Hypothyroxinemia and TPO-Antibody Positivity Are Risk Factors for Premature Delivery: The Generation R Study

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Context: Premature delivery is an important risk factor for child mortality and psychiatric, metabolic, and cardiovascular disease later in life. In the majority of cases, the cause of prematurity cannot be identified. Currently, it remains controversial whether abnormal maternal thyroid function during pregnancy increases the risk of premature delivery. Therefore, we investigated the relation between maternal serum thyroid parameters and the risk of premature delivery in a large prospective population-based study.

Design: Serum TSH, free T_4 (FT_4), T_4, and TPO antibodies (TPOAbs) were determined during early pregnancy in 5971 pregnant women from the Generation R study. Data were available on maternal age, parity, smoking, socioeconomic status, ethnicity, maternal anthropometrics, and urinary iodine levels.

Results: Of all women, 5.0% had a premature delivery (<37 weeks), 4.4% had a spontaneous premature delivery, and 1.4% had a very premature delivery (<34 weeks). High TSH levels and subclinical hypothyroidism were associated with premature delivery but not with spontaneous premature delivery. Maternal hypothyroxinemia was associated with a 2.5-fold increased risk of premature delivery, a 3.4-fold increased risk of spontaneous premature delivery, and a 3.6-fold increased risk of very premature delivery (all $P < .01$). TPOAb positivity was associated with a 1.7-fold increased risk of premature delivery ($P = .01$), a 2.1-fold increased risk of spontaneous premature delivery ($P = .02$), and a 2.5-fold increased risk of very premature delivery ($P = .04$). These effects remained similar after correction for TSH and FT_4 levels.

Conclusions: Hypothyroxinemia and TPOAb positivity are associated with an increased risk of premature delivery. The increased risk in TPOAb-positive women seems to be independent of thyroid function. **(*J Clin Endocrinol Metab* 98: 4382–4390, 2013)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received July 15, 2013. Accepted September 5, 2013.
First Published Online September 13, 2013

Abbreviations: aOR, adjusted odds ratio; ATA, American Thyroid Association; BMI, body mass index; CI, confidence interval; ES, Endocrine Society; FT_4, free T_4; IUGR, intrauterine growth retardation; PROM, premature rupture of membranes; SES, socioeconomic status; SGA, small for gestational age; SP-A, surfactant protein A; TPOAb, TPO antibody.

Premature delivery has been identified as a risk factor for psychiatric, metabolic, cardiovascular, and renal disease later in life (1–3). Furthermore, it has been identified as the largest direct cause of child deaths in almost all high- and middle-income countries (4). In 2010, the estimated incidence of premature deliveries in developed countries was 5% to 12%; however, in most of these women no known risk factors can be identified (5, 6). Severe hypothyroidism and hyperthyroidism during pregnancy are associated with premature delivery, but conflicting results have been published on milder alterations in thyroid function tests over the last 2 decades (7, 8). To date, most studies could not investigate spontaneous deliveries, even though this is a more homogeneous group that much better represents the physiology of prematurity.

Two studies have demonstrated a relation between increased TSH levels and a higher risk of premature delivery (9, 10), but both studies lacked data on free T_4 (FT_4) or TPO antibodies (TPOAbs). In contrast, Allan et al (11) and Negro et al (12) did not find an increased risk of prematurity in women with a high TSH level, but the definition of an increased TSH level varied between these studies. Conflicting results on the relation between subclinical hypothyroidism (elevated TSH and normal FT_4) during pregnancy and premature delivery have been published as well (13–18). Whether hypothyroxinemia (normal TSH with low FT_4) increases the risk of premature delivery has only been investigated by 3 groups (14, 16, 19). Even though hypothyroxinemia was not associated with premature delivery, a study by Cleary-Goldman et al (16) found that hypothyroxinemia in the first but not in the second trimester was associated with premature onset of labor.

TPOAb positivity is generally accepted as a risk factor for prematurity (18, 20–23), although not all studies could confirm this association (17, 19, 24, 25). It is still not known whether the possible increased risk of prematurity in TPOAb-positive women is due to an effect on the thyroid or a direct effect of autoimmunity itself, because no study has investigated TPOAb positivity as a risk factor for prematurity independent of thyroid status.

