REVIEW

Medical treatment in pregnant women with subclinical hypothyroidism: systematic review and meta-analysis

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Abstract

Objectives: to determine the effectiveness of medical therapy in reducing complications associated with subclinical hypothyroidism during pregnancy.

Methods: in 2021, a systematic review of available cohort studies was carried out in three databases, with no publication date limit. Study selection and data extraction were performed in duplicate. Random-effects meta-analysis was performed, and odds ratios were calculated, with the corresponding 95% confidence intervals. Cohort risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). The certainty of the evidence was assessed using the GRADE methodology.

Results: five studies were included for qualitative and quantitative synthesis. A statistically significant relationship was found between medical treatment in pregnant women with subclinical hypothyroidism with respect to spontaneous abortion (p=0.03; OR=0.77; CI95%=0.61-0.97), and no statistically significant relationship was found for delivery preterm (p=0.46; OR=1.11; CI95%=0.85-1.44), nor for abrupt placentae (p=0.56; OR=1.60; CI95%=0.33-7.66). Three studies were at moderate risk of bias, and two were at low risk of bias. In all the results the certainty was very low.

Conclusions: medical treatment of subclinical hypothyroidism during pregnancy can have a beneficial effect in reducing cases of spontaneous abortion.

Key words *Subclinical hypothyroidism, Thyroxine, Preterm labor, Placental abruption, Miscarriage*

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Introduction

Thyroid disorders are common today, approximately 5-10% of the world population suffers from some pathology related to the thyroid; this figure has been increasing in recent years, this may be due to the fact that patients currently receive greater medical monitoring.[1] Currently, patients with thyroid pathologies represent 30 to 40% of the population in the endocrinology consultation. Most of these cases occur in women during pregnancy,[2] for this reason the American Society of Endocrinology (The Endocrine Society) and the American Association of Clinical Endocrinologists (AACE) mention that pregnant women are a vulnerable population and recommend that perform a thyroid hormone screening during prenatal check-ups,[3] in America it is estimated that around 15% of pregnant women are diagnosed with subclinical hypothyroidism.[4] In Latin America there are no exact statistics because the dosage of thyroid hormones is not always included in the prenatal control plan. Despite this, some records show that approximately 2-5% of pregnant women are diagnosed with subclinical hypothyroidism.[5]

Subclinical hypothyroidism is defined as an elevation of thyroid-stimulating hormone (TSH), accompanied by secretion of thyroid hormones (T3 and T4) in normal ranges.[4] In pregnant women, a TSH level greater than 2.5mIU/L is considered, accompanied by T3 and T4 levels in normal ranges for the diagnosis of subclinical hypothyroidism. As this is a subclinical pathology, the signs and symptoms are not usually evident, so the diagnosis depends on laboratory tests (dosage of TSH and T4). These exams are not included in the prenatal controls of many countries, especially in Latin America, therefore, there is a percentage of hypothyroid pregnant women who are not diagnosed in a timely manner and therefore do not receive medical treatment. In addition, there is a variability of confounding factors such as ethnic origin, iodine intake, and the specific laboratory method, which makes diagnosis difficult.[6,7]

A meta-analysis of 18 cohort studies found that pregnant women with untreated subclinical hypothyroidism are at increased risk of pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death compared with euthyroid women.[8] However, the effects of treatment remain unclear, therapeutic benefits have been described in decreasing rates of miscarriage and preterm birth,[4,7,9] but also possible harmful effects of treatment.[4,7]

Systematic reviews (SRs) summarize the results of available and carefully designed studies, in addition to providing a high level of evidence on the effectiveness of interventions in health issues. The SRs intend to be rigorous, informative, exhaustive, and explicit. This type of review can be of 2 types, qualitative and quantitative or meta-analysis, the latter allows us to perform a statistical analysis of the results of each selected study.[10]

In search of medical evidence for the pathology described above, the objective was to determine the effectiveness of medical therapy to reduce the complications associated with subclinical hypothyroidism during pregnancy.

