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Systematic Review and Meta Analysis

Association of gestational thyroid function and thyroid peroxidase antibody positivity with postpartum depression: a prospective cohort study and systematic literature review with meta-analysis

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Abstract

Importance: Postpartum depression (PPD) has a major impact on maternal and offspring well-being, with multiple possible risk factors: Studies on the association of thyroid peroxidase antibody (TPOAb) positivity and thyroid function with PPD provide heterogeneous results.

Objective: To study the association of thyroid function and TPOAb positivity with PPD.

Design: We assessed the association of TPOAb and thyroid function with PPD in a population-based prospective cohort study and performed a systematic literature review and meta-analysis.

Methods: We measured thyroid stimulating hormone (TSH), free thyroxine (FT4), and TPOAb between 9- and 17-week gestation. Postpartum depression was assessed with Edinburgh Postpartum Depression Scale at 2-month postpartum and Brief Symptom Inventory at 2-, 6-, and 36-month postpartum. Additionally, we performed a systematic literature review and meta-analysis assessing this association.

Results: In the present study, there was no association of thyroid function with PPD (TSH: odds ratio [OR] 0.83, 95% CI 0.58-1.19, $P = .32$; FT4: OR 0.99, 95% CI 0.95-1.05, $P = .86$) or TPOAb positivity with PPD (OR 0.79, 95% CI 0.47-1.33, $P = .37$). An impaired thyroidal response to human chorionic gonadotropin (hCG), a surrogate marker for TPOAb positivity, was associated with a lower risk of PPD (P for interaction TSH = 0.04; FT4 = 0.06). Our systematic review and meta-analysis included 3 articles that were combined with the present study. There was no statistically significant association of TPOAb positivity with PPD (OR 1.93, 95% CI 0.91-4.10, $P = .08$), but the results were heterogeneous ($I^2 = 79\%$).

Conclusions and relevance: There was no significant association of TPOAb positivity, TSH, or FT4 with PPD. Our systematic review and meta-analysis revealed high heterogeneity of the current literature. Although TPOAb-positive women should be monitored for postpartum thyroiditis, our findings do not support routinely screening for PPD.

Keywords: postpartum depression, iodide peroxidase, thyrotropin, thyroxine

Significance

Our prospective cohort study, systematic review, and meta-analysis did not find an association of thyroid autoimmunity (thyroid peroxidase antibody [TPOAb] positivity) and thyroid function (thyroid stimulating hormone [TSH] and free thyroxine [FT4]) with postpartum depression. This study also revealed high heterogeneity of current literature about this topic, leading us to the conclusion that, although TPOAb-positive women should be monitored for postpartum thyroiditis, this does not translate into routinely screening for postpartum depression.

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Introduction

Postpartum depression (PPD) is a serious mental health disorder, affecting approximately 13% of postpartum women worldwide.[1] This prevalence could be underestimated because of the lack of specificity of diagnostic criteria and the heterogeneity of the disorder itself.[2] Postpartum depression has a major impact on maternal health and well-being and is associated with impaired mother–infant bonding and emotional and cognitive problems in the offspring.[3–6] Therefore, it is crucial to gain insight into the etiology of PPD and optimize the identification of high-risk subgroups.

The etiology of PPD likely involves a combination of social, psychological, and biological factors including possibly thyroid dysfunction.[7–10] Hypothyroidism symptoms such as low mood, cognitive problems, and fatigue overlap with the clinical phenotype of depression with hypothyroidism being an established risk factor for depression.[11,12] Thyroid physiology undergoes major changes during pregnancy in order to provide sufficient thyroid hormone for both the mother and the fetus.[13] High concentrations of human chorionic gonadotropin (hCG) stimulate the thyroid through its affinity for the thyroid stimulating hormone (TSH) receptor, placental type 3 deiodinase increases thyroid hormone degradation, thyroid-binding protein concentrations increase, and thyroxine is placentally transferred to the fetus.[14] Multiple studies have examined the association of thyroid hormones during pregnancy and PPD and have suggested a link, with higher TSH levels and/or lower free thyroxine (FT4) levels associated with a higher risk of PPD.[15–17] Furthermore, it has been suggested that women who are positive for thyroid peroxidase antibodies (TPOAbs) have a higher risk of developing PPD.[18–23] In contrast, other studies reported no such associations.[24–29] However, most of these studies were small and of limited methodological quality.

Estimating the association between gestational thyroid function and TPOAb positivity with PPD may provide insights into the etiology of PPD and could help to identify high-risk cases. Therefore, we aimed to investigate the association between gestational thyroid function and TPOAb status during pregnancy and PPD by using data from a large prospective birth cohort and a systematic assessment of the literature. We specifically studied gestational thyroid function and gestational TPOAb positivity because for most women, pregnancy is the first time during which TSH, FT4, and TPOAb concentrations are checked and concentrations differ from a non-pregnancy state due to pregnancy-specific physiology.

Subjects and methods

Generation R Study

Study design and population

This study was embedded in the Generation R Study, a population-based prospective birth cohort from early fetal life onward in Rotterdam, the Netherlands.[30] Pregnant women living in Rotterdam with an expected delivery date between April 1, 2002 and January 1, 2006 were enrolled.[30] For this study, all women with data on early pregnancy (<18 weeks) thyroid function and/or TPOAbs and PPD symptoms assessments were eligible for inclusion. Thyroglobulin antibody (TgAb) measurements were not performed in the Generation R cohort. We excluded those with multiple pregnancies, history of in vitro fertilization treatment, history of thyroid disease, or thyroid hormone-altering medication usage. This study was approved by the Erasmus MC Medical Ethics Committee and performed in accordance with the 1964 Helsinki Declaration; written informed consent was obtained from all participants.

