Maternal Thyroid Disease and Preterm Birth: Systematic Review and Meta-Analysis

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Context: Thyroid disease in pregnancy is increasing with rising average maternal ages in developed countries. The evidence for an association between preterm birth and thyroid disease has been confounded by small studies with varying outcomes and methodology.

Objective: The aim of this meta-analysis is to review the literature regarding thyroid disease including subclinical and overt hypothyroidism, hyperthyroidism, and isolated hypothyroxinemia and the specific outcome of preterm birth.

Data Sources: A search of PubMed and Embase databases was performed in May 2015. A fixed-effects model was used to calculate the overall combined odds ratio (OR) with its corresponding 95% confidence interval (95% CI) to evaluate the relationship between thyroid disease and preterm delivery.

Study Selection: Studies were considered eligible if they met the following criteria: prospective cohort study or a case control study; the exposure of interest was maternal thyroid disease, including subclinical hypothyroidism, overt hypothyroidism, hyperthyroidism, or isolated hypothyroxinemia; the outcome of interest was preterm delivery; and data regarding numbers of preterm births in each cohort were reported.

Data Extraction: Data were recorded in a database evidence table including any incidence data for maternal thyroid disease and preterm birth compared to a reference group.

Data Synthesis: Fourteen cohort studies and one case control study involving 2 532 704 participants were included. The combined OR of preterm delivery for pregnant women with overt hypothyroidism compared with the reference group was 1.19 (95% CI, 1.12–1.26; $P < .00001$). There was also a significant risk of preterm birth in women with hyperthyroidism (OR, 1.24 [95%, CI 1.17–1.31]; $P < .00001$). Subclinical hypothyroidism and isolated hypothyroxinemia showed no significant increase in OR. Sensitivity analysis made no change to these results.

Conclusion: Both overt hypothyroidism and hyperthyroidism are associated with a small but statistically significant increase in OR for preterm birth not seen in subclinical hypothyroidism or isolated hypothyroxinemia. **(*J Clin Endocrinol Metab* 100: 4325–4331, 2015)**

Preterm birth remains a challenge for modern obstetrics with rates estimated to be continually increasing in developed countries (1). It has been recognized that preterm birth is a heterogeneous condition, with two-thirds of cases resulting from either spontaneous labor or rupture of membranes and the remainder from iatrogenic causes.

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Abbreviations: CI, confidence interval; OR, odds ratio; TSH, thyroid-stimulating hormone.

Even within patients presenting in spontaneous preterm labor, it has been recognized that there may be many different pathological processes contributing to the outcome. Describing all the possible contributing pathology to preterm birth may result in a long-sought improvement in preterm birth rates (2).

Maternal thyroid disease has been linked with an increase in preterm birth in previous studies but the association remains contentious, with some studies concluding a strong association and others concluding that there was none. Thyroid disease is relatively common in reproductive age women, with overt hypothyroidism or hyperthyroidism combined affecting 3–4% of women and subclinical hypothyroidism affecting possibly as many as a further 10% based on large population study estimates (3). In addition, World Health Organization data estimate that about 30% of the world population has inadequate iodine intake despite the best efforts of supplementation programs, which may contribute to the burden of thyroid disease (4).

A previous review concluded that there was a possible association, but was limited by the heterogeneity and small sample size of the included studies (5). Since that time, the publication of at least two large population based epidemiological studies suggests the need for a new review and meta-analysis.

The aim of this systematic review and meta-analysis is to review the literature specifically related to thyroid disease and the outcome of preterm birth. A clear view of the available evidence may be able to provide better direction for future research efforts and suggest possible preventative measures.

Materials and Methods

Search strategy and study selection

A literature search was conducted in PubMed and Embase in May 2015 using the following search terms: thyroid disease, hypothyroidism, hyperthyroidism, subclinical hypothyroidism, hypothyroxinemia, preterm delivery, preterm labor, preterm birth, premature delivery, premature labor, or premature birth, without setting any search limits. Citation tracking of included studies and recent reviews was also performed. Studies were considered eligible if they met the following criteria: 1) the study design was a prospective cohort study or a case control study; 2) the exposure of interest was maternal thyroid disease including subclinical hypothyroidism, overt hypothyroidism, hyperthyroidism, or isolated hypothyroxinemia; 3) the outcome of interest was preterm delivery; and 4) data regarding numbers of preterm births in each cohort were reported. Data from abstracts, review articles, editorials, case reports, and letters were not included.