Methods

The protocol for this systematic review and meta-analysis has been registered with the International Prospective Registry of Systematic Reviews (PROSPERO; identifier CRD42021220196). This study was approved by the Research Ethics Committee of the Faculty of Human Medicine of the Ricardo Palma University (PG-31-2020). It was developed according to the guidelines of the PRISMA statement.[11] Studies involving investigations of complications associated with subclinical hypothyroid pregnant women, divided into a group that received timely medical treatment and another group without intervention. Records in Spanish, and English; are carried out by medical personnel, which are available in their complete version. Letters to the editor, case reports, descriptive studies, editorials, comments, press articles, clinical trials, reviews, and conference abstracts were excluded.

The LILACS (Latin American and Caribbean Literature on Health Sciences), SciELO (Scientific Electronic Library Online), and PubMed (National Library of Medicine) databases were consulted. The search was carried out between January 02 and March 02, 2021.

All documents containing the combination of the descriptors "subclinical hypothyroidism" OR "hypothyroidism" AND "Thyroxine" OR "Treatment" AND "Premature birth" OR "preterm labor" OR "Abruptio Placentae" OR "Abortion, Spontaneous" OR "intrauterine death" OR "fetal loss". The search was performed by two independent and blinded authors (Abuhadba-Cayao KA and Talavera JE). The search was not limited by publication date.

The selection of articles was carried out independently by two authors (Abuhadba-Cayao KA and Talavera JE), blinded. The research team (Vera-Ponce VJ and De La Cruz-Vargas JA) was used to resolve differences.

One author downloaded all found references to EndNote 20 and removed duplicates. The author then exported those references to the Rayyan QCRI page (https://rayyan.qcri.org/). Titles and abstracts were screened for selection of potential studies for inclusion. Finally, the research team independently assessed the full-text version of each potential study for eligibility. Authors Abuhadba-Cayao KA and Talavera JE reviewed titles and abstracts to select potential studies for inclusion. Finally, these authors independently assessed the full-text version of each potential study for eligibility. Disagreements were

resolved with the research team (Vera-Ponce VJ and De La Cruz-Vargas JA).

Two authors (Abuhadba-Cayao KA and Talavera JE) independently extracted data of interest. For dichotomous outcomes, absolute frequencies were extracted. The Cochrane data collection form was used, used through the Cochrane Virtual extension, Review Manager 5.4, later a collection form was designed using Microsoft Excel 2016 (Microsoft Washington). The information of each selected article was organized using the data of the Author, year of publication, country of development, population characteristics, sample characteristics, intervention, follow-up time, conflict of interest between authors, and results of each study (abortion, preterm labor, abrupt placentae). Any disagreement was discussed with the research team (Vera-Ponce VJ and De La Cruz-Vargas JA) and resolved by consensus.

Two authors (Abuhadba-Cayao KA and Vera-Ponce VJ) independently assessed the quality of eligible studies. The risk of bias in the cohorts was evaluated using the adapted Newcastle-Ottawa Scale (NOS).[12] The NOS assesses three domains: 1. selection of the study groups (items: representativeness of the exposed cohort, selection of the cohort not exposed, verification of exposure, and demonstration that the result of interest did not occur at the beginning of the study); 2. Group comparability (elements: cohort comparability based on design or analysis); and 3. Exposure and outcome verification (items: outcome assessment, follow-up long enough for outcomes to occur, adequacy of cohort follow-up). One point was awarded for each item (two points per comparability item) according to methodological adequacy. The NOS awards a maximum score of 9 points. A score ≥7 was considered to mean a low risk of bias, a score of 4-6 meant a moderate risk of bias, and a score <4 meant a high risk of bias.[13] Risk of bias was assessed using the Cochrane Review tool. Manager 5.4., in this way the bias graphs of each study were obtained. Any differences were discussed with the research team (Talavera JE and De La Cruz-Vargas JA) and resolved by consensus.

