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EDITOR'S CHOICE

WILEY

Maternal hypothyroidism and adverse outcomes of pregnancy

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Abstract

Objective: Hypothyroidism has been associated with pregnancy complications, but uncertainty prevail regarding the severity and the role of thyroid autoimmunity. This study aimed to evaluate adverse pregnancy outcomes by exposure to maternal hypothyroidism and thyroid autoimmunity.

Design: Retrospective cohort study.

Patients: 14,744 singleton pregnancies from the North Denmark Region Pregnancy Cohort (2011–2015).

Measurements: Maternal thyroid stimulating hormone (TSH), thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab) were retrospectively measured in early pregnancy blood samples (ADVIA Centaur XPT, Siemens Healthineers). Adjusted odds ratio (aOR) with 95% confidence interval (CI) was used to estimate associations between maternal hypothyroidism (TSH cut-offs: 6.0 and 10 mIU/L), thyroid autoimmunity (TPO-Ab cut-off: 60 U/ml, Tg-Ab cut-off: 33 U/ml), and adverse pregnancy outcomes.

Results: Pregnancy outcomes were 93.2% live births, 6.5% spontaneous abortions, and 0.3% stillbirths. The frequency of spontaneous abortion was 6.5% when TSH was below 6.0 mIU/L, 6.5% when above 6.0 mIU/L (aOR 1.0 [95% CI: 0.5–2.0]), and 12.5% when above 10 mIU/L (aOR: 2.0 [95% CI: 0.8–5.2]). For outcome of preterm birth, the frequency was 5.4% when TSH was below 6.0 mIU/L, 7.8% when above 6.0 mIU/L (aOR 1.5 [95% CI: 0.7–2.9]), and 11.4% when above 10 mIU/L (aOR: 2.6 [95% CI: 0.9–7.3]). No association was found between thyroid autoantibodies and spontaneous abortion (TPO-Ab: aOR: 1.0 [0.8–1.3], Tg-Ab: 1.0 [0.8–1.2]) or preterm birth (TPO-Ab: aOR: 1.0 [0.8–1.2], Tg-Ab: 0.9 [0.7–1.2]).

Conclusion: A high frequency of adverse pregnancy outcomes was seen among pregnancies exposed to maternal TSH above 10 mIU/L, whereas no association with thyroid autoantibodies was seen.

KEYWORDS
preterm birth, spontaneous abortion, thyroglobulin, thyroid peroxidase, TSH

1 | INTRODUCTION

Hypothyroidism is among the common chronic diseases in pregnant women.[1] During pregnancy, maternal thyroid hormones are vital for foetal growth and brain development[2] and a hypothesis of foetal programming by maternal hypothyroidism is biologically plausible.[3,4] Clinical guidelines unanimously state that overt hypothyroidism in pregnant women should be treated to prevent complications.[5] On the other hand, no universal screening for maternal overt hypothyroidism is implemented, and the current recommendation is limited to selective screening among pregnant women considered at risk for thyroid disease.[5]

The role of maternal thyroid hormones and the adverse effects of maternal hypothyroidism when left untreated is evident from experimental findings and from the historical descriptions of cretinism in children born to mothers with severe hypothyroidism caused by iodine deficiency.[6] Furthermore, the hallmark study by Haddow et al.[7] substantiated a risk of adverse child outcomes associated with untreated maternal hypothyroidism, which has been corroborated in other reports.[8] Large studies have substantiated that the frequency of undetected and untreated overt maternal hypothyroidism is around 0.3%,[9] which is about 10 times more frequent than congenital hypothyroidism revealed by universal newborn screening.[10] Thus, many criteria for screening[11] are met when considering overt hypothyroidism, but a critical determinant is on the definition of actual disease and indication for treatment.