Data extraction

The exposure was thyroid disease and the outcome of interest was preterm birth, defined as birth before 37 weeks of completed gestation. Data were recorded in a database evidence table including any incidence data for maternal thyroid disease and preterm birth compared to a reference group. Information was extracted from each selected article on study characteristics, quality, and test results.

Assessment of quality of the included studies

The Newcastle–Ottawa scale was used to assess methodological quality of the selected studies (6). Information on adequacy of definition of cohorts, representativeness of the sample, selection and evaluation of controls, comparability, ascertainment of exposure, and outcome were evaluated for cohort studies. The study was considered to have low risk of bias if it scored a maximum of 4 for selection, 2 for comparability, and 3 for assessment of outcome or ascertainment of exposure. Any study that scored 1 or 0 for selection or 0 for comparability or for outcome assessment was categorized as having a high risk of bias. Studies that scored in between were rated as having a medium risk of bias.

Statistical analysis

Data were analyzed using RevMan, version 5.3. The overall combined odds ratio (OR) was calculated with its 95% confidence interval (CI) to assess the strength of the relationships between thyroid disease and preterm delivery risk. The significance of the combined OR calculated using the Mantel-Haenszel statistical method, was determined by the Z test, and a P value of $<.05$ was considered significant. In our study, two models of meta-analysis for dichotomous outcomes were considered: the random-effects model (DerSimonian and Laird) and the fixed-effects model (7). To assess the between-study heterogeneity more precisely, both the χ^2-based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation resulting from heterogeneity were calculated (8, 9). The I^2 index expressing the percentage of the total variation across studies because of heterogeneity was calculated to assess the between-study heterogeneity. I^2 values of 25, 50, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively. If moderate or high heterogeneity existed as defined here, the random-effects model was used to pool the results; otherwise, the fixed-effects model was used to pool the results when the I^2 value was $<50\%$.

Results

Study selection and study characteristics

The search strategy identified 58 publications. Fifteen of these were review articles or meta-analyses and were excluded. Twelve studies were primarily focused on the issue of thyroid autoantibodies and were also excluded. One study was exclusively conducted in twin pregnancy and so was excluded (10). Four studies related to various interventions in thyroid disease and were excluded (11–14). Four further articles were excluded after review either because of low numbers (defined as n values for thyroid

Table 1. Characteristics of Included Studies

Included Studies	Timing of Thyroid Function Testing	Location	Number of Centers	Laboratory Validation	Subclinical Hypothyroidism	Hypothyroidism	Hyperthyroidism	Isolated Hypothyroxinemia
Cohort studies								
Casey, 2005	<20 weeks	US	Single	Yes	Yes			
Chen, 2014	All trimesters	China	Single	Yes	Yes			
Cleary-Goldman, 2008	First and second trimesters	US	15	Yes	Yes			Yes
Korevaar, 2013	<18 weeks	Netherlands	Single	Yes	Yes	Yes	Yes	Yes
Männistö, 2009	<20 weeks	Finland	Multiple	Yes	Yes	Yes	Yes	
Sahu, 2010	13–26 weeks	India	2	No	Yes	Yes		
Su, 2011	<20 weeks	China	Multiple	Yes	Yes		Yes	Yes
Wang, 2012	<12 weeks	China	12	Yes	Yes			
Andersen, 2013	Before, during, and after pregnancy	Denmark	Multiple	No		Yes	Yes	
Casey, 2007	<20 weeks	US	Single	Yes				Yes
Léon, 2015	<24 weeks	Spain	4	Yes		Yes	Yes	Yes
Wikner, 2008	<13 weeks	Sweden	Multiple	No		Yes		
Hamm, 2009	15–16 weeks	Canada	Multiple	Yes				Yes
Ong 2014	9–14 weeks	Australia	Multiple	Yes	Yes			
Case control								
Hirsch, 2013	3–32 weeks (control group, 4–24 weeks but not significantly different)	Israel	Multiple	Yes		Yes		

disease <10) or because the cohort was a normal cohort where thyroid-stimulating hormone (TSH) screening had been performed without finding any cases of thyroid disease (15–18). One study compared hypothyroid women with and without appropriate therapy and so was excluded on the grounds of a lack of normal controls (19). Preterm birth figures were not reported for two studies and could not supplied by the authors (20, 21). The latter may have been excluded in any case because it focused only on women with a TSH >6, which is a very different criteria to the other included studies. One population-based study was excluded because it did not separate thyroid disease into hypothyroidism and hyperthyroidism (22). For one study, the authors were able to provide detailed information regarding preterm birth; however, there were only six cases of overt hypothyroidism in the study (23). Their results have been included for subclinical hypothyroidism but not for overt hypothyroidism in keeping with the exclusion of very small studies (n < 10). Two studies were excluded because of their focus on preterm birth as an exposure rather than an outcome (24, 25). Fifteen studies remained for inclusion in the meta-analysis.