Thyroid measurements

Maternal serum samples were obtained in early pregnancy (median 13.2 weeks; 95% range, 9.6-17.5). Plain tubes were centrifuged, and serum was stored at −80 °C. Thyroid stimulating hormone and FT4 were determined in maternal serum samples using chemiluminescence assays (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY, USA).[31] The intra- and interassay coefficients of variation were <4.1% for TSH and <5.4% for FT4. Population-based reference intervals were calculated in accordance with the 2017 American Thyroid Association guidelines (TSH: 0.03-4.04 mU/L; FT4: 10.4-22.0 pmol/L).[31] Maternal TPOAbs were measured using the Phadia 250 immunoassay (Phadia AB),[31] and TPOAb positivity was defined using a 60 IU/mL cutoff as specified by the manufacturer and using a 20 IU/mL functional pregnancy-specific cutoff as previously assessed.[32]

Assessment of depression

The primary outcome was PPD symptoms assessed 2 months after delivery using the Edinburgh Postpartum Depression Scale (EPDS). Secondary outcomes were the depression subscale score on the Brief Symptom Inventory (BSI) at 2, 6, and 36 months after delivery. The EPDS is an effective, widely used screening tool for PPD that has been validated for the Dutch population.[33–35] The EPDS is a self-report questionnaire consisting of 10 items scored on an ordinal scale from 0 to 3, which results in a sum score from 0 to 30. Higher scores of EPDS sum score indicate more severe depressive symptoms. In this study, women with a score of ≥12 were classified as having PPD: Previous research has shown that this cutoff has a sensitivity of over 80% and a specificity of 95% for identifying women with clinically diagnosed PPD in a community sample.[36] Women had to have at least 8 out of 10 items of the EPDS to be included in the analysis.

Brief Symptom Inventory is a validated self-report questionnaire with 53 items assessing psychological distress and psychiatric disorders.[37] For this study, we calculated the continuous total score of the 6-item depression subscale and used the cutoff of ≥0.75 to indicate depression. This cutoff score provides the most desirable specificity and sensitivity according to Dutch BSI manual instructions.[38] Following the manual, no more than one missing item was allowed to minimize selective nonresponse bias.

Statistical analysis

The association of TPOAb positivity, TSH, and FT4 with depression was investigated using multivariable logistic regression models. We analyzed the association of TPOAb positivity and thyroid function with EPDS and BSI scores on a continuous scale using linear regression models (as results were similar to sensitivity analyses using negative binomial regression). As an additional surrogate marker for thyroid autoimmunity, we assessed the statistical interaction of TSH/FT4*hCG as a marker for the thyroidal response to hCG stimulation, which was previously shown to be impaired in

