Original Article

Ethnic Differences in Preterm Birth Risks for Pregnant Women with Thyroid Dysfunction or Autoimmunity: A Meta-analysis*

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Abstract

Objective Abnormal maternal thyroid function is associated with preterm birth. However, this association stays dubious in relevant individual studies for ethnic difference reasons and lack of direct supporting data. This study aimed to evaluate the relationship between preterm birth and thyroid dysfunction or autoimmunity based on ethnic differences.

Methods Relevant studies were identified through searches of MEDLINE, Excerpta Medica, Wan Fang, China Biological Medicine disc, and China National Knowledge Infrastructure from inception to June 15, 2016. Original articles in which an incidence or prevalence of thyroid dysfunction or autoimmunity before second trimester of pregnancy could be extracted were included.

Results Thirty-two unique studies were included for the final meta-analysis. Patients involved were divided into two groups: Group 1 (G1) and Group 2 (G2) comprising of Asian and Caucasian populations, respectively. Positive thyroid antibodies were associated with the occurrence of preterm birth in both G1 [odds ratio (*OR*): 3.62, 95% confidence interval (*CI*): 2.83-4.65] and G2 (*OR*: 1.35, 95% *CI*: 1.17-1.56); hypothyroidism, only in G2 (*OR*: 1.20, *CI*: 1.09-1.33); and subclinical hypothyroidism or hypothyroxinemia, in neither group.

Conclusion Thyroid autoimmunity may be a more favorable factor leading to preterm birth among pregnant women of different ethnicities, compared with thyroid dysfunction.

Key words: Thyroid; Hypothyroidism; Autoimmunity; Preterm birth; Ethnicity

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INTRODUCTION

Preterm birth, occurring in 6%-12% of pregnancy, is defined as the birth of a child prior to 37 weeks of gestation[1-2]. It is the leading cause of neonatal mortality, responsible for 75% of neonatal deaths with no congenital anomalie[1-2]. Preterm birth is also associated with perinatal complications, such as congenital neurologic disability, and psychiatric, metabolic, cardiovascular, and renal diseases[1,3]. To address this problem, numerous works have been conducted over the last decades, yet there is still no great prospect of early prediction and prevention of preterm delivery[4].

As the fetus does not yet produce its own thyroid hormones, adequate functioning of the maternal thyroid is confirmed to be particularly important for the development of the fetal brain during the first trimester[5-6]. Thyroid dysfunction and thyroid autoimmunity are relatively common in women at reproductive age, affecting 2%-3% and

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5%-15% of pregnant women, respectively[6-7]. Both thyroid dysfunction and thyroid autoimmunity are associated with adverse pregnancy outcomes[6,8]. However, over the last 20 years, conflicting results published on alteration of diagnostic criteria of thyroid function tests make the exact prevalence of thyroid diseases in pregnant women and its relationship with preterm labor even more unclear[5,9-10].

A number of studies have shown that inter-individual differences in thyroid hormone levels may, at least partially, be explained by ethnic background[11-12]. Only a few studies analyzed the ethnic differences of thyroid function tests during pregnancy[13-14]. La'ulu et al.[14-15] and other authors[13,16] reported that the reference range values for thyroid parameters may differ among Asians, white, black, and Hispanic Americans, and even in different subgroups of Caucasians. These ethnic differences between different populations emphasize the significance of calculating population-specific reference ranges for TSH during pregnancy, suggesting that the risk of preterm birth should be estimated in the same ethnic population. Therefore, this study aimed to conduct a meta-analysis to analyze the risk of preterm birth for pregnant women with thyroid dysfunction or thyroid autoimmunity based on ethnic variety by including data from randomized controlled trials (RCTs) and cohort studies.

METHODS

Search Strategy

Relevant studies were identified through searches of MEDLINE, Excerpta Medica, Wan Fang, China Biological Medicine disc, and China National Knowledge Infrastructure from inception to June 15, 2016. Search criteria used were related to thyroid dysfunction, thyroid autoimmunity, and preterm birth. The following search terms were used: subclinical hypothyroidism, hypothyroidism, thyroiditis, thyroid peroxidase, thyrotropin, thyrotropin receptor antibody, thyroid-stimulating immunoglobulin, thyroid microsomal antibodies, thyroid dysfunction, hypothyroxinemia, thyroid diseases, pregnancy, pregnancy outcome, immature and premature labor, premature delivery, preterm birth, cohort analysis, longitudinal study, prospective study, retrospective study, follow up, and case-control study. The language limitation for the initial search was set to include only Chinese and English. RCTs, cohort studies, and case-control studies were included.