The characteristics for the included studies are given in Table 1. The studies were published between 2005 and 2015 and include data from 2 532 704 subjects. The two largest studies are obviously different from the remainder in using only a clinical definition of thyroid disease obtained from medical record coding. This can be seen as both a strength and a limitation. The clinical diagnosis presumably means that women with minor fluctuations in thyroid function tests were excluded, whereas other studies of specific screening might have included them and so

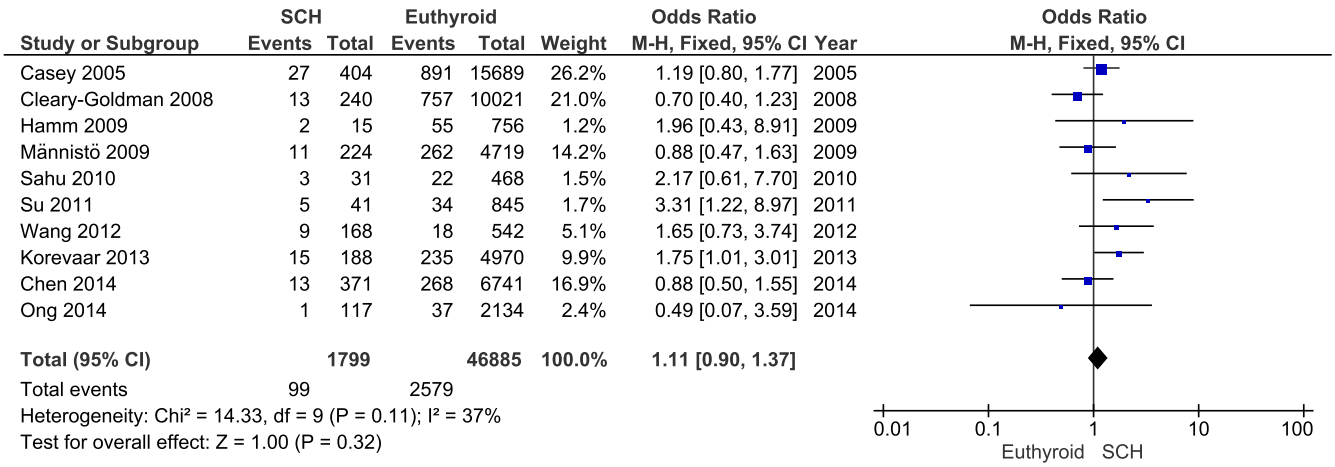

Figure 1. Forest plot of comparison preterm birth and SCH. Details are given for events, number of included subjects, and odds ratio for each study as well as the overall events, subjects numbers, and odds ratio given in bold in the "Total" row. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SCH, subclinical hypothyroidism.

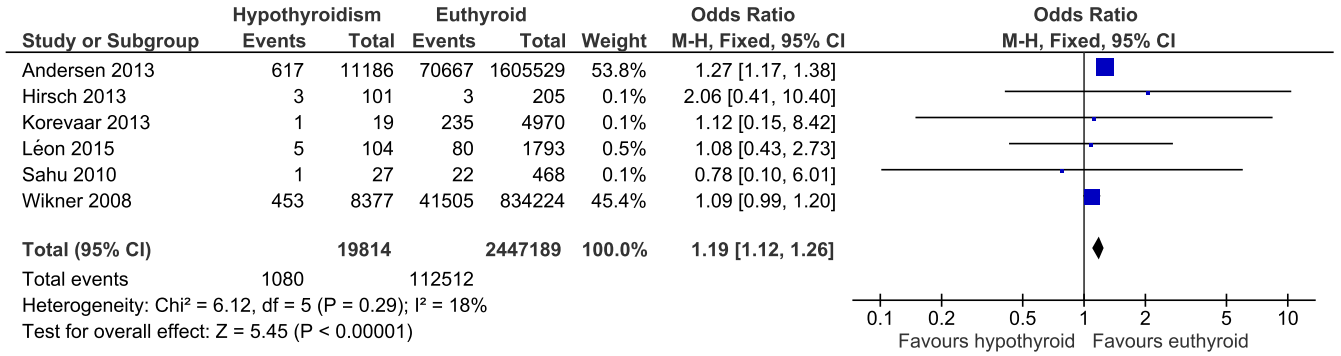

Figure 2. Forest plot of preterm birth and overt hypothyroidism. Details are given for events, number of included subjects, and odds ratio for each study as well as the overall events, subjects numbers, and odds ratio given in bold in the "Total" row. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SCH, subclinical hypothyroidism.

