Research

Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth
A Systematic Review and Meta-analysis

The Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth

IMPORTANCE Maternal hypothyroidism and hyperthyroidism are risk factors for preterm birth. Milder thyroid function test abnormalities and thyroid autoimmunity are more prevalent, but it remains controversial if these are associated with preterm birth.

OBJECTIVE To study if maternal thyroid function test abnormalities and thyroid autoimmunity are risk factors for preterm birth.

DATA SOURCES AND STUDY SELECTION Studies were identified through a search of the Ovid MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and Google Scholar databases from inception to March 18, 2018, and by publishing open invitations in relevant journals. Data sets from published and unpublished prospective cohort studies with data on thyroid function tests (thyrotropin [often referred to as thyroid-stimulating hormone or TSH] and free thyroxine [FT_4] concentrations) or thyroid peroxidase (TPO) antibody measurements and gestational age at birth were screened for eligibility by 2 independent reviewers. Studies in which participants received treatment based on abnormal thyroid function tests were excluded.

DATA EXTRACTION AND SYNTHESIS The primary authors provided individual participant data that were analyzed using mixed-effects models.

MAIN OUTCOMES AND MEASURES The primary outcome was preterm birth (<37 weeks' gestational age).

RESULTS From 2526 published reports, 35 cohorts were invited to participate. After the addition of 5 unpublished data sets, a total of 19 cohorts were included. The study population included 47 045 pregnant women (mean age, 29 years; median gestational age at blood sampling, 12.9 weeks), of whom 1234 (3.1%) had subclinical hypothyroidism (increased thyrotropin concentration with normal FT_4 concentration), 904 (2.2%) had isolated hypothyroxinemia (decreased FT_4 concentration with normal thyrotropin concentration), and 3043 (7.5%) were TPO antibody positive; 2357 (5.0%) had a preterm birth. The risk of preterm birth was higher for women with subclinical hypothyroidism than euthyroid women (6.1% vs 5.0%, respectively; absolute risk difference, 1.4% [95% CI, 0%-3.2%]; odds ratio [OR], 1.29 [95% CI, 1.01-1.64]). Among women with isolated hypothyroxinemia, the risk of preterm birth was 7.1% vs 5.0% in euthyroid women (absolute risk difference, 2.3% [95% CI, 0.6%-4.5%]; OR, 1.46 [95% CI, 1.12-1.90]). In continuous analyses, each 1-SD higher maternal thyrotropin concentration was associated with a higher risk of preterm birth (absolute risk difference, 0.2% [95% CI, 0%-0.4%] per 1 SD; OR, 1.04 [95% CI, 1.00-1.09] per 1 SD). Thyroid peroxidase antibody–positive women had a higher risk of preterm birth vs TPO antibody–negative women (6.6% vs 4.9%, respectively; absolute risk difference, 1.6% [95% CI, 0.7%-2.8%]; OR, 1.33 [95% CI, 1.15-1.56]).

CONCLUSIONS AND RELEVANCE Among pregnant women without overt thyroid disease, subclinical hypothyroidism, isolated hypothyroxinemia, and TPO antibody positivity were significantly associated with higher risk of preterm birth. These results provide insights toward optimizing clinical decision-making strategies that should consider the potential harms and benefits of screening programs and levothyroxine treatment during pregnancy.

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P reterm birth complicates 5% to 15% of births world-wide. It is the most important direct cause of morbidity and mortality in children younger than 5 years,[1] and is an important risk factor for psychiatric, metabolic, cardiovascular, and renal disease later in life.[2,3] However, in the majority of cases, no known risk factors can be identified.[4,5]

Thyroid hormone regulates metabolism, growth, and development in most tissues of the human body, including various physiological processes related to preterm birth, such as placental development and function, fetal growth, and expression of neuropeptides involved in the onset of labor.[6-9] Overt hypothyroidism and hyperthyroidism during pregnancy are well-known risk factors for preterm birth and occur in approximately 0.5% and 0.05% of pregnancies, respectively.[10,11] During pregnancy, thyroid function test abnormalities (subclinical hypothyroidism and isolated hypothyroxinemia) and thyroid autoimmunity are much more frequent than overt thyroid disease.[11] However, it remains to be determined whether such thyroid function test abnormalities are risk factors for preterm birth.

Estimates for the association of subclinical hypothyroidism or isolated hypothyroxinemia with preterm birth in previous observational studies range from odds ratios (ORs) of 0.57 to 3.3.[12-15] The interpretation of these studies is limited by 2 main factors. First, the studies have used different upper limits for thyrotropin (often referred to as thyroid-stimulating hormone or TSH; ranging from >2.5 to >6.0 mIU/L). Second, most are single-center studies and lack statistical power. Furthermore, only a few studies have investigated whether isolated hypothyroxinemia could be a risk factor for adverse pregnancy outcomes.

This study assessed whether thyroid function test abnormalities and thyroid peroxidase (TPO) antibody positivity were associated with preterm birth.

Methods

The Consortium on Thyroid and Pregnancy is a collaboration of prospective birth cohorts that aims to study the association of maternal thyroid function and autoimmunity with adverse pregnancy and child outcomes. For the current study, we followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for Individual Patient Data and preregistered the study protocol (CRD42016043494), which appears in Supplement 1 along with an outline of protocol deviations.