Study Selection

The criteria for inclusion were (1) pregnant women with overt hypothyroidism, subclinical hypothyroidism, hypothyroxinemia, and positive thyroid autoantibody; (2) preterm birth outcome; (3) assessment of thyroid function before second trimester of pregnancy; (4) articles in English or Chinese; and (5) same ethnic population being more than 80% of all patients. The criteria for exclusion were (1) poor quality studies; (2) articles from the same cohort studies (only the newest were included); and (3) subjects with cardiovascular or rheumatic diseases.

Quality Evaluation

Studies were judged on scientific quality according to the CONSORT and STROBE statements[17]. Study quality assessment was performed based on the NewcastleOttawa scale for cohort studies[17] (http://www.ohri.ca/programs/clinicalepidemiology/oxford. asp).

Data Extraction

The procedure was performed independently by two reviewers (L. M, W. FL). Articles included for full text screening were compared during a consensus meeting. In case of disagreement, a third reviewer (W. SW) was consulted for the decision on inclusion or exclusion for full-text evaluation.

Statistical Analysis

In each study, incidence of thyroid dysfunction or thyroid autoimmunity compared to that of controls was expressed both as odds ratios (*OR*) with the corresponding 95% confidence intervals (*CI*). Review Manager software version 5.2 was used to perform the meta-analyses. Statistical heterogeneity was evaluated using the I^2 test[17], with I^2>50% represents moderate to substantial heterogeneity, in which case random-effects models were used to pool summary estimates[17]. Funnel plots present the publication bias. Begg's and Egger's tests were performed to assess publication bias quantitatively. All statistical analyses were conducted using STATA 12.0 software (Stata Corp, College Station, TX, USA). A two-sided P<0.05 was considered statistically significant.

RESULTS

Literature Search

A total of 3,520 articles were selected from the

search results for critical appraisal. After elimination of duplicate and irrelevant studies, 32 unique studies consistent with the inclusion criteria, including 4 Chinese and 28 English, were finally included (Figure 1). Of the 32 articles in this systematic review, 13 reported on hypothyroidism[16,18-26,31,33,41], 18 on subclinical hypothyroidism[16,18-19,22-24,26-34,46-48], 4 on hypothyroxinemia[18,23,27,29], and 18 on thyroid antibodies[16,18-19,27,32,45]. All 32 cohort studies exhibited low risk of bias for selection and NOS score more than 7. Among these studies, 1 article is RCT; 23, prospective cohort studies; 6, retrospective cohort studies, and 2, case-control studies.

Study Characteristics

The characteristics of the articles included are reported in Table 1. The studies were conducted in different ethnicities, such as Caucasians or white, Hispanic, African Americans, and Asians. Given that there were no studies on African American and Hispanic, patients in the involved studies were divided into two groups, namely, Group 1 (G1, Asians) and Group 2 (G2, Caucasians). The size of the cohorts ranged from 306 to 223,512 (total 579,692). There were 42,804 cumulative preterm birth cases.

Effect of Overt Hypothyroidism on Preterm Birth by Ethnic Groups

Data from 13 articles reporting 5,140 patients with overt hypothyroidism and 450,576 controls could be included in the meta-analysis and showed an increased risk of preterm delivery (*OR*: 1.25, 95% *CI*: 1.04-1.51, *P*=0.02; Figure 2). The study

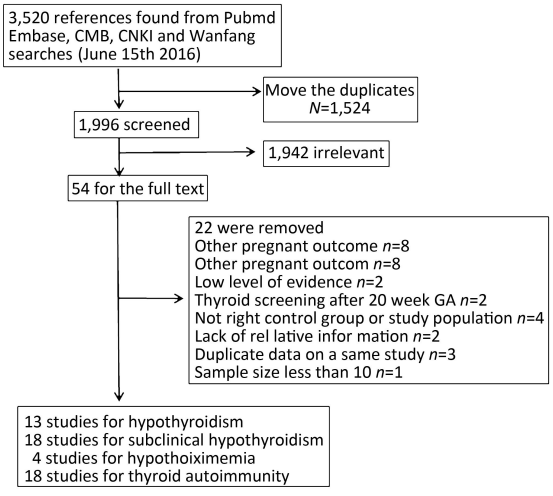

Figure 1. Flow chart of literature search and article selection.