As a consequence, it remains controversial whether milder forms of maternal thyroid dysfunction during pregnancy are associated with premature delivery. Therefore, we investigated the relation between abnormal maternal thyroid function during early pregnancy and the risk of a premature and spontaneous premature delivery in a large prospective population-based study. In these analyses, we included a wide variety of possible interfering factors and also studied the (independent) effect of TPOAb status on premature delivery.

Materials and Methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort from early fetal life onward in Rotterdam, The Netherlands (26).

Population for analyses

Data on early pregnancy TSH and/or TPOAb levels and gestational age at birth were available for 6264 pregnant women. Women with twin pregnancies (n = 128), preexisting thyroid disease (n = 85), thyroid (interfering) medication usage (n = 4), and fertility treatment (n = 76) were excluded. The final population comprised 5971 women who were included in one or more analyses, of whom 5622 women had available data on FT_4 levels.

Ethics approval

The general design, all research aims, and the specific measurements in the Generation R Study were approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all participants.

Birth outcomes

Prematurity was defined as a gestational age at birth <37 weeks and very premature delivery was defined as a gestational age at birth <34 weeks. Spontaneous (very) premature was defined as a spontaneous onset of premature labor before the 37th or 34th week of gestation and included women who did not deliver after induction of labor or by an elective caesarean section. Premature rupture of membranes (PROM) was defined as ruptured membranes before 37 weeks of gestation.

Thyroid measurements

Maternal serum samples were obtained in early pregnancy (median, 13.2 weeks; 95% range, 9.6–17.6 weeks). Plain tubes were centrifuged, and serum was stored at −80°C. TSH and FT_4 levels in maternal serum samples were determined using chemiluminescence assays (Vitros ECi; Ortho Clinical Diagnostics). The intra-assay and interassay coefficients of variation were <4.1% for TSH at a range of 3.97 to 22.7 mU/L and <5.4% for FT_4 at a range of 14.3 to 25.0 pmol/L. Maternal TPOAbs were measured using the Phadia 250 immunoassay (Phadia AB) and regarded as positive when >60 IU/mL (27).

Iodine measurements

Urinary iodine concentrations were determined in a random subset of 1099 women during early pregnancy (median, 12.9 weeks; 95% range, 9.8–17.2 weeks) as described previously (28).

Covariates

Analyses were adjusted for known determinants of thyroid function and gestational age at birth. Gestational age was defined using fetal ultrasound data on crown-rump length or biparietal diameter for pregnancy dating (26). Information on maternal age, smoking status, socioeconomic status (SES), and ethnicity was obtained by questionnaires during pregnancy. Ethnicity was determined by country of origin and was defined according to the classification of Statistics Netherlands (26). Su-

rinamese women were defined as Creole, Hindustani, or other, whereas Moroccan women were defined as Berber, Arabic, or undefined Moroccan (29). Maternal smoking status was classified as no smoking, smoking until known pregnancy, and continued smoking during pregnancy. SES was defined by educational level, net household income, and employment status (26). Weight and length were measured at intake (the same time as blood sample collection) and were used to calculate body mass index (BMI). Information on fertility treatment, pregnancy outcome, date of birth, birth anthropometrics, and the sex of the child were obtained from community midwives, obstetricians, and hospital registries.

Statistical analysis

Reference ranges were determined by population-based calculations, as described previously (27). Definitions were as follows: hyperthyroidism as a low (<2.5th percentile) TSH level with a high (>97.5th percentile) FT_4 level (hyperthyroidism during pregnancy should be considered as a more biochemical diagnosis than hyperthyroidism in a nonpregnancy state); subclinical hyperthyroidism as a low TSH level with a normal (2.5th–97.5th percentiles) FT_4 level; hypothyroidism as a high TSH level with a low FT_4 level; subclinical hypothyroidism as a high TSH level with a normal FT_4 level; and hypothyroxinemia as a low FT_4 level with a normal TSH level. We studied the risk of premature delivery in these women, with the euthyroid women (ie, women with normal TSH and FT_4 levels) as the reference group.