To identify studies for inclusion, we conducted a systematic literature search for articles on the association of thyroid function or autoimmunity with preterm birth published from database inception to March 18, 2018, without language restrictions, using the Ovid MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, and Google Scholar databases (eMethods in Supplement 2). In addition, unpublished data were identified via open invitations sent to relevant journals,[16,17] international conferences, social media, and personal contacts. The search was repeated on June 19, 2019, to identify studies

Key Points

Question Are thyroid function test abnormalities or thyroid autoimmunity a risk factor for preterm birth?

Findings In this individual participant data meta-analysis of 19 prospective cohort studies including 47 045 women, subclinical hypothyroidism (odds ratio [OR], 1.29), isolated hypothyroxinemia (OR, 1.46), and thyroid peroxidase antibody positivity (OR, 1.33) were each significantly associated with a higher risk of preterm birth.

Meaning These findings provide evidence that subclinical hypothyroidism, isolated hypothyroxinemia, and thyroid peroxidase antibody positivity in pregnant women are risk factors for preterm birth.

published after March 18, 2018, that would have been eligible for inclusion.

We included prospective cohort studies that included participants consecutively without selection criteria related to health status (such as comorbidities or thyroid disease) and had data on thyrotropin concentration, free thyroxine (FT_4) concentration, or TPO antibody measurements and data on gestational age at birth. We excluded studies in which participants received treatment based on abnormal thyroid function tests (predominantly hospital-based cohorts) or studies that only included women with overt thyroid disease.

Possible studies for inclusion were independently assessed for suitability by 2 of the authors (T.I.M.K. and P.N.T.) and any disagreement was resolved by discussion with a third author (R.P.P.). Investigators from each eligible study were invited to join the consortium. Study quality and risk of bias were assessed using the Newcastle-Ottawa scale.

Local institutional review board approval and participant informed consent was obtained for all separate cohorts; no additional approvals were obtained for the current study. After obtaining individual participant data, all participants with data on thyrotropin concentration, FT_4 concentration, or TPO antibody concentration, and gestational age at birth were included. We excluded participants who had a miscarriage or perinatal death, preexisting thyroid disease, thyroid-interfering medication use, in vitro fertilization, or multiple pregnancies.

Primary and Secondary Outcomes

The primary outcome was preterm birth defined as a gestational age at birth of less than 37 weeks. Gestational age was assessed using either ultrasound measurements or time after the last menstrual period. Secondary outcomes were very preterm birth (<32 weeks' gestational age) and the gestational age at birth.

Exposures

Exposure variables included thyroid function test abnormalities, continuous thyroid function test measurements (thyrotropin and FT_4 concentrations), TPO antibody positivity, and thyroglobulin antibody positivity. Thyroid function test abnormalities were defined according to cohort-specific

2.5th and 97.5th population percentiles for thyrotropin and FT_4 concentrations after exclusion of TPO antibody–positive women. Subclinical hypothyroidism was defined as a thyrotropin concentration above the 97.5th percentile and a FT_4 concentration within the normal range (ie, 2.5th-97.5th percentile). Overt hyperthyroidism was defined as a thyrotropin concentration below the 2.5th percentile and a FT_4 concentration above the 97.5th percentile. Subclinical hyperthyroidism was defined as a thyrotropin concentration below the 2.5th percentile and a FT_4 concentration within the normal range. Isolated hypothyroxinemia was defined as a FT_4 concentration below the 2.5th percentile and a thyrotropin concentration within the normal range. Thyroid peroxidase antibody positivity and thyroglobulin antibody positivity were defined in a cohort-specific manner according to cutoffs recommended by the manufacturer. For analyses with continuous thyrotropin and FT_4 concentrations as exposure variables, the concentrations for all cohorts were log-transformed and then standardized to population-specific standard deviation scores after removal of outliers (±4 SD from the mean) to enable comparisons among different cohorts and assays.

Statistical Analyses
Primary Analyses
We studied the association of thyroid function test abnormalities (the reference group was women with normal thyroid), thyrotropin and FT_4 concentrations continuously, and TPO and thyroglobulin antibody positivity with preterm birth and very preterm birth using generalized linear mixed models with a random intercept for each cohort. For the same exposures, the association with gestational age at birth was studied using linear mixed models with a random intercept for each cohort.

The primary analyses were repeated with a 2-step approach by using random-effect models according to the DerSimonian and Laird method to pool estimates and the Firth bias reduction method in case of near or complete separation in smaller cohorts. Heterogeneity across studies was assessed using the I^2 statistic. To evaluate potential publication bias, funnel plots and Egger tests were used. All analyses were adjusted for maternal age, body mass index (BMI), ethnicity, smoking, parity, gestational age at blood sampling, and fetal sex. We used multilevel multiple imputation[18] for missing data on covariates. Five imputed data sets were created and pooled for analyses using Rubin rules.[19]

Secondary and Sensitivity Analyses
We performed a prespecified sensitivity analysis for which analyses on thyroid function or thyroid function test abnormalities were additionally adjusted for TPO antibody positivity. A post hoc sensitivity analysis assessed whether the association of TPO antibody positivity with preterm birth and very preterm birth differed for each increase in continuous thyrotropin concentration by adding a product interaction term into the models and stratification of analyses according to thyrotropin cutoffs recommended by the guidelines of the American Thyroid Association.[20] To assess TPO antibody positivity, a post hoc sensitivity analysis explored different

cutoffs based on a recent study showing a dose-dependent effect on thyroid function (alternative cutoffs: 94th population percentile, higher absolute concentrations of >100 and >500 mIU/L, and higher relative concentrations of 2 × and 5 × the assay cutoff).[21] In addition, a prespecified analysis explored whether the association of thyrotropin concentration, FT_4 concentration, or TPO antibody positivity differed according to differences in gestational age at the time of blood sampling, BMI, or parity.