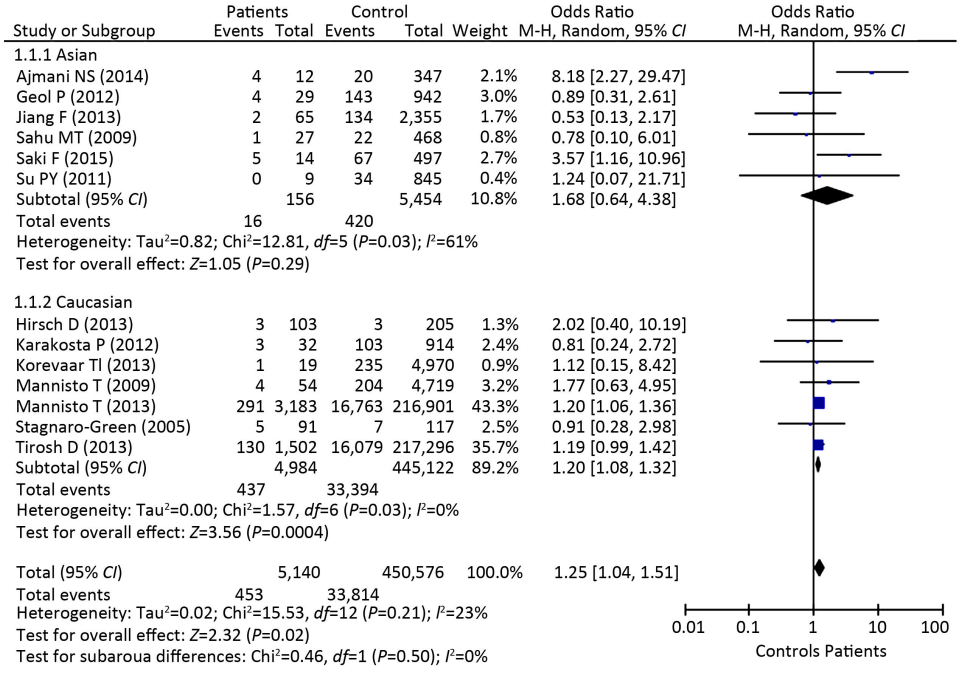

Figure 2. Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with overt hypothyroidism with eythyroid controls according to the risk of preterm birth, 37 weeks gestation. Significant association between overt hypothyroidism and preterm birth was observed in Caucasians.

Table 1. Characteristics and Quality Features of the 32 Studies Included in the Systematic Review of the Association between Thyroid Dysfunction and Preterm Birth