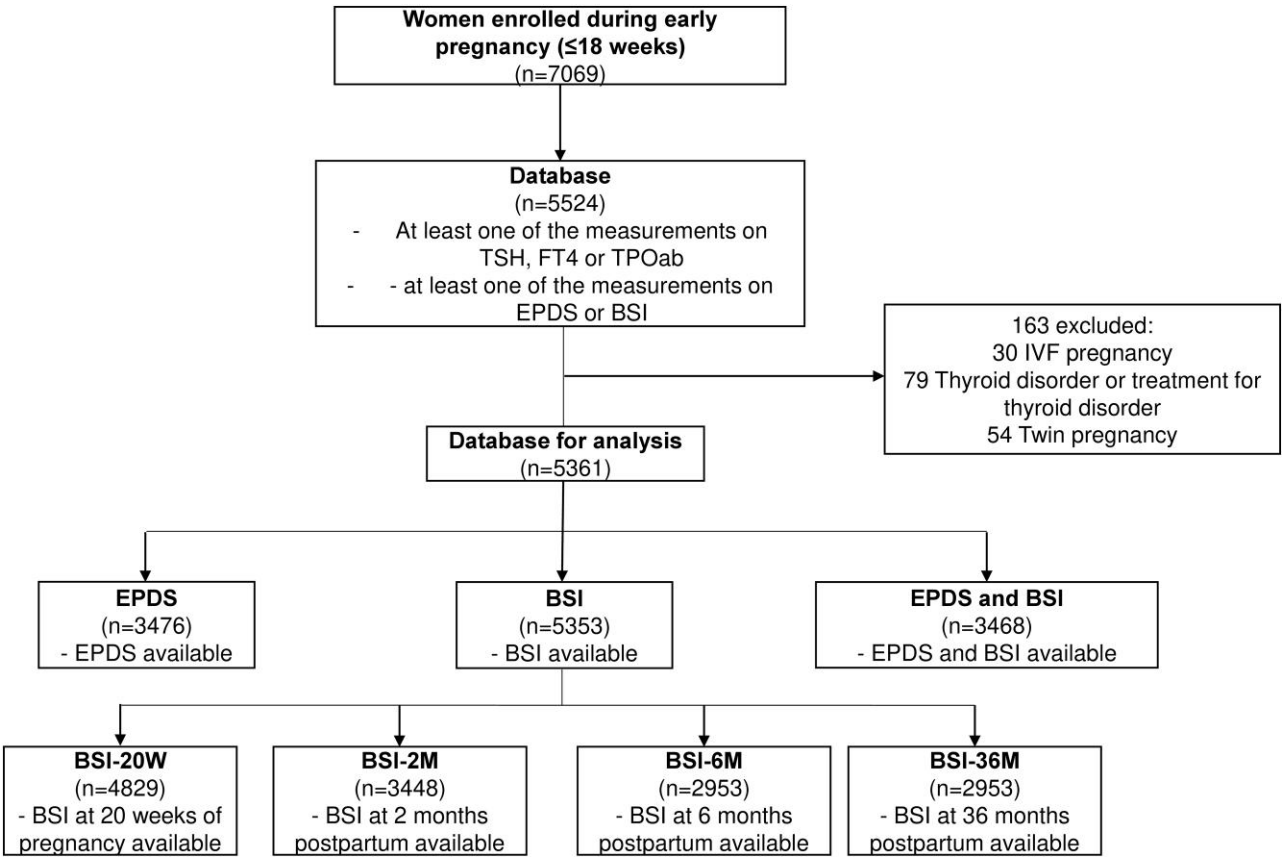


Figure 1. Flowchart of patients' selection of Generation R Study. BSI, Brief Symptom Inventory; EPDS, in vitro fertilization; FT4, free thyroxine; IVF, in vitro fertilization; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone.

TPOAb-positive women.[39] To study this, continuous interaction terms were added to the models and potentially relevant effects were assessed through stratified analyses and heatmap plots if the *P* for interaction was <.15.[40] Furthermore, we also studied the subgroup of TPOAb-positive women with a TSH above 2.5 mU/L because these women are considered a high-risk subgroup.[41]

We selected covariates for our models based on biological confounding plausibility, a 10% change in effect estimate of the variable of interest, or a 5% reduction of residual variance of the model. Covariates included maternal age, education level, ethnicity, body mass index (BMI), household income, and gestational age at blood sampling. The 2-sided significance level was set at $P < .05$. We used multiple imputations to account for missing data; 25 imputed data sets were created and pooled for analyses. All statistical analyses were performed using R statistical software version 4.0.4 and SPSS version 21.0 for Windows.

Systematic literature review and meta-analysis

We reported our systematic review according to the PRISMA statement[42] (see Table S1). We systematically searched MEDLINE ALL via Ovid, EMBASE via embase.com, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL databases from inception to September 23, 2022. The search combined terms for perinatal depression or mental diseases during pregnancy with thyroid, thyroid hormones, or thyroid autoimmunity (see File S1 page 1 for the full search strategies in all databases), and additional articles were identified through snowballing approach, scanning reference lists of included articles, and including original articles that met our eligibility criteria. We included prospective or retrospective cohort and case-control studies assessing nonselected study populations (ie, population-based or studies without inclusion criteria related to health status) that had TSH, FT4, and/or TPOAb positivity data measured during pregnancy and reported an odds ratio (OR), relative risk, or numbers that enabled for calculation of these measures for the outcome of interest (PPD) as defined according to clinical assessment, hospital registrations, or any validated questionnaire (ie, EPDS questionnaire or Research Diagnostic Criteria) (for a full list of inclusion and exclusion criteria, see Table S2). Two independent reviewers (F.S. and V.C.) evaluated the titles and abstracts derived from the search to select those that met the eligibility criteria. A third reviewer (J.O.) was involved to settle any disagreements. The same authors (F.S. and V.C.) extracted data from the selected papers according to a predefined codebook that included study design, sample size and characteristics, outcomes, and conclusions among others (see Table 4). Assessment of study methodological quality was performed by 2 authors (F.S. and V.C.) using the Newcastle-Ottawa Scale (NOS).[43] This scale evaluates the quality of a study assessing the selection, comparability, and exposure/outcome of the study itself through a 9-point system, with 0 points representing a very low-quality study and 9 points indicating a high-quality study.

We combined data from original studies using a DerSimonian–Laird random effect model to obtain pooled OR with 95% CI for the association of TPOAb positivity with PPD and calculated I^2 as a measure of heterogeneity. We evaluated possible publication bias with a statistical test (Egger's test) and obtained visual representation via funnel plots for assessing major deviations only considering the (too) low number of studies for proper statistical testing. Meta-analyses were performed in R statistical software version 4.1.2.

Results

Generation R Study

After exclusions, the study population comprised 5361 women with data on TSH, FT4, and/or TPOAb, and EPDS or BSI (Figure 1). The median (95% range) age of the study population was 30.5 years (19.7-38.8), with a median gestational age at inclusion of 13.2 weeks (9.6-17.5), the majority were women of Dutch ethnicity, and 5.7% were TPOAb positive (Table 1).

There was no association of TPOAb positivity with PPD as assessed using the EPDS (OR 0.79, 95% CI 0.47-1.33, $P = .37$) or as assessed by the BSI at 2 months (OR 0.71, 95% CI 0.39-1.19, $P = .21$), 6 months (OR 1.13, 95% CI 0.69-1.79, $P = .61$), or 36 months postpartum (OR 0.64, 95% CI 0.28-1.28, $P = .25$; Table 2). There was no association of TSH or FT4 with PPD (as assessed by EPDS, TSH [OR 0.83, 95% CI 0.58-1.19, $P = .32$], FT4 [OR 0.99, 95% CI 0.95-1.05, $P = .86$]; similar results were identified for the BSI; see Table 2). These results were similar when analyzing the association of TPOAb positivity with the natural logarithm of the PPD score (Table 3). Similarly, there was no association with PPD for the subgroup of TPOAb-positive women with a TSH above 2.5 mU/L (see Table S3).

As a surrogate marker for thyroid autoimmunity, we studied the interaction of TSH or FT4 with hCG. There was evidence that the association of TSH (P for interaction = .04) or FT4 (P for interaction = .06) differed according to the hCG concentration (Figure 2A and B). The combination of a high TSH with a high hCG (presumably representing a poorer thyroidal response to hCG stimulation, as already found in previous studies by Korevaar et al.[39] and Teng et al.[44]) was associated with a lower risk of PPD (Figure 2A). Consistently, the combination of low FT4 with a high hCG (representing a poorer thyroidal response to hCG stimulation) was associated with a lower risk of PPD (Figure 2B). Additional adjustment for fetal sex did not meaningfully change the results (data not shown).