A 2-sided threshold for statistical significance of <.05 was used. Because no adjustment was made for multiple testing, findings from the secondary analyses and sensitivity analyses should be interpreted as exploratory. All statistical analyses were performed using R version 3.4.4 (R Project for Statistical Computing).
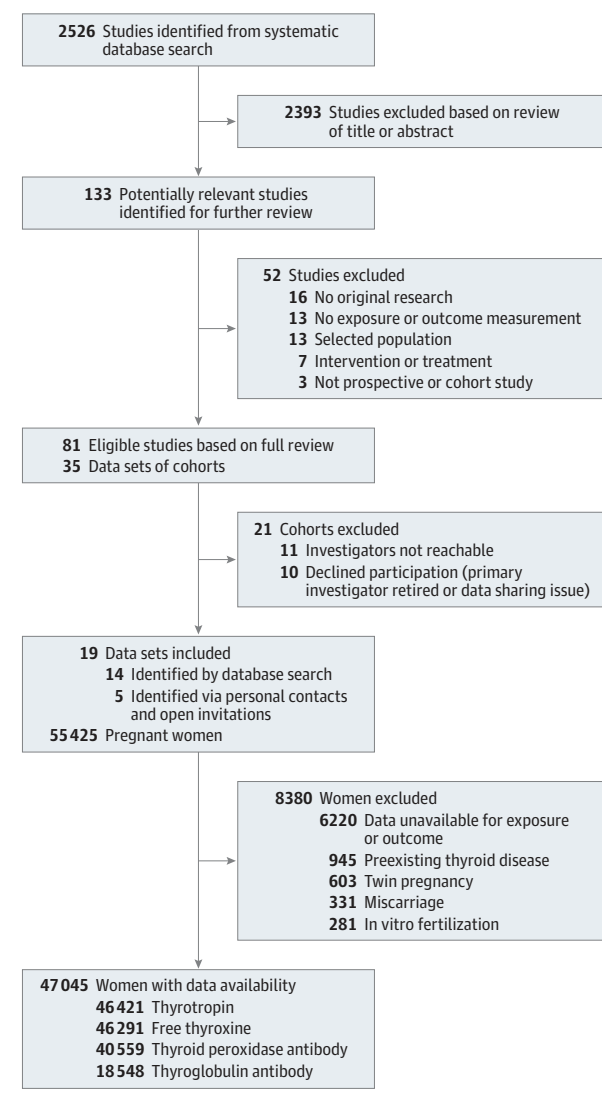
Results

From 2526 published reports, 133 remained eligible for inclusion based on screening of the title and abstract (**Figure 1**). After reading the full text, a total of 35 cohorts were invited to participate. Five unpublished data sets were added via personal contacts and responses from open invitations. Four studies were published after the index date of our systematic search that otherwise would have been eligible for inclusion. A total of 19 cohorts from Europe, the United States, Chile, Australia, Pakistan, and Japan responded to the invitation and were able to participate.

After exclusions, the final study population comprised 47 045 participants (Figure 1), of whom 1234 (3.1%) had subclinical hypothyroidism (increased thyrotropin concentration with normal FT_4 concentration), 904 (2.2%) had isolated hypothyroxinemia (decreased FT_4 concentration with normal thyrotropin concentration), and 3043 (7.5%) were TPO antibody positive. Preterm birth and very preterm birth occurred in 2357 (5.0%) and 349 (0.7%) pregnancies, respectively (**Table**). Cohort-specific population characteristics, details on data collection, cohort-specific number of participants with available thyroid function and gestational age at birth, data quality assessment by the Newcastle-Ottawa scale (indicating high-quality data for all cohorts), and cohort-specific percentile cutoffs for thyroid function test abnormalities (thyrotropin and FT_4 concentrations) appear in eTables 1-4 in Supplement 2.

Data on specific covariates were missing for up to 33% of the women and from as many as 3 cohorts (total percentage of missing data for maternal age: 0.3% [0 cohorts]; gestational age at the time of blood sampling: 0.4% [0 cohorts]; parity: 5.8% [1 cohort]; smoking status: 7.2% [1 cohort]; sex of the child: 21.4% [2 cohorts]; BMI: 32.9% [3 cohorts]). The women that were not included due to missing data on gestational age at birth had similar mean standardized thyrotropin concentrations in SDs vs those who were included (−0.03 vs 0, respectively; P = .28), but different mean standardized FT_4 concentrations in SDs (0.06 vs 0; P = .05) and different proportions with TPO antibody positivity (13.0% vs 7.5%; P < .001) (eTable 5 in Supplement 2).