First Author	Year	Ethnicity	Study Type	Participants	Hormone Levels	Patients	Controls
Karakosta P[16]	2012	Caucasian	Prospective cohort	1,170 women with singleton pregnancies	TSH (0.05-2.53 mIU/L) FT4 (1.58-2.54 ng/L) TPO-Ab (<35 IU/mL) TG-Ab (<40 IU/mL)	47 with subclinical hypothyroidism, 32 with overt hypothyroidism	914 euthyroid
Korevaar TI[18]	2013	Caucasian	Prospective cohort	5,971 Pregnant women	TSH (3.97-22.7 mIU/L) FT4 (1.85-3.23 ng/L) TPO-Ab (<60 IU/mL)	1,008 patients with thyroid dysfunction or TPO-Ab positive	4,970 euthyroid
Mannisto T[19]	2009	Caucasian	Prospective cohort	9,247 singleton pregnancy women	TSH (0.19-3.6 mIU/L) FT4 (1.54-2.64 ng/L) TPO-Ab (<167.7 IU/mL) TG-Ab (<47.7 IU/mL)	560 patients with thyroid dysfunction or TPO-Ab positive	4,719 euthyroid patients with or without Ab
Mannisto T[20]	2013	Caucasian	Prospective cohort	223,512 singleton pregnancy women	data not shown	3,183 patients with overt hypothyroidism	216,901 euthyroid
Tirosh D[21]	2013	Caucasian	Retrospective cohort	87,213 women with 232,293 deliveries	data not shown	1,502 deliveries by overt hypothyroidism	217,296 deliveries with euthyroid
Goel P[22]	2012	Asians	Prospective cohort	1,020 Pregnant women	TSH (0.6-5.0 mIU/L) FT4 (1.6-2.5 ng/L) TPO-Ab (<80 kIU/L)	29 with overt hypothyroidism, 34 with subclinical hypothyroidism	942 without hypothyroidism
Su PY[23]	2011	Asians	Prospective cohort	1,017 women with singleton pregnancies	TSH (0.3-3.6 mIU/L) FT4 (0.8-1.7 ng/L)	41 with subclinical hypothyroidism, 9 with overt hypothyroidism, 43 with hypothyroxinemia	845 euthyroid
Sahu MT[24]	2009	Asians	Prospective cohort	633 Pregnant women	TSH (0.5-5.5 mIU/L) FT4 (between 2.5th and 97.5th) TPO-Ab (<35 kIU/L)	41 with subclinical hypothyroidism, 29 with overt hypothyroidism	522 euthyroid
Hirsch D[25]	2013	Caucasian	Retrospective cohort	306 pregnant women	TSH (<20 mIU/L)	101 sever hypothyroidism	205 euthyroid
Jiang F[26]	2013	Asians	Retrospective cohort	2,484 Pregnant women	TSH (0.1-2.5 mIU/L) FT4 (1.25-2.91 ng/L) TPO-Ab (<34 IU/mL) TG-Ab (<115 IU/mL)	65 with subclinical hypothyroidism, 64 with overt hypothyroidism	2,355 euthyroid
Blumenfeld Z[27]	2008	Caucasian	Prospective cohort	10,990 women with singleton pregnancies	TSH (between 2.5th and 97.5th) FT4 (between 2.5th and 97.5th) TPO-Ab (<35 IU/mL) TG-Ab (<40 IU/mL)	240 subclinical hypothyroidism	10,518 euthyroid
Casey BM[28]	2005	Caucasian	Prospective cohort	25,756 women with singleton pregnancies	TSH (between 2.5th and 97.5th) FT4 (>0.68 ng/L)	404 with subclinical hypothyroidism	15,689 euthyroid
Casey BM[29]	2007	Caucasian	Prospective cohort	17,298 singleton pregnant women	TSH (0.08-3.0 mIU/L) FT4 (>0.86 ng/L)	598 with subclinical hypothyroidism	16,011 euthyroid
Schneuer FJ[30]	2012	Caucasian	Prospective cohort	2,801 women with a singleton pregnancies	TSH (0.08-2.37 mIU/L)	2,127 with subclinical hypothyroidism	106 euthyroid
Ajmani NS[31]	2014	Asians	Prospective cohort	400 Pregnant women	TSH (0.1-2.5 mIU/L) FT4 (0.8-2.0 ng/L)	36 with subclinical hypothyroidism, 12 with overt hypothyroidism	347 euthyroid
Lan Yu[32]	2012	Aisans	Retrospective cohort	1,710 Pregnant women	TSH (0.1-2.5 mIU/L) FT4 (0.89-1.76 ng/L)	91 with subclinical hypothyroidism	98 euthyroid