For the statistical analysis, a random-effects meta-analysis was performed in the RevMan program to measure the effectiveness of treatment for subclinical hypothyroidism in pregnant women during pregnancy. An outcome was included in the meta-analysis if at least two studies reported quantitative data for that outcome. The summary measure chosen to measure effect size was odds ratio (OR) since all variables were dichotomous. All association measures were calculated with 95% confidence intervals and a value of $p<0.05$ was considered significant.

We describe the amount of heterogeneity with Cochran's Q statistic, I2 statistic, and Tau2. An I^2 ≥40% signified heterogeneity.[13] Publication bias was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation)[14] test, which classifies each outcome of the evidence as very low, low, moderate, or high certainty. the systematic review. Analyzes were performed using Review Manager 5.4.

Results

Epidemiological characteristics

A total of 416 articles were identified after searching the databases. Duplicates were then removed and 413 articles were reviewed, of which 25 were reviewed to full text, and 20 were excluded. Finally, five articles[4,8,15-17] were selected for qualitative and quantitative synthesis (Figure 1).

The total number of participants was 7085. The studies were of a cohort design. Sample sizes ranged from 79 to 5405 participants. All the studies took place in a hospital environment, following the prenatal check-ups of the patients. Regarding the definition of subclinical hypothyroidism, all studies used TSH levels ≥2.5mIU/L as a diagnostic cut-off value, with T4 values in normal ranges. All used laboratory results and clinical history records as data sources (Table 1).

Outcomes assessed by included studies

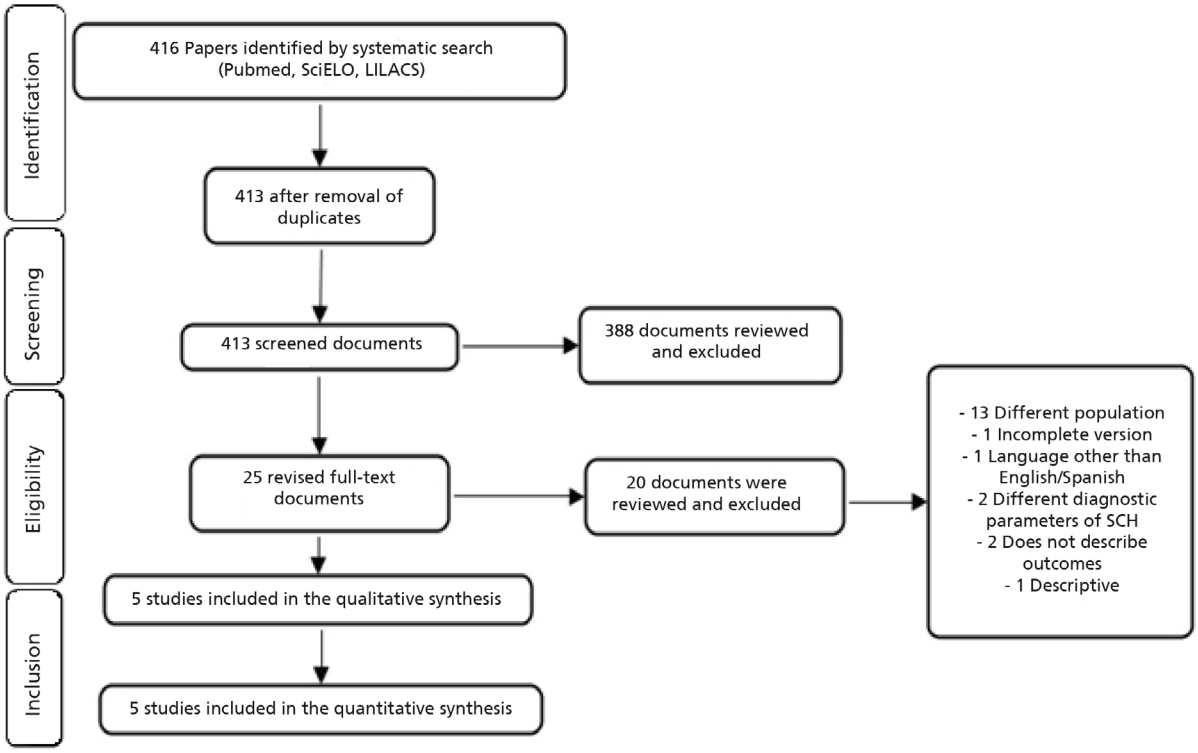
The frequency of outcomes for spontaneous abortion was 8 to 23%, preterm delivery was 7 to 11%, and abrupt placentae was 0.8 to 2%. Three studies[15-17] had their cohort-based on subclinical hypothyroid pregnant women, dividing it into two groups of subclinical hypothyroidism studies, with and without treatment. These studies had the common outcome of spontaneous abortion, preterm delivery, and abrupt placentae. Two studies presented both control groups, Bernardi *et al*.,[16] divided their cohort into patients with subclinical hypothyroidism, and euthyroid, in turn, calculated the rate of live births in two subgroups, subclinical hypothyroidism with or without treatment; Wang *et al.*[15] had the same distribution in his cohort group, but in his study, when evaluating the subclinical hypothyroidism groups with and without treatment, he found spontaneous abortion and preterm delivery as outcomes.