Figure 1. Flowchart of the Study and Participant Selections

Table. Characteristics of the Total Study Population (N = 47 045)

	No. of Participants/Total No. (%)[a]	Median (95% Range)
Maternal Demographics		
Age, y	46 893	29.0 (5.2)[b]
Gestational age at blood sampling, wk	46 876	12.9 (7.0-39.7)
Body mass index[c]	31 728	23.9 (4.4)[b]
Parity		
0	24 180/44 336 (54.5)	
1	13 217/44 336 (29.8)	
2	4435/44 336 (10.0)	
≥3	2504/44 336 (5.6)	
Smoking status		
Nonsmoker or past smoker	38 733/43 662 (88.7)	
Current smoker	4929/43 662 (11.3)	
Education level[d]		
Low	9677/31 574 (30.6)	
Middle	10 647/31 574 (33.7)	
High	11 250/31 574 (35.6)	
Maternal Concentrations		
Thyrotropin, mIU/L[e]	46 421	1.33 (0.13-4.52)
Free thyroxine, pmol/L	46 291	13.0 (7.2-21.9)
Thyroid peroxidase antibody positivity	3043/40 559 (7.5)	
Thyroglobulin antibody positivity	1080/18 548 (5.8)	
Pregnancy Characteristics		
Gestational age at birth, wk	47 045	39.9 (35.3-42.0)
Sex		
Male	18 936/37 355 (50.7)	
Female	18 419/37 355 (49.3)	
Late preterm birth (gestational age <37 wk)[f]	2357/47 045 (5.0)	
Early preterm birth (gestational age <32 wk)	349/47 045 (0.7)	

SI conversion factor: To convert free thyroxine to ng/dL, divide by 12.871.

[a] The total No. indicates the No. of participants with available data on the thyroid function tests. Cohort-specific descriptive characteristics appear in eTable 1 in Supplement 2.

[b] Expressed as mean (SD).

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Defined as estimated years of education beyond primary school (low: 0-4 years; middle: 4-8 years; high: >8 years).
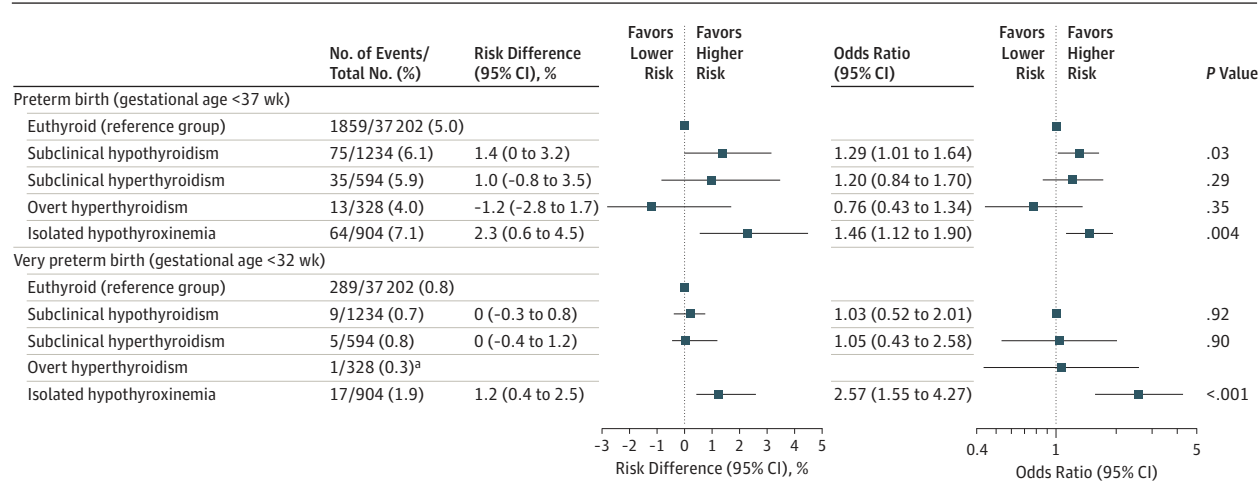
[e] Often referred to as thyroid-stimulating hormone or TSH.

[f] Includes very preterm birth (<32 weeks' gestational age).

Preterm and Very Preterm Birth

Thyroid Function Test Abnormalities

Women with subclinical hypothyroidism had a higher risk of preterm birth vs euthyroid women (6.1% vs 5.0%, respectively; absolute risk difference, 1.4% [95% CI, 0% to 3.2%]; OR, 1.29 [95% CI, 1.01 to 1.64]), but not of very preterm birth (0.7% vs 0.8%; absolute risk difference, 0% [95% CI, −0.3% to 0.8%]; OR, 1.03 [95% CI, 0.52 to 1.20]; **Figure 2**). Women with isolated hypothyroxinemia had a higher risk of preterm birth vs euthyroid women (7.1% vs 5.0%, respectively; absolute risk difference, 2.3% [95% CI, 0.6% to 4.5%]; OR, 1.46 [95% CI, 1.12 to 1.90]) and a higher risk of very preterm birth (1.9% vs 0.8%; absolute risk difference, 1.2% [95% CI, 0.4% to 2.5%]; OR, 2.57 [95% CI, 1.55 to 4.27]). Among women with overt hyperthyroidism, there was no statistically significant difference in the rate of preterm birth vs euthyroid women (4.0% vs 5.0%, respectively; absolute risk difference, −1.2% [95% CI, −2.8% to 1.7%]; OR, 0.76 [95% CI, 0.43 to 1.34]; Figure 2).