obscured real associations. This is particularly relevant to gestational hyperthyroidism, which may be included as hyperthyroidism in screening studies performed in the first trimester but resolve spontaneously and never require therapy. The studies using screening for selection report their laboratory criteria for diagnosis and have mostly produced their own laboratory specific reference ranges. All 15 included studies had a low risk of bias for selection and outcome assessment on the Newcastle–Ottawa scale.

Preterm birth and subclinical hypothyroidism

Ten studies ranging from small to moderate in size reported on preterm birth in subclinical hypothyroidism. Meta-analysis showed that pregnant women with subclinical hypothyroidism had no obvious increased odds of preterm delivery compared with the reference group (OR, 1.11; 95% CI, 0.90–1.37; $P = .32$; Figure 1). Sensitivity analyses by sequential omission of individual studies did not materially alter the overall combined OR, suggesting that the combined OR was valid and credible. There was low heterogeneity among the studies included, with Q 14.33 ($P = .11$) and the I^2 statistic 37.2. Two studies with highly varying results were the main contributors to the observed heterogeneity, Cleary-Goldman et al (26) and Su et al (27).

Preterm birth and overt hypothyroidism

There were six studies reporting on the outcome of overt or clinical hypothyroidism and preterm birth including two of the largest studies. Meta-analysis showed that the overall combined OR of preterm delivery risk for pregnant women with overt hypothyroidism compared with the reference group was 1.19 (95% CI, 1.12–1.26; $P < .00001$; Figure 2). Sensitivity analyses by sequential omission of individual studies did not materially alter the overall combined OR, suggesting that the combined OR was valid and credible. There was minimal heterogeneity among the studies, with Q 6.1 ($P = .29$) and the I^2 statistic 18.4. In addition to high N values, this contributes to the small CI and high statistical significance of the result.

Preterm birth and hyperthyroidism

Five studies included hyperthyroidism as an exposure. Meta-analysis showed that the overall combined OR of preterm delivery risk for pregnant women with hyperthyroidism compared with the reference group was 1.24 (95% CI, 1.17–1.31; $P < .00001$; Figure 3). Sensitivity analyses by sequential omission of individual studies did not materially alter the overall combined OR, suggesting that the combined OR was valid and credible. There was low heterogeneity among the studies, with Q 5.6 ($P = .23$)

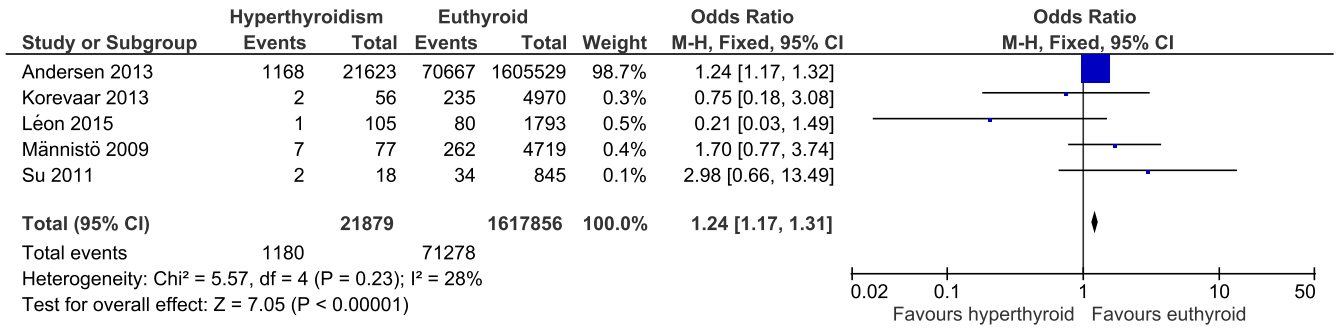

Figure 3. Forest plot of preterm birth and hyperthyroidism. Details are given for events, number of included subjects, and odds ratio for each study as well as the overall events, subjects numbers, and odds ratio given in bold in the "Total" row. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SCH, subclinical hypothyroidism.