Risk of bias

In the NOS Selection category, two studies presented a high risk of bias because they did not demonstrate that the outcomes were not present before the study began. In the second category, comparison, two studies had an indeterminate bias as they did not control for additional outcomes; and finally, when evaluating the category of outcomes, only one study had a high risk of bias, since it did not report an adequate follow-up time for the outcomes of interest and did not declare the % of patients who lost follow-up. Two ways of presenting the study's risk of

Figure 1

Study selection flowchart.



bias are shown (Figures 2B and 2C). The risk of bias is mentioned for each study (Figure 2C). When evaluating them globally, 3 studies with moderate risk of bias and 2 with low risk of bias were found.

Global effects on outcome

From this, the studies were organized for their quantitative synthesis, and 3 groups were formed. The first group, made up of 3 studies, presented homogeneity (I^2=0%); and spontaneous abortion was evaluated as a complication in subclinical hypothyroid pregnant women who received and did not receive medical treatment, it was found that there is a beneficial effect of medical treatment in pregnant women with subclinical hypothyroidism with respect to spontaneous abortion (p=0.03; OR=0.77; CI95%=0.61-0.97) (Figure 3A).

In the second group, made up of 3 studies, preterm delivery was assessed as a complication, high heterogeneity was found (I^2=86%), and no statistically significant effect was found that favors medical treatment against this complication (p=0.46; OR=1.11; CI95%=0.85-1.44) (Figure 3B).

Finally, when evaluating abrupt placentae as an outcome in the third group, with non-significant heterogeneity (I^2=34%), no effect was found in favor of medical treatment with respect to this complication (p=0.56; OR=1.60; CI95%=0.33-7.66) (Figure 3C).

Sensitivity and group analysis

Sensitivity analysis was performed for the spontaneous abortion outcome, and the study by Wang *et al.*[15] was excluded due to its opposite effect value, giving us homogeneity among the remaining three studies (I^2=0%). But it was included in the analysis of the outcome of preterm birth because it did not affect the heterogeneity of the group.

Certainty of the evidence

We created a Summary of Findings table, using the GRADE methodology to assess the certainty of the evidence found and to be able to make the respective recommendations. For which we included those results that were considered important for the doctor. Three outcomes were found, spontaneous abortion, preterm delivery, and abrupt placentae, for all of them the certainty was very low (Table 2).