Continuous Analyses of Thyroid Function

Continuous analyses showed that each 1-SD higher maternal thyrotropin concentration was significantly associated with a 4% higher relative risk of preterm birth (absolute risk difference, 0.2% [95% CI, 0% to 0.4%] per 1 SD; OR, 1.04 [95% CI, 1.00 to 1.09] per 1 SD), but not very preterm birth (absolute risk difference, 0% [95% CI, −0.05% to 0.10%] per 1 SD; OR, 1.04 [95% CI, 0.93 to 1.16] per 1 SD; **Figure 3** and eTable 6 in Supplement 2). Each 1-SD higher maternal FT_4 concentration was not associated with preterm birth, but was significantly associated with a 12% lower risk of very preterm birth (absolute risk

Figure 2. Association of Thyroid Function Test Abnormalities With Preterm Birth

	No. of Events/ Total No. (%)	Risk Difference (95% CI), %	Favors Lower Risk / Favors Higher Risk	Odds Ratio (95% CI)	Favors Lower Risk / Favors Higher Risk	P Value
Preterm birth (gestational age <37 wk)						
Euthyroid (reference group)	1859/37 202 (5.0)					
Subclinical hypothyroidism	75/1234 (6.1)	1.4 (0 to 3.2)		1.29 (1.01 to 1.64)		.03
Subclinical hyperthyroidism	35/594 (5.9)	1.0 (−0.8 to 3.5)		1.20 (0.84 to 1.70)		.29
Overt hyperthyroidism	13/328 (4.0)	−1.2 (−2.8 to 1.7)		0.76 (0.43 to 1.34)		.35
Isolated hypothyroxinemia	64/904 (7.1)	2.3 (0.6 to 4.5)		1.46 (1.12 to 1.90)		.004
Very preterm birth (gestational age <32 wk)						
Euthyroid (reference group)	289/37 202 (0.8)					
Subclinical hypothyroidism	9/1234 (0.7)	0 (−0.3 to 0.8)		1.03 (0.52 to 2.01)		.92
Subclinical hyperthyroidism	5/594 (0.8)	0 (−0.4 to 1.2)		1.05 (0.43 to 2.58)		.90
Overt hyperthyroidism	1/328 (0.3)[a]					
Isolated hypothyroxinemia	17/904 (1.9)	1.2 (0.4 to 2.5)		2.57 (1.55 to 4.27)		<.001

All analyses were adjusted for maternal age, body mass index, ethnicity, smoking, parity, gestational age at blood sampling, and fetal sex. Euthyroid was defined as the 2.5th-97.5th cohort-specific percentile for thyrotropin (often referred to as thyroid-stimulating hormone or TSH) and free thyroxine (FT_4) concentrations; subclinical hypothyroidism, increased thyrotropin concentration with a normal FT_4 concentration; subclinical hyperthyroidism, decreased thyrotropin concentration with a normal FT_4 concentration; overt hyperthyroidism, decreased thyrotropin concentration with an increased

FT_4 concentration; and isolated hypothyroxinemia, a normal thyrotropin concentration with a decreased FT_4 concentration. These clinical entities were calculated for cohorts that had thyrotropin concentration, FT_4 concentration, and thyroid peroxidase antibody data available. Absolute differences and corresponding 95% CIs were back-calculated from the results of multivariable models and adjusted for baseline risk imprecision.

[a] There were too few samples to conduct a reliable analysis.

difference, −0.10% [95% CI, −0.20% to −0.01%] per 1 SD; OR, 0.88 per 1 SD [95% CI, 0.79 to 0.95]; Figure 3 and eTable 6 in Supplement 2).

TPO Antibody and Thyroglobulin Antibody Positivity

Thyroid peroxidase antibody-positive women had a higher risk of preterm birth vs TPO antibody-negative women (6.6% vs 4.9%, respectively; absolute risk difference, 1.6% [95% CI, 0.7% to 2.8%]; OR, 1.33 [95% CI, 1.15 to 1.56]; **Figure 4**) and very preterm birth (1.7% vs 0.7%; absolute risk difference, 1.0% [95% CI, 0.6% to 1.7%]; OR, 2.45 [95% CI, 1.81 to 3.32]; Figure 4). There was no significant association of thyroglobulin antibody positivity with preterm birth vs those with thyroglobulin antibody negativity (4.3% vs 4.4%, respectively; absolute risk difference, −0.5% [95% CI, −1.6% to 0.9%]; OR, 0.88 [95% CI, 0.64 to 1.20]; eTable 6 in Supplement 2).

Gestational Age at Birth

The results relating to the gestational age at birth were similar to those for preterm and very preterm birth (eTable 7 in Supplement 2).

Sensitivity Analyses

In the prespecified sensitivity analysis, the results for thyrotropin concentration, FT_4 concentration, and TPO antibody positivity remained similar when all 3 exposures were added to the same model, but the association of subclinical hypothyroidism with preterm birth was no longer statistically significant after additional adjustment for TPO antibody positivity (eTable 8 in Supplement 2).

In the post hoc sensitivity analysis on the association of TPO antibody positivity with preterm and very preterm birth, the P value for interaction for risk of preterm birth with higher thyrotropin concentrations among TPO antibody-positive women was .08; for very preterm birth, P < .001 for interaction; and for gestational age at birth continuously, P = .006 for interaction. Subsequent stratified analyses showed that TPO antibody-positive women and a thyrotropin concentration above 4.0 mIU/L had an excess risk of preterm birth vs TPO antibody-negative women (7.1% vs 4.9%, respectively; absolute risk difference, 2.7% [95% CI, 0.2%-6.3%]; OR, 1.55 [95% CI, 1.05-2.27]). However, stratified analyses could not be performed for very preterm birth (Figure 4).