Table 1. General population characteristics of 5361 mothers from the Generation R Study.

	Value	
TSH (mU/L)[a] median (95% range)	1.35	(0.04-4.50)
FT4 (pmol/L)[a] median (95% range)	14.8	(10.4-22.3)
TPOab positivity[a], *n* (%)	286	(5.7)
EPDS positivity[b], *n* (%)	253	(7.3)
BSI-2 positivity[b], *n* (%)	253	(7.3)
BSI-6 positivity[b], *n* (%)	246	(8.3)
BSI-36 positivity[b], *n* (%)	136	(4.3)
Gestational age at intake (weeks) median (95% range)	13.2	(9.6-17.5)
Age at intake (years) median (95% range)	30.5	(19.7-38.8)
BMI median (95% range)	23.5	(18.5-35.6)
Parity, *n* (%)		
0	3136	(58.5)
1	1584	(29.5)
2	464	(8.7)
≥3	177	(3.3)
Smoking status, *n* (%)		
No	3863	(72.0)
Until pregnancy was known	503	(9.4)
Yes	995	(18.6)
Education level, *n* (%)		
None or primary only	482	(9.0)
Secondary phase 1	767	(14.3)
Secondary phase 2	1636	(30.5)
Higher phase 1	1144	(21.3)
Higher phase 2	1332	(24.9)
Ethnic origin, *n* (%)		
Dutch	2946	(54.9)
Indonesian	170	(3.2)
Cape Verdian	200	(3.7)
Moroccan	277	(5.2)
Dutch Antilles	153	(2.9)
Surinamese	432	(8.1)
Turkish	415	(7.7)
Other western	483	(9.0)
Other non-Western	285	(5.3)
Child sex, *n* (%)		
Male	2702	(50.4)

Data are median (95% range) or n (%). Data are shown after imputation of missing data.
Abbreviations: BMI, body mass index; BSI, Brief Symptom Inventory; BSI-2, BSI at 2-month postpartum; BSI-6, BSI at 6-month postpartum; BSI-36, BSI at 36-month postpartum; EPDS, Edinburgh Postpartum Depression Scale; FT4, free thyroxine; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.
[a]Thyroid hormone measurements are available for $n = 5013$ (TSH), $n = 5050$ (FT4), and $n = 5010$ (TPOAb).
[b]The EPDS and BSI scores are available for $n = 3476$ (EPDS), $n = 3448$ (BSI-2), $n = 2953$ (BSI-6), and $n = 3190$ (BSI-36).

Systematic review and meta-analysis

We identified 1817 articles of which 1292 articles remained after excluding duplications. Of these, 74 were eligible for inclusion after title and abstract screening. We also screened 33 additional articles through citation tracking. We finally included 3 prospective cohort studies for meta-analysis (Figure 3). These studies included a total of 1659 pregnant women, 246 of whom had PPD. Results were combined with the Generation R Study described above. All studies were performed in the Netherlands and 3 out of 4 studies adjusted for confounding factors. Study characteristics are shown in Table 4. The overall quality of the selected studies was moderate to high according to the NOS (Table 5). All studies reported on the association of TPOAb positivity with PPD, but only 2 (including the Generation R Study) assessed the association of gestational thyroid function with PPD.

All included studies from the literature observed a higher risk of PPD among women with TPOAb positivity, compared with TPOAb-negative women.

After the addition of Generation R data, TPOAb-positive women did not have a statistically significant higher risk of PPD (OR 1.93, 95% CI 0.91-4.10). Excluding the study without confounder adjustment did not meaningfully change the results (Figures S1 and S2). There was substantial between-study heterogeneity ($I^2 = 79\%$; Figure 4), with some limitation of this result's statistical power given by the

Table 2. The association of TPOAb and thyroid function with EPDS and BSI cutoff.

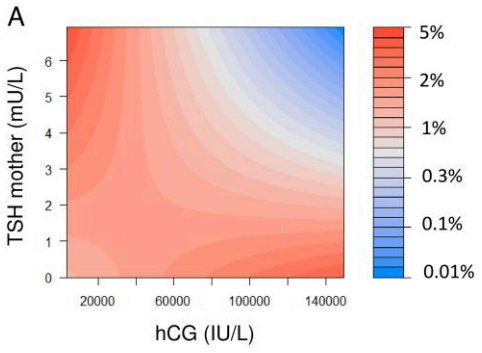
	EPDS		BSI-2		BSI-6		BSI-36	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
TPOAb > 20 IU/mL	0.79 (0.47-1.33)	.37	0.71 (0.39-1.19)	.21	1.13 (0.69-1.79)	.61	0.64 (0.28-1.28)	.25
TPOAb > 60 IU/mL	0.85 (0.45-1.60)	.62	0.82 (0.41-1.49)	.54	0.88 (0.45-1.61)	.71	0.79 (0.30-1.73)	.59
TSH	0.83 (0.58-1.19)	.32	0.84 (0.59-1.20)	.36	0.77 (0.54-1.08)	.14	0.78 (0.50-1.23)	.29
FT4	0.99 (0.95-1.05)	.86	1.00 (0.95-1.05)	.91	1.00 (0.95-1.06)	.85	1.00 (0.95-1.07)	.80

Table 2 shows multiple logistic regression of TPOAb positivity (defined with a cutoff of >20 and >60 IU/mL) and of TSH and FT4 with the risk of postpartum depression (EPDS > 12; BSI > 0.75). Regression analyses are adjusted for maternal age, education level, ethnicity, BMI, household income, and gestational age at blood sampling for TPOAb assessment.
Abbreviations: BSI, Brief Symptom Inventory; BSI-2, BSI at 2-month postpartum; BSI-6, BSI at 6-month postpartum; BSI-36, BSI at 36-month postpartum; EPDS, Edinburgh Postpartum Depression Scale; FT4, free thyroxine; TPOAb, thyroid peroxidase antibodies; TSH, natural logarithm of TSH (thyroid stimulating hormone).