Discussion

Main results

Five cohort studies were included that analyzed the effectiveness of medical treatment in subclinical hypothyroid pregnant women to prevent complications

Table 1

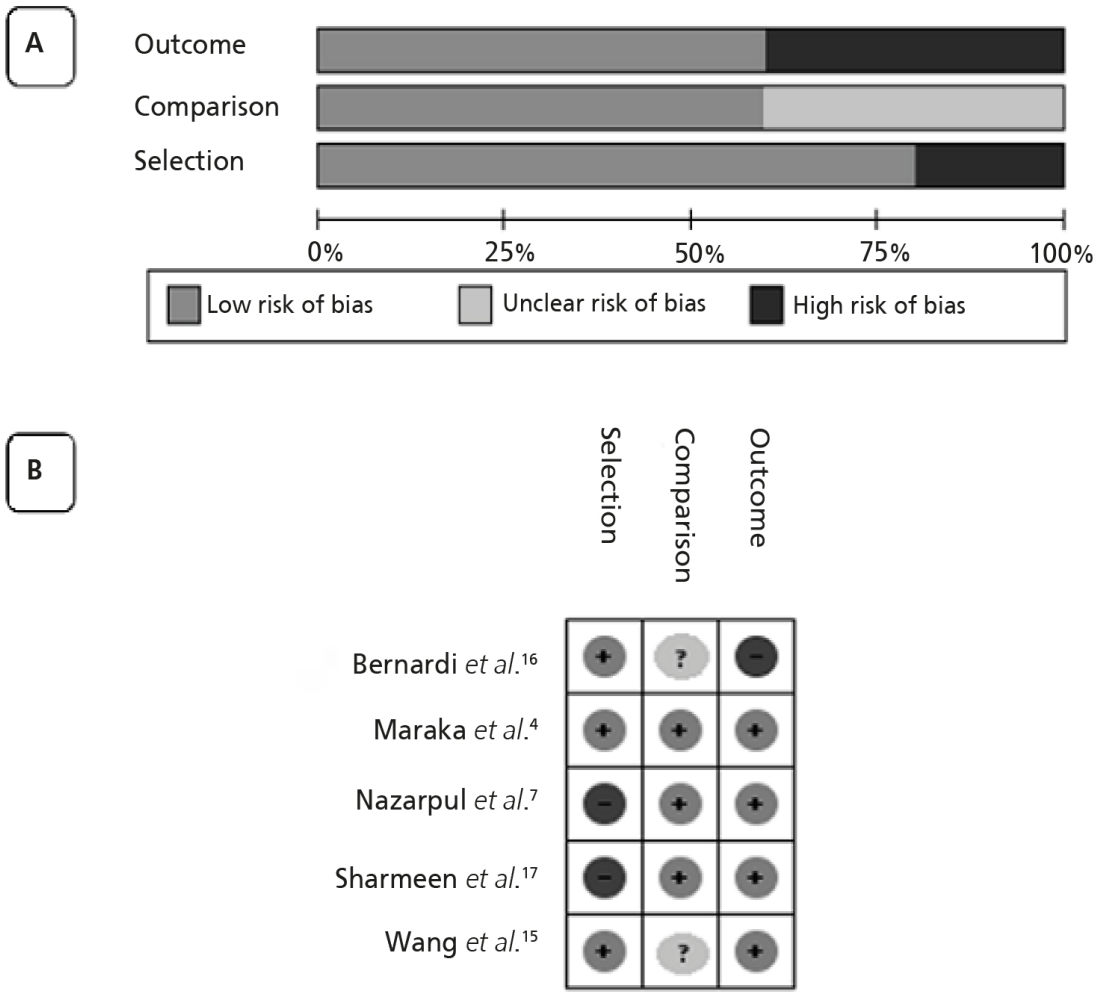
Characteristics of the individual studies included.