In a post hoc sensitivity analysis, alternative TPO antibody concentration cutoffs were significantly associated with a higher risk of preterm birth, but the results were similar to those identified for manufacturer-based cutoffs (eTable 9 in Supplement 2). In the prespecified analysis on the association of thyroid function with preterm birth, TPO antibody positivity or thyroglobulin antibody positivity did not differ significantly according to the gestational age at the time of blood sampling, BMI, or parity (P > .07 for interaction for all analyses without meaningful differences after stratification; eTables 10 and 11 in Supplement 2).

The primary analyses were similar using a 2-step approach; however, some cohort-specific analyses with very few cases exhibited inflated ORs (eFigures 1 and 2 in Supplement 2). The funnel plots did not indicate any bias and the I^2 values were mostly less than 40%. However, for the analyses of TPO antibody-positive women, the I^2 values were 77%

Figure 3. Association of Thyrotropin and Free Thyroxine (FT$_4$) Concentrations With Preterm Birth
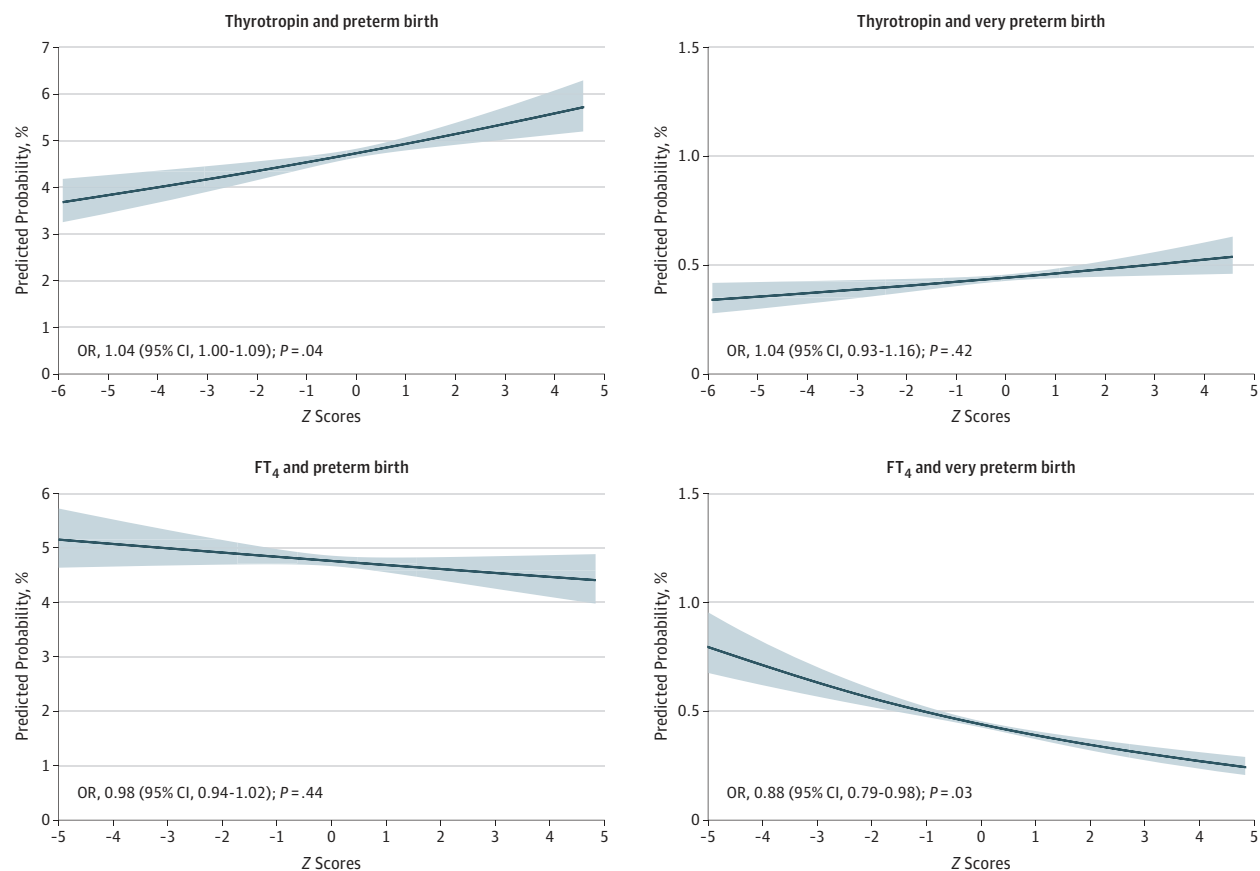
Preterm birth was defined as less than 37 weeks' gestational age and very preterm birth was defined as less than 32 weeks' gestational age. The thyrotropin and FT$_4$ concentrations for all cohorts were log transformed and then standardized to population-specific standard deviation scores after removal of outliers (±4 SD from the mean) to enable comparison between different cohorts and assays. All analyses were adjusted for maternal age, body mass index, ethnicity, smoking, parity, gestational age at blood sampling, and fetal sex. OR indicates odds ratio.

for preterm birth and 69% for very preterm birth (eFigure 2 in Supplement 2).