Continued

First Author	Year	Ethnicity	Study Type	Participants	Hormone Levels	Patients	Controls
Saki F[33]	2014	Asians	Prospective cohort	600 pregnant women	TSH (0.2-3 mIU/L) FT4 (0.13-2.29 ng/L) TPO-Ab (<34 IU/mL)	66 with subclinical hypothyroidism, 14 with overt hypothyroidism, 75 with TPO-Ab positive	497 euthyroid, 511 TPO-Ab negative women
Liu XH[34]	2011	Asians	Retrospective cohort	939 Pregnant women	TSH (0.1-3.34 mIU/L) FT4 (1.1-1.85 ng/L) TPO-Ab (<9 IU/mL)	33 with with subclinical hypothyroidism, 86 with TPO-Ab positive, 17 with hypothyroixinemia	725 euthyroid patients without Ab
Ashoor G[35]	2011	Caucasian	Retrospective cohort	4,318 women with singleton pregnancies	TSH (0.03-5.65 mIU/L) FT4 (1.3-13.9 ng/L) TPO-Ab (<60 IU/mL) TG-Ab (<60 IU/mL)	441 patients with TPO-Ab positive, 593 patients with TG-Ab positive	4,318 euthyroid patients without Ab
Haddow JE[36]	2010	Caucasian	Prospective cohort	10,062 women with singleton pregnancies	TPO-Ab (<35 IU/mL) TG-Ab (<100 IU/mL)	1,470 patients with TPO-Ab or TG-Ab positive	8,592 euthyroid patients without Ab
Negro R[37]	2006	Caucasian	Prospective cohort	1,074 Pregnant women, euthyroid	TSH (0.27-4.2 mIU/L) FT4 (9.3-18.0 ng/L) TPO-Ab (<100 IU/mL)	58 patients TPO-Ab positive	869 euthyroid patients with TPO-Ab negative
Ghafoor F[38]	2010	Asians	Prospective cohort	1,500 euthyroid pregnant women	TPO-Ab (<100 U/mL)	168 TPO-Ab positive	1,332 TPO-Ab negative
Iijima T[39]	1997	Asians	Prospective cohort	1,179 healthy euthyroid pregnant women with singleton gestation	TG-Ab, antimicrosomalAb (<1:100)	125 antimicrosomalAb positive, 32 TG-Ab positive	951women euthyroid patients without Ab
Nambiar V[40]	2011	Asians	Prospective cohort	483 Pregnant women	TSH (0.4-4 mIU/L) FT4 (1.3-3.2 ng/L) TPO-Ab (<35 IU/mL)	33 TPO-Ab positive	322 euthyroid
Stagnaro-Green[41]	2005	Caucasian	case-control	552 women who had delivered	TSH (0.2-5 mIU/L) FT4 (0.58-1.61 ng/L) TPO-Ab and/or TG-Ab (<0.20 arbitrary units by ELISA)	37 TPO-Ab and/or TG-Ab positive women	211 euthyroid patients without Ab
Negro R[42]	2011	Caucasian	Prospective cohort	4,562 pregnant women	TSH (<2.5 mIU/L) TPO-Ab (<100 IU/mL)	245 patients TPO-Ab positive	3,348 euthyroid patients with TPO-Ab negative
Glinoer D[43]	1994	Caucasian	Prospective cohort	1,660 Pregnant women	TSH (≤3 mIU/L) TPO-Ab (<35 IU/mL)	87 TPO-Ab positive	606 euthyroid patients without Ab
Bhattacharyya R[44]	2016	Asian	Prospective cohort	400 Pregnant women	TSH (0.35-2.5 mIU/L) FT4 (0.89-1.7 ng/L) TPO-Ab (<35 IU/mL)	42 TPO-Ab positive	337 TPO-Ab negative
Chen X[45]	2015	Asian	Prospective cohort	401 Pregnant women	TSH (0.2-3 mIU/L) FT4 (0.76-1.34 ng/L) TPO-Ab (<34 IU/mL)	26 TPO-Ab positive	182 euthyroid patients with TPO-Ab negative
Yang JJ[47]	2015	Asian	Retrospective cohort	15,000 Pregnant women	TSH (0.2-5.22mIU/L) FT4 (1.00-1.74 ng/L) TPO-Ab (<34 IU/mL)	806 with subclinical hypothyroidism	2,000 euthyroid
Rosario PW[48]	2015	Caucasian	Prospective cohort	660 Pregnant women	TSH (0.04-2.68 mIU/L) FT4 (between 2.5th and 97.5th) TPO-Ab (<34 IU/mL)	31 with subclinical hypothyroidism	629 euthyroid
Nassie DI[49]	2016	Caucasian	Prospective cohort	251	TSH (0.88-3.08 mIU/L) FT4 (0.69-0.94 ng/L) TPO-Ab (<150 IU/mL) TG-Ab (<75 IU/mL)	146 with subclinical hypothyroidism	105 euthyroid

Note. Ab, antibody; Antithyroid microsomal antibody are the previous nomenclature for TPO antibodies. All studies have an adequate sample size (n>10). All the studies were cohorts or case-control studies.

in G2 showed a significant association between overt hypothyroidism and preterm birth (*OR*: 1.20, 95% *CI*: 1.08-1.32, *P*=0.0004; Figure 2). By contrast, no significant difference was observed in G1 (*OR*: 1.68, 95% *CI*: 0.64-4.38, *P*=0.29; Figure 2).