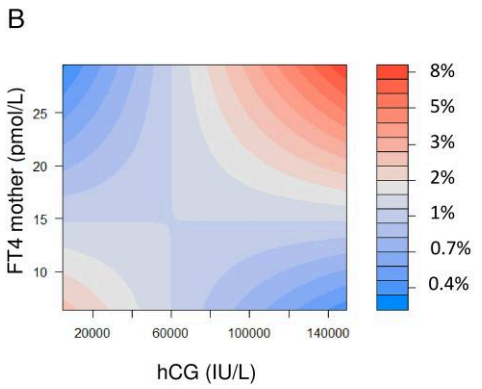
Table 3. The association of TPOAb with the natural log of the postpartum depression symptom score.

	EPDS		BSI-2		BSI-6		BSI-36	
	B (SE)	*P* value	*B* (SE)	*P* value	*B* (SE)	*P* value	*B* (SE)	*P* value
TPOAb > 20 IU/mL	−.011 (0.048)	.83	−.004 (0.015)	.76	.001 (0.017)	.97	.002 (0.012)	.85
Tpoab > 60 IU/Ml	−.005 (0.059)	.93	.007 (0.018)	.68	−.008 (0.021)	.69	−.003 (0.015)	.83

Table 3 shows linear regression of TPOAb positivity (defined with a cutoff of >20 IU/mL and >60 IU/mL) with the natural log of the postpartum depression symptom score. Regression analyses are adjusted for maternal age, education level, ethnicity, BMI, household income, and gestational age at blood sampling for TPOAb assessment.
Abbreviations: BSI, Brief Symptom Inventory; BSI-2, BSI at 2-month postpartum; BSI-6, BSI at 6-month postpartum; BSI-36, BSI at 36-month postpartum; EPDS, Edinburgh Postpartum Depression Scale; TPOAb, thyroid peroxidase antibody.



		Quartiles of hCG	
		Lowest	Highest
		OR	OR
Quintiles of TSH mother	Q5	1.29	0.58
	Q3	ref	ref
	Q1	0.38	2.17
P for overall difference: 0.04			



		Quartiles of hCG	
		Lowest	Highest
		OR	OR
Quintiles of FT4 mother	Q5	0.40	1.63
	Q3	ref	ref
	Q1	1.13	0.84
P for overall difference: 0.06			

Figure 2. The association of TSH and FT4 with the risk of postpartum depression stratified by hCG. (A) shows multiple logistic regression with quintiles of TSH in lowest and highest quartile of hCG with the risk of postpartum depression (EPDS > 12). (B) shows multiple logistic regression with quintiles of FT4 in the lowest and highest quartile of hCG with the risk of postpartum depression (EPDS > 12). Regression analyses are adjusted for maternal age, education, ethnicity, and household income. EPDS, in vitro fertilization; FT4, free thyroxine; hCG, human chorionic gonadotropin; OR, odds ratio; TSH, thyroid stimulating hormone.