Discussion

Subclinical hypothyroidism, isolated hypothyroxinemia, and TPO antibody positivity were associated with higher risk for preterm birth. Isolated hypothyroxinemia and TPO antibody positivity were associated with higher risk for very preterm birth. The association of TPO antibody positivity with preterm birth did not appear to be related to differences in thyroid function, but was modified by the thyrotropin concentration as exemplified by the higher risk of preterm birth in TPO antibody–positive women and a thyrotropin concentration above 4.0 mIU/L.

Because randomized trials of treatment of thyroid function test abnormalities during pregnancy are scarce, observational studies form the basis of clinical guidelines on thyroid function and pregnancy.[20] However, previous observational studies on the association of thyroid function and autoimmunity with preterm birth have used widely different defini-

tions for thyroid function test abnormalities. This variation limits the ability to develop clearly defined recommendations in international guidelines and perform aggregate data meta-analysis. Furthermore, most studies lacked statistical power to study the risk of very preterm birth, a more clinically relevant outcome related to high mortality and morbidity, the demand for specialist neonatal services, and financial burdens.[22-24] By collecting individual participant data, the current study allowed for standardization of the definition of thyroid function test abnormalities.

To our knowledge, the current study is the first individual participant data meta-analysis that shows isolated hypothyroxinemia is associated with a higher risk of preterm birth and very preterm birth and produced estimates in the same range as well-known risk factors such as adolescent or older maternal age, low BMI, obesity, smoking, and bacterial vaginosis.[12,13,25-27] These results are in line with those from a previous population-based study, but opposite to those from an aggregate data meta-analysis including 5 studies.[15,28] Isolated hypothyroxinemia is a pregnancy-specific disease entity with a multifactorial underlying pathophysiology that has remained relatively understudied.[29]

Figure 4. Association of Thyroid Peroxidase (TPO) Antibody Positivity With Preterm Birth

	No. of Events/ Total No. (%)	Risk Difference (95% CI), %	Favors Lower Risk	Favors Higher Risk	Odds Ratio (95% CI)	Favors Lower Risk	Favors Higher Risk	P Value
Preterm birth (gestational age <37 wk)								
TPO antibody negative (reference group)	1847/37 516 (4.9)							
TPO antibody positive	202/3043 (6.6)	1.6 (0.7-2.8)			1.33 (1.15-1.56)			<.001
TPO antibody positive and								
Thyrotropin within normal range	174/2566 (6.8)	1.8 (0.7-2.9)			1.36 (1.15-1.60)			<.001
Thyrotropin >2.5 mIU/L	64/989 (6.5)	1.8 (0.2-3.7)			1.36 (1.05-1.76)			.01
Thyrotropin >4 mIU/L	29/406 (7.1)	2.7 (0.2-6.3)			1.55 (1.05-2.27)			.02
Very preterm birth (gestational age <32 wk)								
TPO antibody negative (reference group)	268/37 516 (0.7)							
TPO antibody positive	53/3043 (1.7)	1.0 (0.6-1.7)			2.45 (1.81-3.32)			<.001
TPO antibody positive and[a]								
Thyrotropin within normal range	52/2566 (2.0)	1.3 (0.8-2.0)			2.86 (2.10-3.89)			<.001
Thyrotropin >2.5 mIU/L	7/989 (0.7)[b]							
Thyrotropin >4 mIU/L	0/406 (0)[b]							

-3 -2 -1 0 1 2 3 4 5
Risk Difference (95% CI), %

0.4   1   5
Odds Ratio (95% CI)

All analyses were adjusted for maternal age, body mass index, ethnicity, smoking, parity, gestational age at blood sampling, and fetal sex. Absolute differences and corresponding 95% CIs were back-calculated from the results of multivariable models and adjusted for baseline risk imprecision.

[a] Thyroid peroxidase antibody–positive women and thyrotropin (often referred

to as thyroid-stimulating hormone) concentrations within the normal range or higher than 2.5 mIU/L and 4 mIU/L were compared with TPO antibody-negative women regardless of their thyrotropin concentration.

[b] There were too few samples to conduct a reliable analysis.

Available evidence predominantly links isolated hypothyroxinemia to suboptimal neurocognitive development of the offspring,[29,30] but international guidelines do not recommend levothyroxine treatment in women with isolated hypothyroxinemia because randomized clinical trials have not proven a beneficial effect on child IQ.[20] In 2 large randomized clinical trials in which women with isolated hypothyroxinemia were treated with levothyroxine during the first half of pregnancy, there was no statistically significant difference in preterm birth with treatment. In 1 trial of pregnant women with either subclinical hypothyroidism or isolated hypothyroxinemia, preterm birth occurred in 5.6% of the levothyroxine group vs 7.9% of the control group.[31] In the second trial with pregnant women who had isolated hypothyroxinemia, preterm birth occurred in 12% of the levothyroxine group vs 8% of the placebo group and birth at less than 34 weeks' gestational age occurred in 4% of the levothyroxine group and 3% of the placebo group.[32]

Consistent with the results of the current study, women with isolated hypothyroxinemia in the 2 trials[31,32] had higher preterm birth rates than euthyroid women did in the current meta-analysis. The results of the current study provide further insights on potential risks of isolated hypothyroxinemia that may help to optimize clinical decision-making strategies, taking into account all potential harms and benefits of screening programs and subsequent levothyroxine treatment. Further studies will be required to elucidate the underlying pathophysiology of isolated hypothyroxinemia and to study if it is also a risk factor for other adverse pregnancy outcomes.

