine sodium could reduce the incidence of premature deliveries or abortions in pregnant patients with hypothyroidism. Approximately 66.7% of pregnant women suffer from hypothyroidism, and this is often associated with adverse events during pregnancy, such as premature delivery, abortion, placental abruption, gestational hypertension, and gestational diabetes mellitus (28). This is much higher than the 20.8% incidence of hypothyroidism observed in non-pregnant women. Yassa *et al.* (29) demonstrated that hypothyroidism increases the risk of premature delivery in pregnant women, due to detachment of the placenta after 20 weeks of gestation. Cecere *et al.* (30) reported a significant increase in the risk of sudden placental

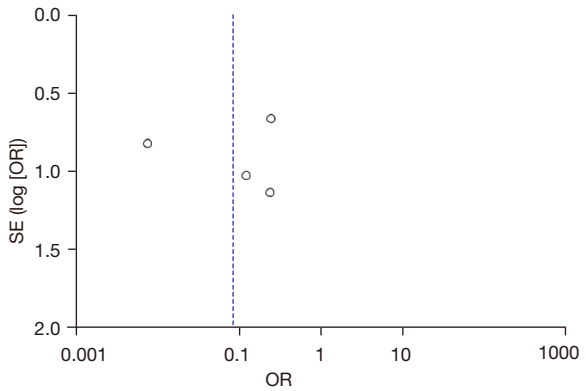

Figure 15 A funnel plot of the effects of levothyroxine sodium on abnormal low birth weight in pregnant women with hypothyroidism. SE, standard error; OR, odds ratio.

abruption in patients with thyroid function. Newborns under 2,500 g are considered low birth weight infants. Akhtar *et al.* (31) found that the incidence of low birth weight in hypothyroidism patients was 8.05 times higher than in normal pregnant women. Postpartum hemorrhage is classified as blood loss ≥1,000 mL within 24 hours after delivery, with associated symptoms or hypoxic symptoms of blood loss, and this remains the primary cause of maternal death worldwide (32). This meta-analysis demonstrated that levothyroxine sodium reduced obstetric complications in pregnant women with hypothyroidism and is consistent with the results of Zhao *et al.* [2018] (33). There were several limitations to this current study. First, only Chinese and English literatures are included, and the number of literatures may be insufficient. Second, for much of the included literature, the blinding and distribution methods were unclear. Furthermore, the number of high-quality literatures was small, and this may have affected the reliability of some data. Clinical researchers should pay attention to the implementation of blinding methods and the quality of clinical RCTs should be improved according to the clinical RCT report benchmark (ranking).

Conclusions

The use of levothyroxine sodium in the treatment of patients with pregnancy complicated with hypothyroidism demonstrated good efficacy. The incidences of premature delivery, abortion, placental abruption, gestational hypertension, and bleeding were greatly reduced in such patients. Therefore, the combined treatment of levothyroxine sodium can ensure the safety of the mother and the infant while achieving a successful delivery. Indeed, levothyroxine sodium may be an effective potential treatment regimen for pregnant women with hypothyroidism.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-269/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-269/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sullivan SA. Hypothyroidism in Pregnancy. Clin Obstet Gynecol 2019;62:308-19.
2. Shrestha A, Tripathi P, Dongol A. Pregnancy Outcomes in Patients with Hypothyroidism. Kathmandu Univ Med J (KUMJ) 2019;17:57-60.
3. Toloza FJK, Abedzadeh-Anaraki S, Maraka S. Subclinical hypothyroidism in pregnancy. Curr Opin Endocrinol Diabetes Obes 2019;26:225-31.