Author (Country)	Average age, inclusion or exclusion criteria	Population*	Intervention	Control	Follow-up	Outcome	Funding	Conflict of interest
Bernardi *et al.*[16] (EEUU)	•Age 22-42 years.•Inclusion criteria: history of miscarriage <10s gestation. • Exclusion criteria: multiple pregnancies, miscarriage due to chromosomopathies.	I: 69 C:221 I_1:24 I_2.15	I: SCH C: Euthyroid I_1:SCH-levothyroxine I_2:SCH-No treatment	Prenatal checkups	Immediate	•Spontaneous abortion •Preterm labor	University of Chicago	Undeclared
Maraka *et al.*[4] (EEUU)	•Age: 18-55 years.•Inclusion criteria: diagnosis before 4 weeks after the first checkup or 3 months later. •Exclusion criteria: women without health insurance coverage, multiple gestations.	I:843 C:4562	I: SCH-levothyroxine C: SCH-No treatment	Prenatal checkups	Immediate	•Spontaneous abortion •Preterm labor •Abruptio placentae	Self-financed	All authors have completed the ICMJE uniform disclosure form.
Nazarpour *et al.*[7] (Irán)	•Age 27 years.•Inclusion criteria: having been part of the ehran Thyroid and Pregnancy Study •Exclusion criteria: multigestation, TPOAb+	I: 183 C:183	I: SCH-levothyroxine C: SCH-No treatment	Prenatal checkups	During gestation	•Pretermdelivery •Abruptioplacentae	Research Institute for Endocrine Sciences	No conflict of interest
Sharmeen *et al.*[17] (Bangladesh)	•Age 15-44 years •Inclusion criteria: diagnosis within 6 months prior to the study. •Exclusion criteria: multigestation, chronic pathologies.	I: 29 C:21 I_1:26 I_2.3	I: SCH C: Euthyroid I_1:SCH-levothyroxine I_2:HSC-No treatment	Prenatal checkups	During gestation	•Spontaneous abortion	Self-financed	Undeclared
Wang *et al.*[15] (China)	•Age: 19-45 years. •Inclusion criteria: first trimester pregnant. •Exclusion criteria: multigestation, chronic pathologies.	I: 168 C:542 I_1:28 I_2.168	I: SCH C: Euthyroid I_1:SCH-levothyroxine I_2:SCH-No treatment	Prenatal checkups	During gestation	•Spontaneous abortion •Preterm delivery	Self-financed	Undeclared

* Population: Pregnant women diagnosed with subclinical hypothyroidism; ** Definition of subclinical hypothyroidism: elevated TSH concentration (greater than 2.5mIU/L) with concurrent normal thyroid hormone concentrations.

Figure 2

(A) Risk of bias assessment by domain using the Cochrane risk of bias tool; (B) Risk of bias assessment using the Cochrane risk of bias tool.



(spontaneous abortion, preterm birth, and abrupt placentae). Three studies with homogeneous populations[8,15,17] evaluated spontaneous abortion as a complication in subclinical hypothyroid pregnant women who received and did not receive medical treatment. The effectiveness of medical treatment against spontaneous abortion was demonstrated. In the case of other complications, three studies evaluated preterm delivery[4,15,16] and two studies evaluated abrupt placentae;[15,16] no significant effect of medical treatment was found, which may be due to the high heterogeneity of the populations, respectively.

Comparison with previous studies

In the first group, a protective effect of medical treatment with levothyroxine for spontaneous abortion was found. This finding coincides with the results obtained by Meng Rao, who carried out a systematic review to determine the effect of levothyroxine supplementation on the rate of pregnancy loss among pregnant women with subclinical hypothyroidism and autoimmune thyroiditis, where it is shown that supplementation of levothyroxine in subclinical hypothyroid pregnant women is related to a lower risk of spontaneous abortion.[18]

In the second group of analysis, no relationship was found between treatment with levothyroxine and preterm delivery. This was different in the studies by Maraka *et al.*,[4] Nazarpour *et al.*[7] and Wang *et al.*,[15] where a relationship was found between preterm delivery as a complication of untreated subclinical hypothyroidism. However, in the study by Mora[19] similar results were found, the pregnant women with subclinical hypothyroidism studied were divided into two groups (the first with intervention and the second without intervention). No significant differences were found in both groups, 9% were hospitalized for threatened preterm labor. Therefore, further studies are necessary to clarify the role of levothyroxine in preterm labor.[19]

In the last group of analysis, no relationship was found between treatment with levothyroxine and abrupt placentae. In a study by Foster WG,[20] done on 404 women

Figure 3

Meta-analysis of the effect of medical treatment on (A) spontaneous abortion; (B) preterm delivery; (C) abruptio placentae; in pregnant women with subclinical hypothyroidism.