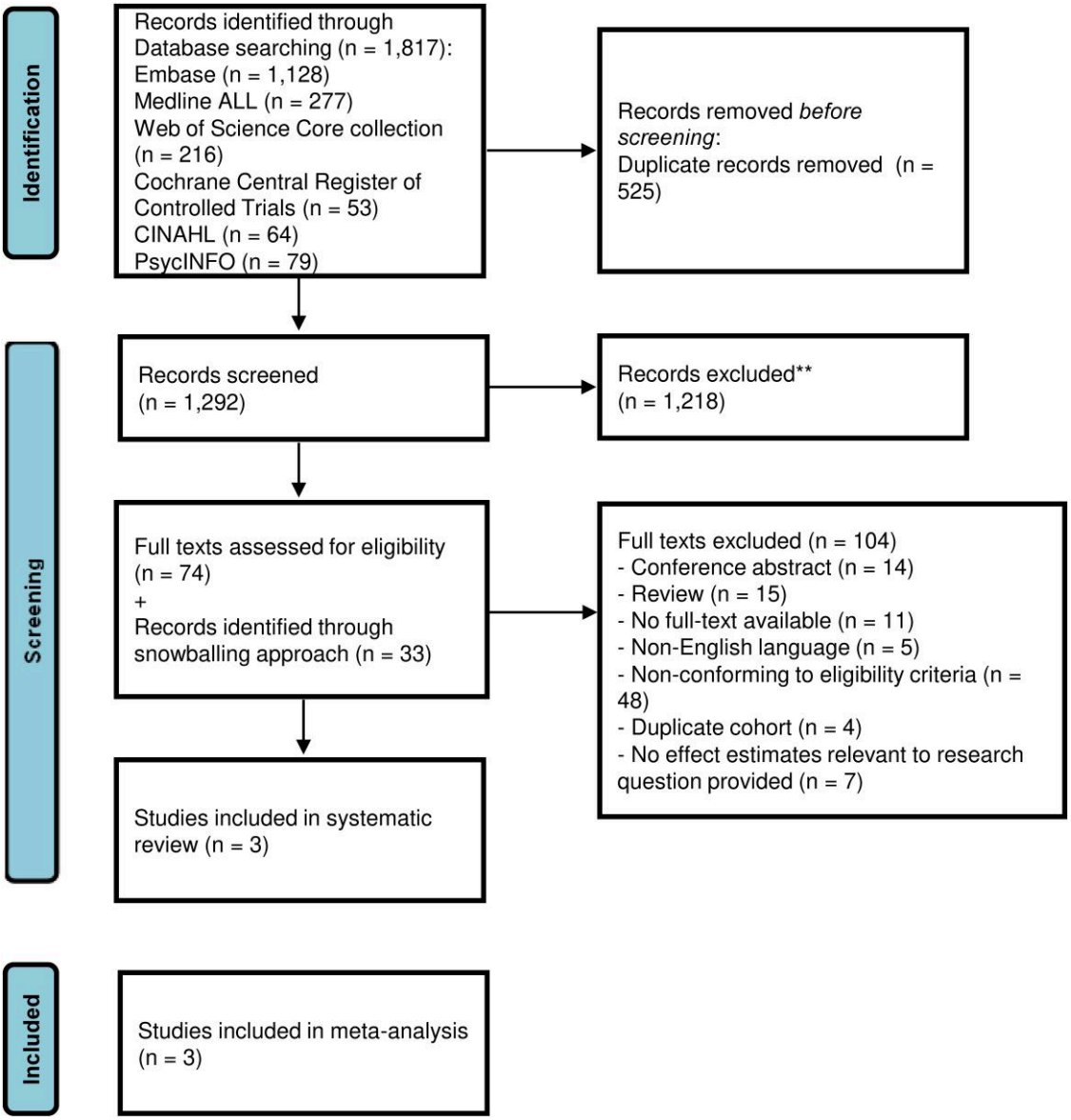


Figure 3. Flowchart of study selection, according to updated Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) 2020 flow diagram.

inclusion of few studies, and some Egger plot asymmetries suggesting publication bias, albeit not statistically significant ($P = .44$; Figure 5).

Discussion

In the Generation R Study, there was no association of gestational TSH or FT4 concentrations or TPOAb positivity with PPD. If anything, TPOAb-positive women had a lower risk of PPD based on point estimates and this was confirmed when the thyroidal response to thyroid stimulation by hCG was assessed as a surrogate for thyroid autoimmunity. When systematically assessing and meta-analyzing the literature on this topic and combining these with the results of the Generation R study, TPOAb positivity was not associated with a significantly higher risk of PPD, while not enough data could be extracted to assess the association of gestational thyroid function with PPD.

The included studies assessed the occurrence of PPD via different assessments and time points that likely contribute to the heterogeneity. The Pop and Kuijpens studies defined PPD according to Research Diagnostic Criteria, which consists in a semistructured interview by one investigator unaware of thyroid function; the interview was performed at 4-, 10-, 16-, 22-, 28-, and 34-week postpartum in the study by Pop et al., at 12- and 32-week gestation and at 4-, 12-, 20-, 28-, and 36-week postpartum in the study by Kuijpens et al. The study by Wesseloo et al. used the EPDS every pregnancy trimester and 4 times during the postpartum period (6 weeks and 4, 8, and 12 months). Furthermore, Pop et al. did not exclude women with a history of depression, while Kuijpens et al. excluded women with a previous episode of depression before/at 12-week gestation only in a second analysis, whereas Wesseloo et al. excluded women with a history of depression and all women with depression during their pregnancy. The latter is of particular relevance since the outcome studied

Table 4. Characteristics and results of included studies on the association between thyroid (dys)function/thyroid autoimmunity and postpartum depression.

Author, publication year, year of data collection	Study design, sample size, region/country of the study	TPOAb positivity prevalence (%), measurement time points (weeks), assay, and cutoff	Number of cases of PPD (%), diagnostic tool, assessment time points (month)	Exclusion criteria	PPD odds ratio (95% CI)	Confounding factors analyses were adjusted for
Pop, 1993, 1988-1990	Prospective observational, 293, The Netherlands	27/293 (9.2%),[b] 32 G, Microsomal antibodies Fujirebio, Inc. Japan; cutoff NA	61/293 (20.8%), Research Diagnostic Criteria, 4-10-16-22-28-34 PP	None	1.73 (0.92-3.28)[c]	—
Kuijpens, 2001, NA	Prospective observational, 291, Kempenland, the Netherlands	41/291 (14.1%), 12 and 32 G; 4, 12, 20, 28, 36 PP, Immunometric Enzyme Combikit, Orgentec GmbH, Mainz, Germany); >50 IU/mL	117/291 (40.1%), Research Diagnostic Criteria, 3-8 G; 1-3-5-7-9 PP	In a second analysis, all women with an episode of depression before 12 weeks gestation were excluded (n = 70)	3.8 (1.3-8.9) at 4 weeks PP; 3.6 (1.3-7.3) at 12 weeks PP. Adjusted: 2.8 (1.7-4.5)	—
Wesseloo, 2018, 2013-2014	Prospective cohort, 1075, South-East of the Netherlands	121/1075 (11.3%), 10-12 G, Cobas® e 601, Roche Diagnostics, Mannheim, Germany; >20 IU/mL	68/1075 (6.3%), EPDS (cutoff ≥ 13), 1.5-4-8-12 PP	Non-singleton pregnancy or history of a severe psychiatric disorder, self-reported lifetime history of depression, depression during pregnancy, known thyroid disease, other endocrine/ auto-immune disorders, EPDS > trimester cutoffs during pregnancy[d]	3.5 (1.3-9.4)[a]. Adjusted: 3.8 (1.3-11.6)[a] (4 months PP)	Anxiety during pregnancy, age, preterm delivery, primiparity, recent life-events, mode of delivery, health problems of the baby and social support during the postpartum period

Abbreviations: EPDS, Edinburgh Postpartum Depression Scale; G, gestation; NA, not available; PPD, postpartum depression; TPOAb, thyroid peroxidase antibody.
[a]*P* value < .05.
[b]Microsomal antibodies.
[c]Risk ratio (RR) (95% CI).
[d]Trimester 1 ≥ 11; trimester 2 and 3 ≥ 10.