The Endocrine Society (ES) and American Thyroid Association (ATA) guidelines recommend the use of population-based trimester-specific reference ranges. When population-based reference ranges are unavailable, upper limits for TSH of >2.5 mU/L in the first or >3.0 mU/L in the second trimester are recommended (7, 8). In this article the term "high TSH" has been subdivided according to these recommendations, and references to these values are made throughout.

To achieve a normal distribution, TSH values were logarithmically transformed.

Intrauterine growth retardation (IUGR) is a major cause of iatrogenic prematurity and may be an intermediate between thyroid function and gestational age at birth. In this study, IUGR was defined by small for gestational age (SGA) at birth (defined as a gestational age–adjusted birth weight below the 2.5th percentile in the study cohort [<2.13 SD]). However, sensitivity analysis showed that correction for SGA did not influence our analyses, and, therefore, SGA was not adjusted for.

Women with comorbidities (including preexisting diabetes, chronic hypertension, hypercholesterolemia, chronic heart disorder, systemic lupus erythematosus, and preeclampsia) were also excluded in all analyses because a number of studies have shown that these women may have higher TSH levels and/or a higher prevalence of TPOAb positivity and prematurity. This finding is line with our study, in which women with comorbidities had higher mean TSH levels (1.86 vs 1.59 mU/L in women without comorbidities), showed a trend toward an increased prevalence of TSH levels of >97.5th percentile (adjusted odds ratio [aOR], 1.47; 95% confidence interval [CI], 0.87–2.48; $P = .14$) and were more likely to have a premature delivery (aOR, 4.54; 95% CI, 3.26–6.33; $P < .01$).

Median urinary iodine excretion was used to determine population iodine status as advocated by the World Health Organization (with <150 μg/L as insufficient, 150–249 μg/L as adequate, and >500 μg/L as excessive) (30).

We used multiple imputation for covariates with >5.0% missing data. Five imputed datasets were created and pooled for analyses. Smoking, SES, and ethnicity were added to the model (missing due to nonresponse in 12.8%, 7.2%, and 5.7%, respectively). Furthermore, we added gestational age at birth, TSH, FT_4, and TPOAb levels, maternal age, parity, fetal sex, and maternal BMI to the model as prediction variables only. No significant differences in descriptive characteristics were found between the original and imputed datasets. All statistical analyses were performed using SPSS (version 20.0 for Windows; SPSS Inc).

Results

The study population consisted of 5971 women of whom 5.0% had a premature delivery (<37 weeks of gestation) and 1.4% had a very premature delivery (<34 weeks of gestation). Descriptive characteristics are shown in Table 1. The prevalence of TPOAb positivity was 5.6%, of hypothyroidism was 0.3%, of subclinical hypothyroidism was 3.4%, of hyperthyroidism was 1.0%, of subclinical hyperthyroidism was 1.4%, and of hypothyroxinemia was 2.6%. Median urinary iodine excretion was 223 μg/L, indicating an iodine-sufficient population (30). No differences in urinary iodine status were seen between mothers of term newborns (median, 223 μg/L), mothers of premature newborns (median, 221 μg/L), or mothers of very premature newborns (median, 248 μg/L) ($P = .83$).

Elevated TSH levels, (subclinical) hypothyroidism and hyperthyroidism, and the risk of prematurity

Table 2 shows the risk of prematurity for women with elevated TSH levels and (subclinical) hypothyroidism and hyperthyroidism. Women with TSH levels of >97.5th percentile had an increased risk of premature and very premature delivery. A TSH level of >97.5th percentile was no longer associated with premature delivery or very premature delivery after the exclusion of TPOAb-positive women or after the exclusion of women with comorbidities. There was no association between high TSH levels and spontaneous (very) premature delivery. Current Endocrine Society and ATA guidelines recommend the use of an upper limit for TSH of 2.5 mU/L in the first trimester and of 3.0 mU/L in the second and third trimesters when population-based trimester-specific reference ranges are not available (7, 8). Women with elevated TSH levels according to these cutoff values also did not have an increased risk of a premature delivery. Similar results were found when only spontaneous deliveries were considered or when TPOAb-positive women were excluded.