Effect of Subclinical Hypothyroidism on Preterm Birth by Ethnic Groups

There were 66,647 individual data from 18 studies, including 3,192 pregnant women with subclinical hypothyroidism and 63,455 controls. Difference in the risk of preterm birth was not observed between patients with subclinical hypothyroidism and euthyroid controls in both ethnic groups [G1 (*OR*: 1.37, 95% *CI*: 0.98-1.92, *P*=0.06; Figure 3); G2 (*OR*: 1.23, 95% *CI*: 0.96-1.57, *P*=0.10; Figure 3)].

Effect of Hypothyroxinemia on Preterm Birth by Ethnic Groups

Four studies were investigated for hypothyroxinemia, including 653 pregnant women with hypothyroxinemia and 31,847 controls. The relation between hypothyroxinemia and preterm birth was investigated in one study of G1. The study reported no difference between patients and controls (G1, *OR*: 0.57, 95% *CI*: 0.08-4.28, *P*=0.58). Meta-analysis on three studies of G2 resulted in a pooled *OR* of 1.48 and 95% *CI* of 0.96-2.28 (*P*=0.07; Figure 4). No association between hypothyroxinemia and preterm birth was observed in G2.

Effect of Thyroid Autoimmunity on Preterm Birth by Ethnic Groups

Eighteen studies, including 4,182 pregnant women with positive antibodies and 42,733 healthy controls, were investigated for thyroid autoimmunity. Meta-analysis revealed an increased risk of preterm birth in patients, with positive thyroid antibodies, of both G1 (*OR*: 2.85, 95% *CI*: 1.68-4.85, *P*=0.0001; Figure 5) and G2 (*OR*: 1.44, 95% *CI*: 1.06-1.95, *P*=0.02; Figure 5).

Publication Bias

Funnel plots present the publication bias (data not shown). Begg's and Egger's tests were performed to assess publication bias quantitatively. No evidence of publication bias was found in the sensitivity testing of every subgroup analysis (Table 2).

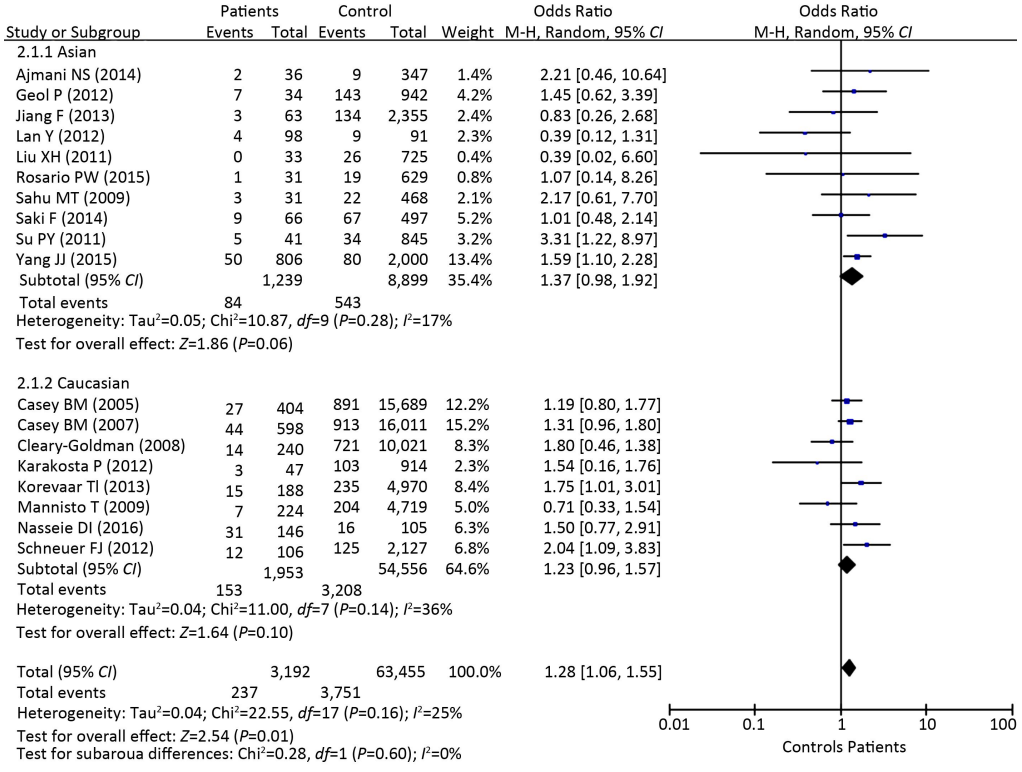

Figure 3. Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with eythyroid controls according to the risk of preterm birth. No association between subclinical hypothyroidism and preterm birth was observed.