In the current study, TPO antibody positivity was associated with a higher risk of preterm birth, consistent with previous smaller meta-analyses using aggregate data and studies on miscarriage.[12,13] Two recent clinical trials showed that preconception treatment of euthyroid TPO antibody–positive women who had either a previous miscarriage or fertility treatment with low-dose levothyroxine neither reduced the rate of preterm birth, nor any other pregnancy or neonatal outcomes.[33,34] These studies did not include women with thyroid function test abnormalities.[33,34] The results of the current study show a higher risk for TPO antibody-positive women and a thyrotropin concentration higher than 4.0 mIU/L, which confirms the results from a small randomized clinical trial showing that levothyroxine treatment in TPO antibody-positive women lowers preterm birth rates only if the thyrotropin concentration was higher than 4.0 mIU/L.[35]

Taken together, the results of this study are in alignment with the recommendation of the American Thyroid Association that different thyrotropin cutoffs should be used for TPO antibody-positive women vs TPO antibody-negative women.[20] A sensitivity analysis showed that the association of subclinical hypothyroidism with preterm birth was no longer apparent after additional adjustment for TPO antibody positivity, suggesting that it is the TPO antibody positivity that occurs in one-third of women with subclinical hypothyroidism that underlies any associations of subclinical hypothyroidism with preterm birth. However, this study lacked statistical power for a subgroup analysis on the association of TPO antibody positivity in combination with a thyrotropin concentration higher than 2.5 mIU/L for preterm birth or higher than 4.0 mIU/L for very preterm birth.

There remains an important role for observational studies in the evaluation of thyroid function test abnormalities during pregnancy. For example, observational studies have indicated that the interpretation of the results of large randomized

trials[31-34] may be limited because of risks related to potential over-treatment, a late start of levothyroxine therapy, or sole inclusion of women with normal thyroid.[36-39] Moreover, observational studies are needed to study detrimental clinical outcomes with a relatively low incidence such as very preterm birth, given the impracticality of randomized trials for such outcomes. For example, to study if levothyroxine therapy could reverse excess preterm birth risks as identified in this study for isolated hypothyroxinemia, TPO antibody positivity, and TPO antibody positivity with a thyrotropin concentration greater than 4.0 mIU/L, a total of 3674, 6090, and 3814 women, respectively, would have to be randomized, which in the case of population screening would translate to the screening of 196 470, 95 530, and 448 706 women (with a 2-sided α level of .05, a power level of 80%, and a lost to follow-up rate or declined participation rate of 15%).

The results of the current study do not change the consideration that there is currently insufficient evidence for a benefit of routine thyroid function screening in pregnant women; the potential harms and benefits of levothyroxine for other clinically meaningful outcomes should be taken into account as well. The results support the concept of a reflex TPO antibody measurement in women with a thyrotropin concentration higher than 4.0 mIU/L, and gestational thyrotropin monitoring for TPO antibody–positive women prior to conception. The current study in itself does not validate a reflex FT_4 concentration or TPO antibody measurement for women with a normal thyrotropin concentration until further randomized trials are performed.

The results of the current study add to the limited knowledge on the complicated and multifactorial mechanisms underlying preterm and very preterm birth.[40] Because thyroid hormone regulates key processes in placental and fetal growth and development, the associations for FT_4 concentration could be mediated via effects on either placental function, fetal growth, or both.[8,9,11,40,41] Alternatively, thyroid hormone and TPO antibody positivity could be involved in infectious and inflammatory pathways leading to preterm birth.[42,43] Another potential mechanism by which low thyroid hormone availability could be associated with preterm birth is that it may lead to an earlier onset of labor via an increase in oxytocin and vasopressin, but a decrease in progesterone, or through thyroid hormone effects specific for the cervix, endometrium, or fetal membranes.[7,44-47] Further studies on pathways via which thyroid hormone is involved in the pathogenesis of preterm birth are needed to further optimize risk identification.

Limitations

This study has several limitations. First, there was a lack of statistical power to optimally investigate the risk of very preterm birth in specific clinically relevant subgroups. Although very preterm birth is clinically more relevant than late preterm birth, the relatively sparse occurrence of TPO antibody positivity combined with a thyrotropin concentration higher than 2.5 or 4.0 mIU/L necessitates an even larger data set than that available in the current study to examine associations with very preterm birth.

Second, only 5 of the 19 studies had data available on thyroglobulin antibodies. Although this association was studied in a large number of women, data were only available for 40.0% of included women, which may have affected the results.

Third, pregnancy-related changes in thyroid-binding proteins could interfere with FT_4 immunoassays. However, the use of assay-specific reference ranges as advocated by the current American Thyroid Association guidelines and standardization of FT_4 concentrations per cohort or assay should mostly eliminate the potential between-assay differences in absolute FT_4 concentrations.

Fourth, studies that were published while conducting statistical analyses for the current study could not be included. Fifth, because the included studies were observational, residual or unmeasured confounding cannot be excluded. However, the analysis of individual participant data allowed for adjustment for multiple relevant confounders. Sixth, causality cannot be determined from observational studies.

Conclusions

Among pregnant women without overt thyroid disease, subclinical hypothyroidism, isolated hypothyroxinemia, and TPO antibody positivity were significantly associated with higher risk of preterm birth. These results provide insights toward optimizing clinical decision-making strategies that should consider the potential harms and benefits of screening programs and levothyroxine treatment during pregnancy.

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