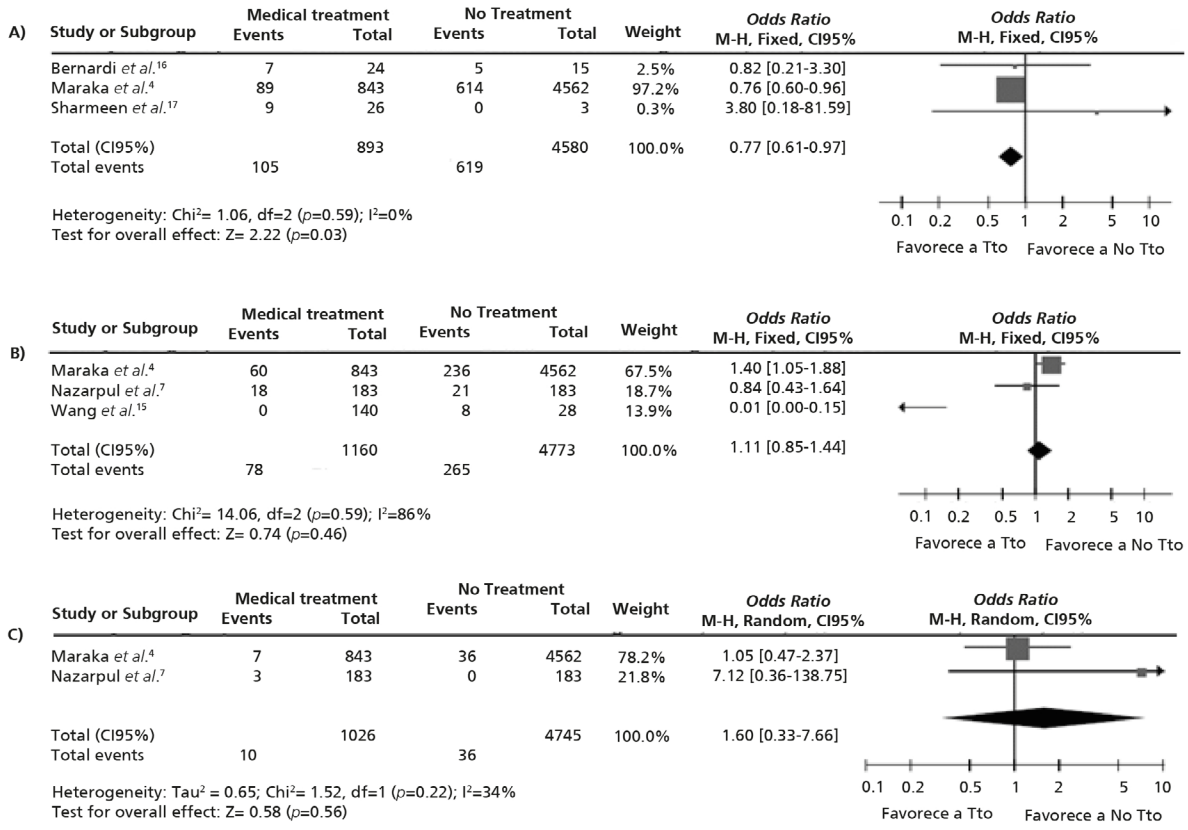


Table 2

Summary of the results to evaluate the certainty of the evidence, using the GRADE system.

Certainty assessment		No. of patients		Effect		
No. of studies	Study design	Medical treatment	No medical treatment	Relative (CI95%)	Absolute (CI95%)	Certainty
Spontaneous abortion						
3	Observational studies	105/893 (11.8%)	619/4580 (13.5%)	OR=0.77 (0.61 - 0.97)	28 less per 1000 (from 48 minus to 4 minus)	⊕◯◯◯ VERY LOW
Preterm delivery						
3	Observational studies	78/1166 (6.7%)	265/4773 (5.6%)	OR=1.11 (0.85 - 1.44)	6 less per 1000 (from 8 minus to 23 more)	⊕◯◯◯ VERY LOW
Abrupto placentae						
2	Observational studies	10/1026 (1.0%)	36/4745 (0.8%)	OR=1.60 (0.33 - 7.66)	4 more per 1000 (from 5 minus to 48 more)	⊕◯◯◯ VERY LOW

who had subclinical hypothyroidism, it was shown that they were three times more likely to have a pregnancy complicated by placental abruption than those without subclinical hypothyroidism. Therefore, timely treatment with levothyroxine could help decrease the chance of having abrupt placentae. No benefit of medical treatment was found, and the studies had low-certainty evidence.