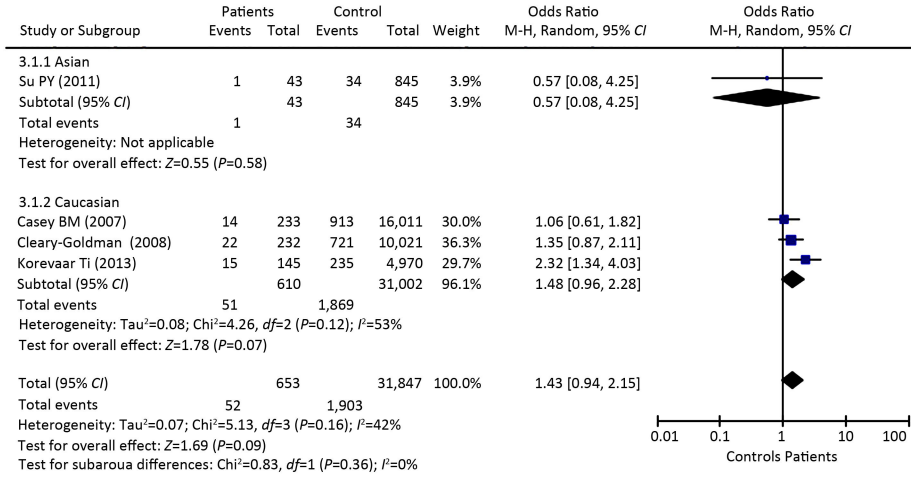

Figure 4. Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with hypothyroxinemia with eythyroid controls according to the risk of preterm birth. No association between hypothyroxinemia and preterm birth was observed.

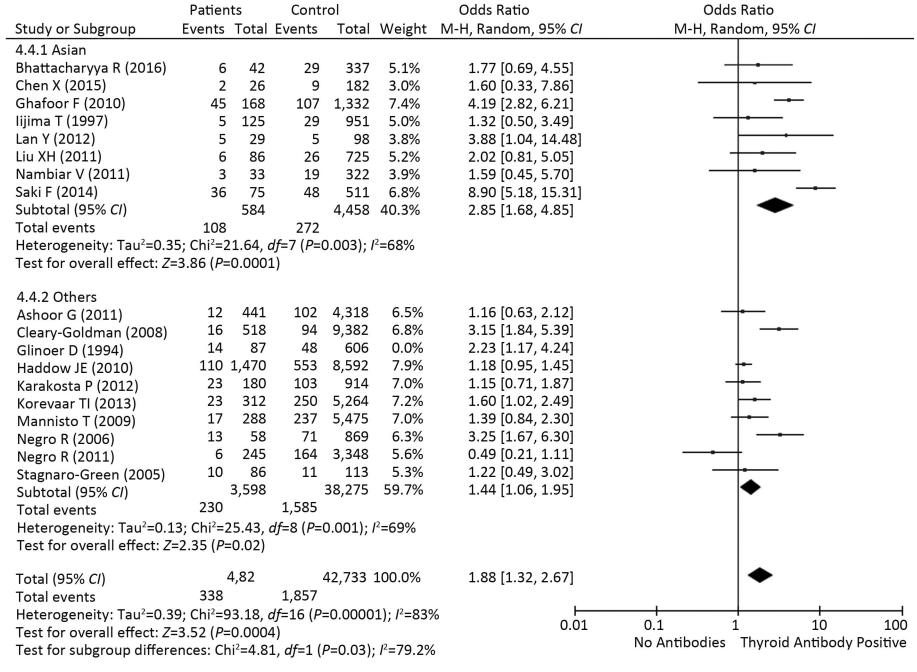

Figure 5. Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients euthyroid thyroid antibody positive patients with euthyroid antibody negative controls according to the risk of preterm birth. Positive thyroid antibodies increased the risk of preterm birth in both subgroups.