Compared with euthyroid women, women with subclinical hypothyroidism had an increased risk of prema-

Table 1. Descriptive Statistics of 5971 Women

Characteristic	Value
Maternal age, y (SD)	29.7 (5.0)
Gestational age at blood sampling, wk (SD)	13.5 (2.0)
Gestational age at birth, wk (SD)	39.9 (1.9)
Premature pregnancies <37 wk, n (%)	299 (5.0)
Spontaneous premature pregnancies, n (%)	196 (4.4)
Very premature pregnancies <34 wk, n (%)	83 (1.4)
Spontaneous premature pregnancies, n (%)	41 (0.9)
Thyroid parameters, median	
TSH, mU/L	1.35
FT_4, pmol/L	14.8
T_4, nmol/L	145
TPOAb positivity, n (%)	312 (5.6)
Parity, n (%)	
Nullipara	3399 (57.4)
Primipara	1763 (29.8)
Multipara	757 (12.8)
Smoking, n (%)	
Nonsmokers	4380 (73.4)
Stopped smokers	546 (9.1)
Smokers	1045 (17.5)
Socioeconomic status, n (%)	
Low	596 (10.0)
Middle	2723 (45.6)
High	2652 (44.4)
Ethnicity, n (%)	
Dutch	3169 (53.1)
Moroccan	348 (5.8)
Turkish	473 (7.9)
Antillean	177 (3.0)
Surinamese	511 (8.6)
Other western	723 (12.1)
Other nonwestern	570 (9.5)
Maternal BMI, kg/m^2, mean (SD)	24.5 (4.4)
Child sex (boys), n (%)	3009 (50.4)
Urinary iodine excretion, μg/L, median	223

Descriptive statistics are for the study population after exclusion of women with twin pregnancies, preexisting thyroid disease, thyroid (interfering) medication usage, or fertility treatment.

ture and very premature delivery. Similar to the TSH levels of >97.5th percentile analyses, subclinical hypothyroidism was no longer associated with premature delivery or very premature delivery when women with comorbidities were excluded. There was no association between subclinical hypothyroidism and spontaneous premature delivery. Women with overt hyperthyroidism or subclinical hyperthyroidism did not have an increased risk of a premature delivery or spontaneous premature delivery.

Hypothyroxinemia and the risk of prematurity

As shown in Table 3, women with hypothyroxinemia had a 2.5-fold increased risk of a premature delivery and a 3.6-fold increased risk of a very premature delivery when all pregnancies were considered. A 3.4-fold increased risk of a spontaneous premature delivery and a 4.2-fold increased risk of a spontaneous very premature delivery were observed. Similar significant results were found when all women with low FT_4 levels were analyzed irrespective of their TSH levels and after the exclusion of TPOAb-positive women or women with comorbidities (data not shown).

TPOAb positivity and the risk of prematurity

Table 4 displays the risk of premature delivery according to TPOAb status. TPOAb positivity was associated with a 1.7-fold increased risk of premature, a 2.5-fold increased risk of very premature, and a 2.1-fold increased risk of spontaneous premature delivery. In euthyroid subjects, TPOAb positivity was not associated with a (very) premature delivery. Compared with TPOAb-negative women, TPOAb-positive women had higher median TSH levels and lower mean FT_4 levels (1.31 vs 2.65 mU/L and 15.2 vs 14.6 pmol/L, respectively; both $P < .01$). To study whether the increased risk of prematurity in TPOAb-positive women is driven through an effect on the thyroid, analyses were also adjusted for TSH and FT_4. Results remained similar after correction for these serum thyroid function parameters.

The lower part of Table 4 shows the risk of a premature delivery in TPOAb-positive women with a concomitant high TSH level. For women with a TSH level >2.5 mU/L in the first trimester or >3.0 mU/L in the second trimester, a trend toward an increased risk of a premature delivery was seen ($P = .06$). However, no effects on spontaneous premature or very premature delivery were detected. Low FT_4 values were not associated with increased risks of a premature delivery in TPOAb-positive women.