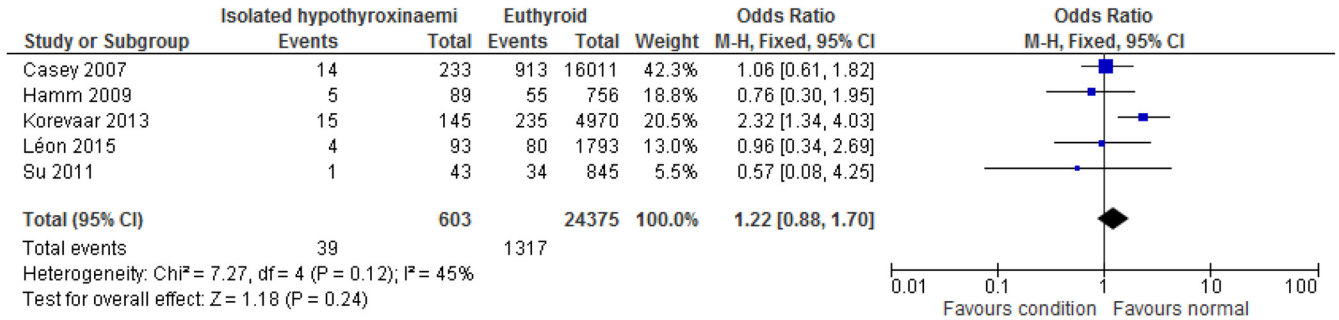

Figure 4. Forest plot of preterm birth and isolated hypothyroxinemia. Details are given for events, number of included subjects, and odds ratio for each study as well as the overall events, subjects numbers, and odds ratio given in bold in the "Total" row. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SCH, subclinical hypothyroidism.

and the I^2 statistic 28.2. In addition to high N values, this contributes to the small CI and high statistical significance of the result. Sensitivity analysis showed that the heterogeneity identified was solely the result of the inclusion of one study (28).

Preterm birth and isolated hypothyroxinemia

Five studies reviewed outcomes for isolated hypothyroxinemia. Meta-analysis showed that pregnant women with isolated hypothyroxinemia had no obvious increased odds of preterm delivery compared with the reference group (OR, 1.22; 95% CI, 0.88 1.70; $P = .24$; Figure 4). Sensitivity analyses by sequential omission of individual studies showed that the result was dependent on the inclusion of one study, Korevaar et al (29), the only study with a finding of a significantly increased risk of preterm birth. As a result, there was moderate heterogeneity among the studies included, however, with Q 7.3 ($P = .12$) and the I^2 statistic 45.0.

Preterm prelabor rupture of membranes and subclinical hypothyroidism

Two studies examined the rare outcome of preterm prelabor rupture of membranes in subclinical hypothyroidism. Meta-analysis showed that pregnant women with subclinical hypothyroidism had no obvious increased odds of preterm delivery compared with the reference group (OR, 1.32; 95% CI, 0.75–2.32; $P = .34$; Figure 5). With only two studies, sensitivity analysis was not performed; however, it should be noted that there was no heterogeneity between the studies, with Q 0.12 ($P = .72$) and the I^2 statistic 0.

Publication bias

Visual inspection of the funnel plots for each analysis did not identify any substantial asymmetry, thus publication bias was not evident in this meta-analysis.

Discussion

This meta-analysis is the first to look specifically at the association between thyroid disease and preterm birth. There have been several publications suggesting a need to update the evidence in this area. One previous meta-analysis on pregnancy outcomes and thyroid disease was able to include only two studies and so concluded that there was no association (30). The current study provides clear evidence for a small but highly statistically significant increase in preterm birth in both hypothyroidism and hyperthyroidism.

The 15 studies included in this meta-analysis were all assessed as well-conducted and at low risk of bias according to the Newcastle–Ottawa System. The two largest studies, the population-based Andersen et al (31) and Wikner et al (32), were the only two to not include reporting of reference rages for diagnosis of thyroid disease. Most of the studies not only reported reference ranges, but