Table 2. Publication bias of Each Subgroup

P-value	Test Methods	Hypothyroidism	Subclinical Hypothyroidism	Hypothyroxinemia	Thyroid Antibodies Positive
All studies	Begg's Test	0.951	0.325	1.000	0.820
	Egger's Test	0.485	0.403	0.660	0.438
Prospective cohort	Begg's Test	0.466	0.827	1.000	1.000
	Egger's Test	0.348	0.745	0.660	0.438

Note. A two-sided $P<0.05$ was considered statistically significant.

DISCUSSION

The present meta-analysis provides clear evidence for a relationship between the presence of thyroid dysfunction or autoimmunity and preterm birth in different ethnic groups.

The presence of thyroid antibodies was significantly related to the occurrence of preterm birth, compared with the absence of antibodies.

Association between preterm birth and patients with subclinical hypothyroidism or hypothyroixinemia was not observed in both ethnic groups. High TSH level or low free T4 level alone seemed to not necessarily increase the risk of preterm birth. An increased risk of preterm birth was only observed in the other ethnic group with hypothyroidism. No evidence was found for a relationship between hypothyroidism and preterm birth in Asians. Asians were less susceptible to high TSH level, compared with Caucasians. Considering limited data available on preterm birth in Asians with hypothyroxinemia, the role of hypothyroxinemia in preterm delivery needs further investigation.

Positive thyroid antibodies were associated with an increased risk of preterm birth in both ethnic groups. Moreover, preterm delivery may occur more frequently in Asians with positive thyroid antibodies, with a 2.85 fold higher risk. These results showed that thyroid autoimmunity may be a key factor for increased risk of preterm delivery among different ethnicities. Although not all individual studies involved reported this association, meta-analysis was conclusive on this point, showing the additional value of pooled studies compared with individual studies. Several hypotheses exist on the causality between thyroid autoimmunity and obstetric complications. First, thyroid antibodies could be associated with a subtle decrease of thyroid function or might reflect a generalized activation of the immune system and specifically a deregulated activity of the immune system at the fetal-maternal interface[9,49]. Because pregnancy represents an inflammatory process with a shift in the regulation of cytokine networks within the local placental-decidual environment, a deregulation of the local inflammatory processes can be associated with miscarriage and premature delivery[5,9,50]. Supporting our results, a recent meta-analysis showed that maternal thyroid autoimmunity increases by twofold the risk of preterm delivery for women with biochemically normal thyroid function[49]. Second, the autoimmunity increases the risk of hypothyroidism, owing to the chronic lymphocytic thyroiditis that is associated with the presence of thyroid antibodies. The thyroid then may fail to respond adequately to the increased demand for thyroid hormone during pregnancy. Thus, a high prevalence of thyroid antibodies is reasonable among women with overt or subclinical hypothyroidism (e.g., 25% in Stagnaro-Green et al.[41], 32% in Korevaar et al.[18], and 50% in Mannisto[19].

This meta-analysis has several limitations. As previously mentioned, the studies used different inclusion criteria for the patients and different cutoff levels for TSH, fT4, and antibodies (Table 1). This limitation should be considered when using the results for clinical application. Meanwhile, the fact that the diagnoses are made based on ICD-9 coding instead of the specific criteria of blood test results is a limitation of some studies with large sample size[23-24]. Moreover, the differences of the first-time collection of maternal serum samples may partially contribute to the limitations. Although we used random-effects models to perform the meta-analyses of the pooled data in case of heterogeneity while the majority of data showed a very similar trend, some degree of population heterogeneity cannot be excluded. In addition, the affected subjects had a large difference (10.8% *vs.* 89.2% in weight, and the ORs are 1.68 in Asians and 1.20 in Caucasians); therefore, these differences may be caused by statistical power (Figure 2).

We conclude that pregnant women with hypothyroidism and thyroid autoimmunity may have an increased risk of preterm birth in different ethnic groups. Thyroid autoimmunity may be a more favorable factor leading to preterm birth among pregnant women of different ethnicities, compared with thyroid dysfunction. The association of subgroups of thyroid antibodies with preterm birth should be further investigated in the future studies.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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AUTHOR CONTRIBUTION

LI Min: Data management, Manuscript writing

WANG Shao Wei: Data management, Manuscript editing

WU Feng Li: Data collection

SHI Jin: Data analysis

YU Pu Lin: Project development, Manuscript editing

PENG Xiu Ling: Data collection

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