Table 5. Newcastle-Ottawa quality assessment scale for included cohort studies.

Study	Selection	Comparability	Outcome	Total
Pop 1993	***	*	***	7/9
Kuijpens 2001	****	*	***	8/9
Wesseloo 2018	****	*	**	7/9

then only includes first onset depression rather than a postpartum relapse. Unfortunately, the reported results are limited and do not allow for quantification of any differences between new onset and relapse depression episodes. Therefore, future meta-analyses should strive for an individual participant data approach to elucidate the clinically meaningfulness of subdividing these entities. Furthermore, there was heterogeneity in the definition of PPD. Most often, not only internationally recognized questionnaires such as EPDS are used to define PPD but also Research Diagnostic Criteria[45] or definitions based on clinical registrations are used. The EPDS is a self-report questionnaire developed to screen for relevant symptoms of PPD rather than for PPD itself, Research Diagnostic Criteria tool is by definition affected by the investigator who conducts the interview. The EPDS questionnaire remains the most reliable and easiest to perform tool in a large-scale context.[33] The discrepancies in PPD assessment tools and time points might significantly affect study outcomes, given the already high variability in the prevalence of PPD related to social (new-born management in his/her different life phases and paternal support) and biological factors (nonthyroidal hormones fluctuations and maternal physical changes during puerperal period) during the postpartum period. The heterogeneity was present despite applying very stringent eligibility criteria (for further details, see Table S2) to ensure a homogenous study methodology focusing on specifically assessing the association of gestational thyroid function or gestational TPOAb positivity and PPD. To cite 1 example, study by Konstantakou et al.[46] was excluded because it studies the correlation of thyroid tests with depression/anxiety questionnaires during pregnancy and the same variables assessed postpartum, thus not studying the association of thyroid tests performed during pregnancy with PPD. This selection, together with the inclusion of Generation R Study, conditioned

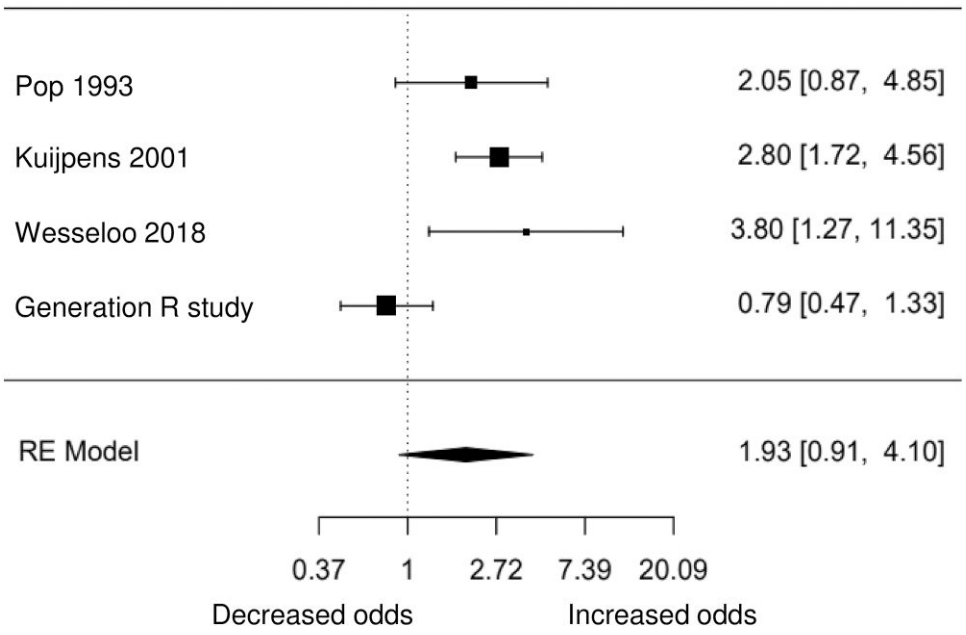


Figure 4. Forest plot for the association between thyroid autoimmunity and postpartum depression. RE, random effect.