Abnormal thyroid parameters and PROM

Of all premature deliveries, 30% are related to PROM (6). We extended our analyses to study whether abnormal thyroid parameters could also be a risk factor for PROM. We found that women with hypothyroxinemia had an increased risk of PROM, as is shown in Table 5. Similar significant results were found when all women with low FT_4 levels were analyzed irrespective of their TSH, as well as after the exclusion of TPOAb-positive women or women with comorbidities (data not shown).

Discussion

Premature delivery is associated with various adverse effects on child health and survival. However, in approximately half of the cases a risk factor cannot be determined (6). In the current study, we demonstrate that pregnant

Table 2. Elevated TSH, Thyroid Disease Entities, and the Risk of Prematurity

	Spontaneous and Iatrogenic Deliveries (n = 5971)					Only Spontaneous Deliveries (n = 4446)			
	Prematurity <37 wk			Prematurity <34 wk		Prematurity <37 wk		Prematurity <34 wk	
	Prematurity % (n)	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*
TSH >97.5th percentiles (>4.04 mU/L)	7.8 (17/217)	1.87 (1.11–3.14)	.02[b]	2.46 (1.04–5.83)	.04	1.28 (0.61–2.68)	.52	0.74 (0.10–5.53)	.77
Nonelevated TSH (reference)[c]	4.7 (235/5370)								
TPOAb+ women excluded	2.3 (3/128)	1.38 (0.66–2.89)	.39	1.97 (0.60–6.47)	.27	1.04 (0.37–2.89)	.95	1.30 (0.17–9.89)	.80
Elevated TSH[d]	5.4 (30/551)	1.15 (0.77–1.70)	.50	1.31 (0.64–2.69)	.46	1.02 (0.61–1.71)	.95	0.58 (0.14–2.47)	.46
Nonelevated TSH (reference)	5.0 (252/5036)								
TPOAb+ women excluded	4.1 (16/386)	0.87 (0.52–1.47)	.60	1.07 (0.42–2.73)	.89	0.77 (0.39–1.54)	.46	0.94 (0.22–4.03)	.93
Hypothyroidism	5.3 (1/19)	1.08 (0.14–8.36)	.94	4.29 (0.50–36.8)	.18				
Subclinical hypothyroidism	8.0 (15/188)	2.04 (1.17–3.56)	.01[e]	2.62 (1.02–6.74)	.05	1.58 (0.75–3.32)	.23	0.91 (0.12–6.86)	.93
Hyperthyroidism	3.6 (2/56)	0.66 (0.16–2.78)	.57			1.02 (0.24–4.39)	.98		
Subclinical hyperthyroidism	6.5 (5/77)	1.39 (0.54–3.55)	.49	1.07 (0.14–8.07)	.95	1.07 (0.14–8.07)	.95		
Euthyroid (reference)[f]	4.7 (235/4970)								

Abbreviation: TPOAb+, TPOAb positiveDisease parameters were calculated using TSH and FT_4.

[a] Analysis were adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, and child sex.

[b] aOR of 1.62 (95% CI, 0.86–3.06), $P = .14$ after exclusion of women with comorbidities.

[c] 2.5th to 97.5th percentiles of TSH.

[d] TSH level of >2.5 mU/L in the first trimester or >3.0 mU/L in the second trimester (ATA and Endocrine Society guidelines).

[e] aOR of 1.54 (95% CI, 0.77–3.09), $P = .23$ after exclusion of women with comorbidities.

[f] Defined as TSH and FT_4 levels within the 2.5th to 97.5th percentiles.

women with low FT_4 levels in the first or second trimester have an increased risk of a premature delivery, which is independent of their TSH level, TPOAb status, or concomitant comorbidities. Women with an elevated TSH level and/or subclinical hypothyroidism also have an increased risk of a premature delivery, but this association does not persist after exclusion of TPOAb-positive women or women with comorbidities. Finally, we show that TPOAb positivity is also associated with an increased risk of premature delivery, and this association is independent of thyroid function.