4. Shan Z, Teng W. Thyroid hormone therapy of hypothyroidism in pregnancy. Endocrine 2019;66:35-42.
5. Zhang Y, Wang H, Pan X, et al. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: A systematic review and meta-analysis. PLoS One 2017;12:e0175708.
6. Lazarus J, Brown RS, Daumerie C, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014;3:76-94.
7. Yoshihara H, Sugiura-Ogasawara M, Goto S, et al. Levothyroxine and subclinical hypothyroidism in patients with recurrent pregnancy loss. Am J Reprod Immunol 2021;85:e13341.
8. Bein M, Yu OHY, Grandi SM, et al. Levothyroxine and the risk of adverse pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. BMC Endocr Disord 2021;21:34.
9. Ding Z, Liu Y, Maraka S, 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 (Lausanne) 2021;12:797423.
10. Rao M, Zeng Z, Zhao S, et al. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol 2018;16:92.
11. Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update 2019;25:344-61.
12. Yu YH, Filion KB, Reynier P, et al. Use of levothyroxine among pregnant women with subclinical hypothyroidism in the United Kingdom: A population-based assessment. Pharmacol Res Perspect 2021;9:e00848.
13. Magri F, Chiovato L, Croce L, et al. Thyroid hormone therapy for subclinical hypothyroidism. Endocrine 2019;66:27-34.
14. Hennessey JV, Espaillat R. Reversible morbidity markers in subclinical hypothyroidism. Postgrad Med 2015;127:78-91.
15. Li N, Yang J, Chen X, et al. Postpartum Follow-Up of Patients with Subclinical Hypothyroidism During Pregnancy. Thyroid 2020;30:1566-73.
16. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract 2010;16:792-7.
17. Costantine MM, Smith K, Thom EA, et al. Effect of Thyroxine Therapy on Depressive Symptoms Among Women With Subclinical Hypothyroidism. Obstet Gynecol 2020;135:812-20.
18. Kim CH, Ahn JW, Kang SP, et al. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2011;95:1650-4.
19. Li MF, Ma L, Feng QM, et al. Effects of Maternal Subclinical Hypothyroidism in Early Pregnancy Diagnosed by Different Criteria on Adverse Perinatal Outcomes in Chinese Women With Negative TPOAb. Front Endocrinol (Lausanne) 2020;11:580380.
20. Ma L, Qi H, Chai X, et al. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 2016;29:1391-4.
21. Maraka S, Singh Ospina NM, O'Keeffe DT, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical Hypothyroidism. Thyroid 2016;26:980-6.
22. Nazarpour S, Ramezani Tehrani F, Simbar M, et al. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 2017;176:253-65.
23. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587-91.
24. Casey BM, Thom EA, Peaceman AM, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med 2017;376:815-25.
25. Zhou M, Wang M, Li J, et al. Effects of thyroid diseases on pregnancy outcomes. Exp Ther Med 2019;18:1807-15.
26. Leduc-Robert G, Iews M, Abdelkareem AO, et al. Prevalence of thyroid autoimmunity and effect of levothyroxine treatment in a cohort of 1064 patients with recurrent pregnancy loss. Reprod Biomed Online 2020;40:582-92.
27. Li SW, Chan SY. Management of overt hypothyroidism during pregnancy. Best Pract Res Clin Endocrinol Metab 2020;34:101439.

28. Cigrovski Berković M, Herman Mahečić D, Marinković Radošević J, et al. Hypothyroidism and pregnancy: still a controversial issue. Gynecol Endocrinol 2020;36:776-80.
29. Yassa L, Marqusee E, Fawcett R, et al. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab 2010;95:3234-41.
30. Cecere J, Purswell B, Panciera D. Levothyroxine supplementation in hypothyroid bitches during pregnancy. Theriogenology 2020;142:48-53.
31. Akhtar MA, Agrawal R, Brown J, et al. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. Cochrane Database Syst Rev 2019;6:CD011009.
32. Liang L, Mao Y, Zhang JR, et al. Analysis of genes related to hypothyroidism during pregnancy. Zhonghua Yi Xue Za Zhi 2019;99:3350-4.
33. Zhao L, Jiang G, Tian X, et al. Initiation timing effect of levothyroxine treatment on subclinical hypothyroidism in pregnancy. Gynecol Endocrinol 2018;34:845-8.

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