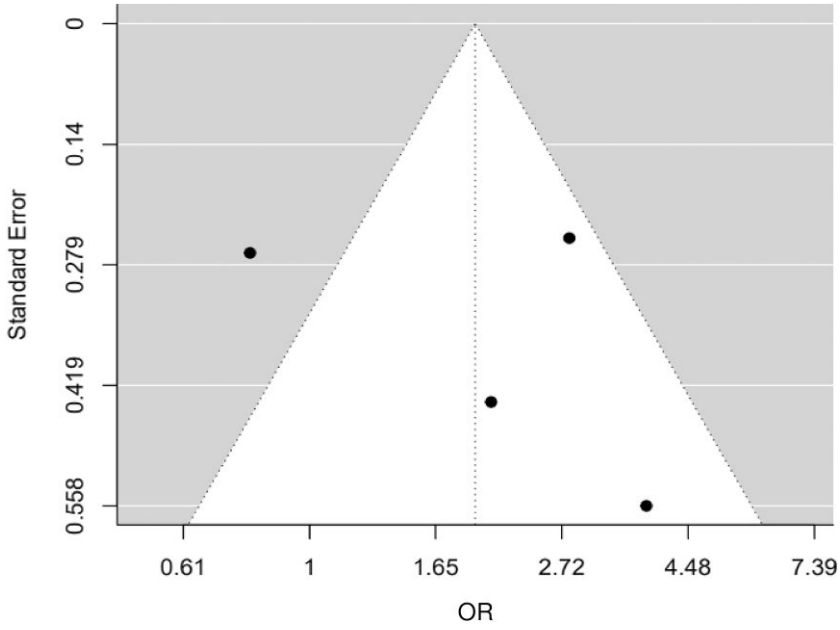


Figure 5. Funnel plot of the included studies on the association between thyroid autoimmunity and postpartum depression. OR, odds ratio.

meta-analysis results, leading to different conclusions compared with another recent meta-analysis on this topic.[47]

Our meta-analysis shows that the currently available data on the association of TPOAb positivity with PPD are very limited. While there was a higher risk of PPD in women with TPOAb positivity, this association did not reach statistical significance mainly due to the negative results of the present study. The large heterogeneity among studies could also be attributable to other factors. First, the definition of TPOAb positivity differed between studies. Thyroglobulin antibody positivity was defined through measurements with different assays and using different cutoffs (including trimester-specific cutoffs). There is also significant heterogeneity in the gestational age of TPOAb measurement ranging from 10-12 gestational weeks in 1 study to 32 gestational weeks in another.

Second, another important aspect is that PPD is determined by a multitude of biological but especially social and psychological factors such as major traumatic life events and a history of depression,[22] which play a much more relevant role than thyroid autoimmunity or thyroid function. Therefore, any absolute effects of TPOAb positivity on PPD risk would be small and unlikely to be clinically meaningful on top of known important risk factors. In addition, the recently identified entity of autoimmune encephalitis, which recognizes its predominant etiology in NMDA receptor antibodies,[48] is worth

mentioning among the possible underlying mechanisms of PPD. However, NMDA receptor antibody encephalitis is uncommon and its manifestation with solely depressive symptoms has not been described to date, while it has been more frequently associated with postpartum psychosis.[49]

We were unable to perform a meta-analysis for our secondary aim to study the association of thyroid function and PPD because of a lack of published data. Besides our Generation R Study, the study by Kuijpens et al.[22] also did not identify any association of gestational thyroid function with PPD, overall suggesting no meaningful association. Furthermore, subanalyses from a large American randomized trial showed that neither gestational subclinical hypothyroidism nor levothyroxine treatment for that indication is associated with postpartum depressive symptoms.[50] It has been suggested that the risk of pregnancy complications is higher especially for women with both TPOAb positivity and a higher TSH or subclinical hypothyroidism.[51–54] A higher TSH in TPOAb positivity most likely reflects more severe autoimmunity and a decreased thyroid functional capacity, and these mechanisms could mediate the additional risk. In the current study, we did not identify a similar pattern. In addition, we also analyzed thyroid functional capacity by studying the interaction of TSH or FT4 with hCG. Those analyses indicated that women with a high TSH with a high hCG, as seen in TPOAb positivity,[39] did not have a higher risk of PPD. If anything, the point estimates indicated a lower risk of PPD similar to analyses for TPOAb positivity. If TPOAb positivity is a risk factor for PPD, then this is most likely mediated through postpartum thyroiditis, and future studies should thus take postpartum thyroid function into account.

We were able to leverage data from a large prospective population cohort study to assess the association of gestational thyroid function and TPOAb positivity with PPD at multiple time points postpartum while adjusting for potential confounders. The major limitation of Generation R Study is that the EPDS questionnaire was not available for all participants, which could lead to underestimation of the PPD prevalence. However, there was no difference in TPOAb positivity between those with or without EPDS data indicating no relevant bias affecting the results (see Table S4). To the best of our knowledge, this is the largest prospective population-based cohort study of the association of thyroid autoimmunity and thyroid function with PPD. Possible reasons of the discordant results of the Generation R Study compared with other studies could either be the discrepancy in time of measurements, the differences in sample size, or possibly the use of different cutoffs for TPOAb assays.

A possible limitation of our meta-analysis is that all 3 studies are from the Netherlands considerably limiting the generalizability of our results, leaving predominantly Western countries.[55] Our meta-analysis was also limited by a lack of power due to general scarcity of data on this topic. Another limitation due to the lack of data on this topic is the inability to analyze other thyroid autoimmunity markers, such as TgAb. However, other studies have proposed that the association between thyroid autoimmunity and PPD is mediated by changes in thyroid hormones,[20,21] and since TPOAbs are more strongly associated with thyroid hormone concentrations, it is less likely that gestational TgAb would have an important role in PPD pathophysiology.[56,57] In addition, publication bias may have played a role, although we could not show this with the Egger plots.

Conclusions

We could not identify an unequivocal association of TPOAb positivity or gestational thyroid function with PPD. This suggests that screening for women with a high risk of PPD with use of TPOAb positivity or gestational thyroid dysfunction is not warranted, and the risk assessment of PPD should be made according to better-substantiated risk factors including major traumatic life events, previous history of depression and depressive symptoms. However, based on currently available data, we cannot exclude the possibility that certain subgroups of women with thyroid autoimmunity or dysfunction could be at higher risk of PPD.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Data availability

The data that support the findings of this study are available from Erasmus Medical Center, which conducted Generation R study. Restrictions apply to the availability of these data, which were used under license for this study.

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