In some studies an increased risk of premature delivery has been described among women with an elevated TSH level (9, 10) or with subclinical hypothyroidism (13–15), whereas other studies could not confirm these findings (11, 12, 16–18). Different cutoffs for TSH have been used in different studies. As advocated by international guidelines, we used population-based reference ranges because, in practice, predetermined cutoff values are prone to result in interobserver errors due to methodological differences. In line with previous studies, our data showed an association of an elevated TSH level and of subclinical hypothyroidism with an increased risk of premature delivery. However, this correlation no longer persisted after exclusion of women with concomitant comorbidities, and there was no association with spontaneous premature delivery. Furthermore, the association between subclinical hypothyroidism and premature delivery disappeared after the exclusion of TPOAb-positive women. This finding supports previous suggestions that the association with a premature delivery is caused by a high prevalence of TPOAb-positive women among women with subclinical hypothyroidism (32% in this study) (14). The ~50% reduction in risk after the exclusion of TPOAb-positive women and/or women with comorbidities suggests independent direct effects on both thyroid function and premature delivery. Taken together, our data do not support the concept that subclinical

Table 3. Hypothyroxinemia and the Risk of Prematurity

	Spontaneous and Iatrogenic Deliveries (n = 5971)					Only Spontaneous Deliveries (n = 4446)			
	Prematurity <37 wk			Prematurity <34 wk		Prematurity <37 wk		Prematurity <34 wk	
	Prematurity % (n)	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*
Hypothyroxinemia	10.3 (15/145)	2.54 (1.42–4.54)	<.01	3.56 (1.50–8.43)	<.01	3.44 (1.76–6.70)	<.01	4.21 (1.34–13.3)	.01
Euthyroid (reference)[b]	4.7 (235/4970)								

[a] Analysis were adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, and child sex.

[b] Defined as TSH and FT_4 levels within the 2.5th to 97.5th percentiles.

Table 4. Maternal TPOAb Status and the Risk of Prematurity

	Spontaneous and Iatrogenic Deliveries (n = 5971)					Only Spontaneous Deliveries (n = 4446)			
	Prematurity <37 wk			Prematurity <34 wk		Prematurity <37 wk		Prematurity <34 wk	
	Prematurity % (n)	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*
TPOAb+ status	7.4 (23/312)	1.70 (1.08–2.67)	.02	2.49 (1.21–5.12)	.01	2.05 (1.04–3.17)	.04	2.21 (0.76–6.45)	.15
Negative (reference)	4.7 (250/5264)								
TPOAb+ status (in euthyroid patients[b])	5.9 (13/219)	1.31 (0.70–2.48)	.40	2.29 (0.88–5.95)	.09	1.31 (0.37–4.62)	.68	2.69 (0.77–9.39)	.12
Negative (reference)	4.6 (206/4467)								
TPOAb+ status (adjusted for TSH/FT_4[c])	7.5 (22/294)	1.70 (1.04–2.79)	.04	2.24 (0.99–5.07)	.05	1.82 (0.98–3.37)	.06	1.87 (0.52–6.80)	.34
Negative (reference)	4.7 (231/4869)								
Among TPOAb+ women only									
TSH >97.5th percentile (>4.04 mU/L)	12.9 (9/70)	3.27 (1.15–9.29)	.03	3.05 (0.50–18.6)	.23	1.61 (0.39–6.67)	.51		
Nonelevated TSH (reference)	5.8 (13/225)								
Elevated TSH[d]	10.4 (14/135)	2.67 (0.95–7.53)	.06	1.85 (0.34–10.2)	.48	1.34 (0.36–5.00)	.67		
Nonelevated TSH (reference)	5.0 (8/160)								
FT_4 below the 2.5th percentile	8.7 (2/23)	1.46 (0.17–12.2)	.72	2.34 (0.02–242)	.71	1.11 (0.09–14.4)	.94		
Euthyroid (reference)[c]	5.4 (11/204)	3.27 (1.15–9.29)	.03	3.05 (0.50–18.6)	.23	1.61 (0.39–6.67)	.51		

Abbreviation: TPOAb+, TPOAb positive. Data are shown for analyses among TPOAb+ women only; data for prematurity <34 weeks in only spontaneous deliveries are not displayed because of insufficient numbers.