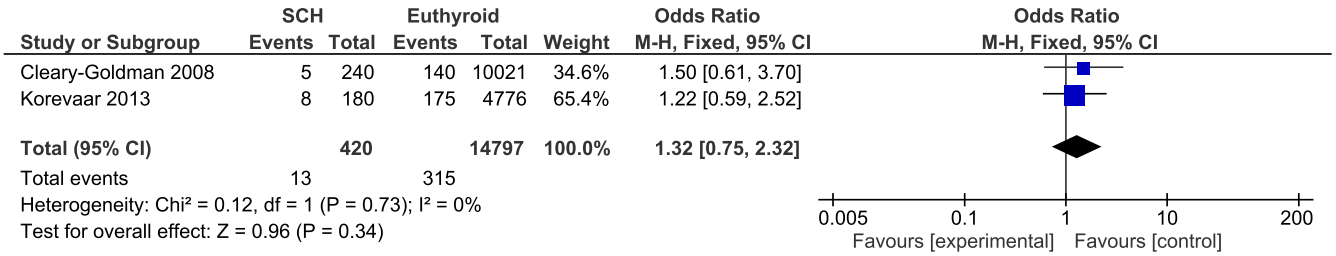

Figure 5. Forest plot of prelabor rupture of membranes and subclinical hypothyroidism. Details are given for events, number of included subjects, and odds ratio for each study as well as the overall events, subjects numbers, and odds ratio given in bold in the "Total" row. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SCH, subclinical hypothyroidism.

had also performed individual laboratory verification of their fifth and 95th percentile results. There is a fundamental difference between screening a population for an exposure and taking an exposure on clinical grounds, which may account for some of the different estimates seen in various conditions. Study heterogeneity in the analysis of hyperthyroidism was entirely contributed by the study of Léon et al (28). This study detailed their analysis of thyroid function results very clearly and evidently included patients on the basis of suppressed TSH (below the fifth percentile), but normal free thyroxine, a category of patients that might best be called subclinical hyperthyroidism, and may have included many women with gestational hyperthyroidism not requiring treatment. The sensitivity analysis shows that this study does not impact the OR result significantly, so it has been included.

The meta-analysis of preterm birth in subclinical hypothyroidism fails to show any positive association despite the inclusion of a total of 48 684 subjects. This should be reassuring to practitioners who are seeing the condition diagnosed in increasing numbers following recommendations by various bodies for more screening for thyroid disease in pregnant women. Isolated hypothyroxinemia is a contentious management problem in pregnancy, and the finding of no significant association in the current study should again reassure practitioners that observation and review may be a safe approach in these women.

A recent meta-analysis examining the association between preterm birth and the presence of antithyroid antibodies found a similar small but statistically significant increased risk for preterm birth specific to those women with positive thyroid peroxidase antibodies 1.69 (95% CI, 1.19–2.41; $P = .003$), but not thyroglobulin antibodies (33). Thyroid dysfunction was a major source of heterogeneity among studies included in their meta-analysis, and the strongest result was obtained when studies of antibody-positive euthyroid women were included. The two are obviously inextricably linked; however, the current study findings of association with both hypothyroidism and hyperthyroidism suggest that any effect is not caused by antibody presence alone. Myometrium possesses thyroid hormone receptor in common with most tissues; however, the presence of TSH and thyrotropin-releasing hormone receptors have been demonstrated in primate uterus (34) and it is reasonable to suppose that they may be present in human uterus. TSH is also known to bind to human chorionic gonadotrophin receptors, which have also been demonstrated to be present in human myometrium (35). Further research is required to identify the biological mechanism.

One of the major limitations of this review is that the included studies were mostly unable to differentiate between spontaneous preterm birth and iatrogenic preterm birth and thus equated the two. About two-thirds of preterm births are usually thought to be spontaneous, so the findings of the various studies here may represent an overestimate. The only study to specifically examine spontaneous preterm birth as a category attributed risk to the presence of antithyroid antibodies apart from the case of isolated hypothyroxinemia, in which risks of both spontaneous premature deliveries and preterm prelabor rupture of membranes were found to be increased (29). Future studies are required to address this issue. One study has suggested that treatment of hypothyroxinemia to maintain free thyroxine in the high normal range may prevent preterm birth in multiparous women, suggesting that if this association could be proven, there may be therapy available (13).

In summary, both overt hypothyroidism and hyperthyroidism are associated with a small but highly statistically significant increased chance of preterm birth. Subclinical hypothyroidism and isolated hypothyroxinemia have no increased risk. Future research should focus on more specific outcomes of early and late preterm births to better define the risks and the role of various therapies directed either at thyroid disease or at preterm birth prevention. Clinicians should take this risk into account in the management of patients with these conditions because the use of predictive tests, such as cervical length or fetal fibronectin, could encourage use of potentially beneficial therapy, such as vaginal progesterone.

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