Biological plausibility

The increase in hCG by 10,000U/L would correspond to a mean increase in free T4 of 0.6pmol L. This affects the entire thyroid hormone axis, obtaining a decrease in TSH of 0.1mUlL.[21]

During pregnancy, the production of thyroxine (T4) can usually increase to compensate for the decrease in free

serum thyroxine concentrations;[22] however, in pregnant women diagnosed with subclinical hypothyroidism, T4 levels remain within normal ranges but at the expense of an elevation of TSH, including the stimulus produced by the α subunit of hCG, influences to balance the production of T4, probably leaving aside functions of this hCG hormone, and because it is essential to maintain pregnancy, a high incidence of infertility and hypogonadotropic anovulation is usually found, in addition to an increased incidence of abortions in this pathology.[23]

Practical implications and perspectives

Unfortunately, the diagnosis and treatment of subclinical hypothyroidism in pregnant women are challenging and still controversial. Due to physiological changes in thyroid function and thyroid hormone metabolism during pregnancy, trimester-specific reference ranges for thyroid-stimulating hormone (TSH) and free thyroid hormones should be established.

It should be noted that several new trials have been published since the last guidelines were published and the next ones are ongoing, which makes the flow of information quite dynamic. Precisely, a recently published review: "controversies in the diagnosis and treatment of subclinical hypothyroidism in pregnancy",[7] showed that therapeutic benefits were observed in the reduction of spontaneous abortion and premature delivery rates when the intervention was performed in the first trimester in women with a TSH level between 2.5 and 10mU/l, mainly with values ≥4mU/l.

Pending the results of future trials, a clinician should be aware of the fact that, in difficult clinical scenarios, implementing low-dose L-T4 at 25-50µg daily is probably not harmful and may be beneficial,[24,25] but high levels of free T4 can have a negative impact on pregnancy outcome and children's IQ and behavior. This is because levothyroxine treatment introduced in the first trimester may prevent pregnancy loss, but may increase the rate of some pregnancy complications, such as preterm birth, gestational diabetes, gestational hypertension, and pre-eclampsia. Therefore, even decisions by the health professional must be individualized.

Future studies should address several areas such as Pregnancy-specific population-derived TSH and free T4 reference ranges are needed for each trimester to avoid false-positive diagnosis and unnecessary treatment.

Limitations

The results of this study must be evaluated by taking into account the level of certainty found, which was very low, and the heterogeneity, which was very high for the group whose outcome was preterm delivery; but with high homogeneity for spontaneous abortion. However, the results of more than 7000 patients were included, all the studies were carried out in a hospital environment with a control group, following the prenatal controls of the patients. For the diagnosis of subclinical hypothyroidism, all studies used a cut-off value of TSH ≥2.5mIU/L, with T4 values within normal ranges.

Medical treatment of subclinical hypothyroidism during pregnancy may have a beneficial effect in reducing cases of spontaneous abortion.

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Authors' contribution

Abuhadba-Cayao KA, Talavera JE, Vera-Ponce VJ, and De La Cruz-Vargas JA contributed significantly to the conception, design, analysis, and interpretation of the data. Abuhadba-Cayao KA, Vera-Ponce VJ and De La Cruz-Vargas JA made relevant contributions to the methodology of the article. Abuhadba-Cayao KA and Talavera JE prepared the first draft of the manuscript. All authors reviewed the entire manuscript and approved the final version.

The authors declare not to have any interest conflicts.

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