[a] Analysis was adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, and child sex.

[b] Defined as TSH and FT_4 levels within the 2.5th to 97.5th percentiles.

[c] Analysis was adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, child sex, TSH, and FT_4.

[d] TSH level of >2.5 mU/L in the first trimester or >3.0 mU/L in the second trimester (ATA and Endocrine Society guidelines).

hypothyroidism is an independent risk factor for premature delivery.

Limited data are available on the risk of prematurity in women with hypothyroxinemia. So far, hypothyroxinemia has not been identified as a risk factor for premature delivery (14, 16, 19). Hypothyroxinemia in the first trimester has been associated with premature labor (defined as persistent uterine contractions accompanied by cervical changes on digital examination before 37 weeks of gestation) (16). The single study that focused on spontaneous deliveries found no difference in the prevalence of hypothyroxinemia (defined as an FT_4 level <5th percentile) between very premature and term deliveries even though women with a premature delivery in this particular study did have a lower median FT_4 level (0.94 vs 0.99 pmol/L; $P < .001$) (19). However, in the current study, we demonstrate a clear association between hypothyroxinemia and both (very) premature and spontaneous (very) premature delivery that is independent of TPOAb positivity (8% among the hypothyroxinemia group) or concomitant comorbidities. A possible explanation for this discrepancy is a difference in iodine status between the studies, because low levels of FT_4 due to iodine deficiency may be transient and/or have consequences different from those for other causes of hypothyroxinemia. In the current study we demonstrate that our population is iodine sufficient. The other studies with negative results were performed in the United States and the United Kingdom. Although these countries are generally considered iodine sufficient, borderline sufficient or even insufficient iodine status during pregnancy has been described in both countries (31, 32).

Data on hypothyroidism suggest that various pathways may be involved in the mechanism via which low FT_4 levels increase the risk of prematurity. For example, oxytocin and vasopressin are known to play a role in the onset of labor (33, 34) and elevated levels of vasopressin have been shown in hypothyroid women. Similarly, animal studies have shown that both vasopressin and oxytocin are elevated in hypothyroid rats (35). Surfactant protein A (SP-A) may also play a role because animal studies have identified SP-A, as a hormone of parturition that modulates the intrauterine inflammatory response related to spontaneous premature labor (36, 37). SP-A is secreted by the lungs and high amounts of SP-A mRNA have been shown in the lungs of pups from hypothyroid mothers (38), whereas administration of T_3 decreased the expression of SP-A genes in fetal rat lungs during late gestation (39).

Even though not all studies point in the same direction (17, 19, 24, 25), TPOAb-positive pregnant women are generally considered to have a higher risk of premature delivery (18, 20–23). A recent meta-analysis showed that TPOAb-positive euthyroid women have an increased risk of a delivery before 37 weeks of gestation, although the

Table 5. Maternal Thyroid Parameters and PROM

	PROM <37 wk				
	Spontaneous and Iatrogenic Deliveries (n = 5971)			Only Spontaneous Deliveries (n = 4446)	
	PROM, % (n)	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*
TSH >97.5th percentiles (>4.04 mU/L)	4.3 (9/209)	1.29 (0.65–2.59)	.47	1.06 (0.46–2.48)	.89
Nonelevated TSH (reference)	3.7 (175/4776)				
TPOAb-positive women excluded	2.3 (3/128)	0.71 (0.22–2.26)	.56	0.56 (0.14–2.33)	.43
Elevated TSH (ES/ATA guidelines)[b]	2.8 (190/4844)	0.71 (0.41–1.21)	.21	0.63 (0.33–1.21)	.16
Nonelevated TSH (reference)	3.9 (15/528)				
TPOAb-positive women excluded	2.2 (8/365)	0.57 (0.28–1.17)	.13	0.56 (0.24–1.29)	.80
Hypothyroidism	5.3 (1/19)	1.47 (0.19–11.3)	.71	1.86 (0.23–15.0)	.56
Subclinical hypothyroidism	4.4 (8/180)	1.35 (0.65–2.81)	.42	1.01 (0.40–2.54)	.98
Hyperthyroidism	1.8 (1/56)	0.42 (0.06–3.08)	.39	0.52 (0.07–3.92)	.53
Subclinical hyperthyroidism	2.7 (2/74)	0.72 (0.17–3.01)	.65	[c]	
Euthyroid (reference)[d]	3.7 (175/4776)				
Hypothyroxinemia	7.2 (10/138)	2.35 (1.18–4.69)	.02	2.74 (1.30–5.75)	<.01
Euthyroid (reference)[b]	3.7 (175/4776)				
Positive TPOAb status	7.5 (22/294)	1.42 (0.82–2.45)	.21	1.43 (0.75–2.71)	.27
Negative (reference)	4.7 (231/4869)				

[a] Analysis was adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, and child sex.

[b] Defined as TSH and FT_4 levels within 2.5th to 97.5th percentiles.

[c] No PROM occurred in subclinical hyperthyroid women with a spontaneous delivery.

mechanism via which TPOAbs may cause premature births is poorly understood (40). Our results confirm this association, and we also show that this effect is present when only women with spontaneous deliveries are analyzed.

To investigate the mechanism behind the relation of TPOAbs and prematurity, we adjusted TPOAb analyses for serum TSH and FT_4 levels. The fact that these results remained similar after correction for these markers of thyroid function suggests that the positive relation between TPOAbs and prematurity is independent of thyroid function, and it is therefore likely to be due to the autoimmune process itself.

To date, this is one of the largest and most detailed studies investigating the effects of abnormal maternal thyroid function during pregnancy on the risk of premature delivery. We discriminated spontaneous from iatrogenic deliveries and investigated the entire range of serum thyroid abnormalities (including hypothyroxinemia and subclinical hypothyroidism). Important additional strengths are that we assessed the iodine status of our population, investigated a possible interfering role for comorbidities and IUGR, and corrected for a wide range of known determinants of premature delivery such as smoking, ethnicity, parity, maternal BMI, and child gender. We also add valuable clinical data, ruling out the possibility that TPOAbs may cause premature delivery via alterations in thyroid function. This study was limited by the fact that we had a lower number of first trimester data. Analyses in women with overt hypothyroidism were unreliable because of the low prevalence. Finally, data on iodine excretion were not available for all women. Nonetheless, iodine excretion analyses in a random sample of 1099 pregnant women did not show any correlations with premature delivery.

In conclusion, women with hypothyroxinemia in particular, but also TPOAb-positive women have a substantially increased risk of a premature delivery. Associations between elevated TSH levels and premature delivery were not seen in spontaneous premature deliveries and depended on the concomitant occurrence of TPOAb positivity and/or comorbidities. Finally, we showed that the association between TPOAb positivity and premature delivery is independent of thyroid function. These data give insight into the effects of abnormal thyroid function during early pregnancy and the risk of a premature delivery and suggest that screening for TPOAb positivity and hypothyroxinemia could be considered, especially among women with other risk factors for premature delivery.

Acknowledgments

The contributions of H. van Toor, B. C. M. Dufour-van den Goorbergh, and Doorlène van Tienoven, laboratory technicians,

are highly appreciated. The Generation R Study is conducted by the Erasmus Medical Center (Rotterdam) in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond, Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. The general design of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam; the Erasmus University Rotterdam; The Netherlands Organization for Health Research and Development; The Netherlands Organisation for Scientific Research; the Ministry of Health, Welfare, and Sport; and the Ministry of Youth and Families.

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This work was supported by The Netherlands Organization for Health Research and Development (VENI Grant 91696017 to R.P.P.) and an Erasmus Medical Center Clinical Fellowship (to R.P.P.).

Disclosure Summary: The authors have nothing to disclose.

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