Even if more evidence is needed regarding universal screening for overt hypothyroidism in pregnant women, the scientific focus has moved towards subclinical maternal thyroid function abnormalities, isolated changes in free thyroxine (fT4), and thyroid autoimmunity per se.[6] However, large randomized controlled trials (RCTs) have not shown any effect of treatment.[6] We recently showed within the North Denmark Region Pregnancy Cohort (NDRPC), that smaller aberrations in maternal thyroid function in early pregnancy thyroid stimulating hormone (TSH) just above the pregnancy-specific reference range) rarely persisted with repeated blood sampling, whereas markedly increased TSH (above 6.0 mIU/L) was likely to reflect persistent hypothyroidism in a pregnant woman.[12] In our view, a focus on persistent thyroid function abnormalities in pregnant women is needed to inform clinical practice.[6,12]

In the present study the aim was to identify pregnancies exposed to maternal hypothyroidism in an early pregnancy blood sample and to evaluate the association with adverse outcomes of pregnancy. Furthermore, we aimed to evaluate the role of thyroid autoimmunity per se as reflected by thyroid autoantibodies measured in the early pregnancy blood sample.

2 | MATERIALS AND METHODS

The NDRPC includes a biobank of early pregnancy blood samples drawn from 2011 to 2015 as part of prenatal screening for chromosomal anomalies.[13] Retrospectively, the blood samples were used for measurements of thyroid function parameters and autoantibodies. The blood samples were drawn in median pregnancy week 10 (range 4–20) with 94% of the samples drawn in the first trimester (before the 13th week of pregnancy) and 99% drawn before the 15th week of pregnancy. The biochemical results were linked to data in the Danish nationwide health registers which provided information on all births as well as maternal characteristics and health care contacts before, during, and after the pregnancy (Supporting Information: Table S1). This study included singleton pregnancies with an outcome of live birth, spontaneous abortion, or stillbirth (Figure 1). Exposure was maternal hypothyroidism in the early pregnancy blood sample, and women with biochemical hyperthyroidism defined as TSH below 0.1 mIU/L were not included (Figure 1). The study population included women with no known thyroid disease in pregnancy as well as women with known and treated nonsurgical hypothyroidism, whereas women with other known thyroid diseases were not included (Figure 1). The subgroup of women with surgical hypothyroidism was excluded from the present study, because the group was small, and the focus was on autoimmune hypothyroidism which is predominant in this age group in Denmark.[14]

Biochemical analyses of TSH, fT4, thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) were performed as single measurements using automatic immunoassays (ADVIA Centaur XPT, Siemens Healthineers) as previously described.[13] Maternal biochemical hypothyroidism was a priori defined as TSH above 6.0 mIU/L, which is the cut-off previously found to define persistent hypothyroidism with repeated early pregnancy blood sampling within the cohort.[12] Furthermore, exposure to TSH above 10 mIU/L was assessed as a marker of overt maternal hypothyroidism with marked TSH elevation.[5,15] In a sub-analysis, we considered pregnancies exposed to maternal TSH above 4.0 mIU/L in TPO- and/or Tg-Ab positive women. We previously showed within the cohort that such lower TSH cut-off was less likely to reflect persistent hypothyroidism in early pregnancy, however, the combined assessment of TSH and thyroid autoantibodies increased the likelihood of persistent hypothyroidism with repeated blood sampling.[12] Exposure to TPO-Ab was defined by a cut-off value of 60 U/ml given by the manufacturer which corresponded to the cut-off of 59 U/ml established within the cohort.[16] For Tg-Ab, the pregnancy-specific cut-off established within the cohort of 33 U/ml was used,[16] and the cut-off recommended by the manufacturer (60 U/ml) was considered in a sensitivity analysis. In addition to the biochemical assessment of maternal thyroid function, information on maternal thyroid disease known in pregnancy (pre-existing meaning it was diagnosed and treated before the pregnancy) or first diagnosed in the years after pregnancy was obtained from the Danish National Prescription Register (DNPR)[17] and the Danish National Hospital Register (DNHR)[18] (Supporting Information: Table S1). Maternal nonsurgical hypothyroidism was classified among women who had a diagnosis of hypothyroidism or a redeemed prescription of Levothyroxine (LT4) and no registration of thyroid cancer, thyroid surgery, or hyperthyroidism.[19] Exposure to LT4 treatment in pregnancy was defined

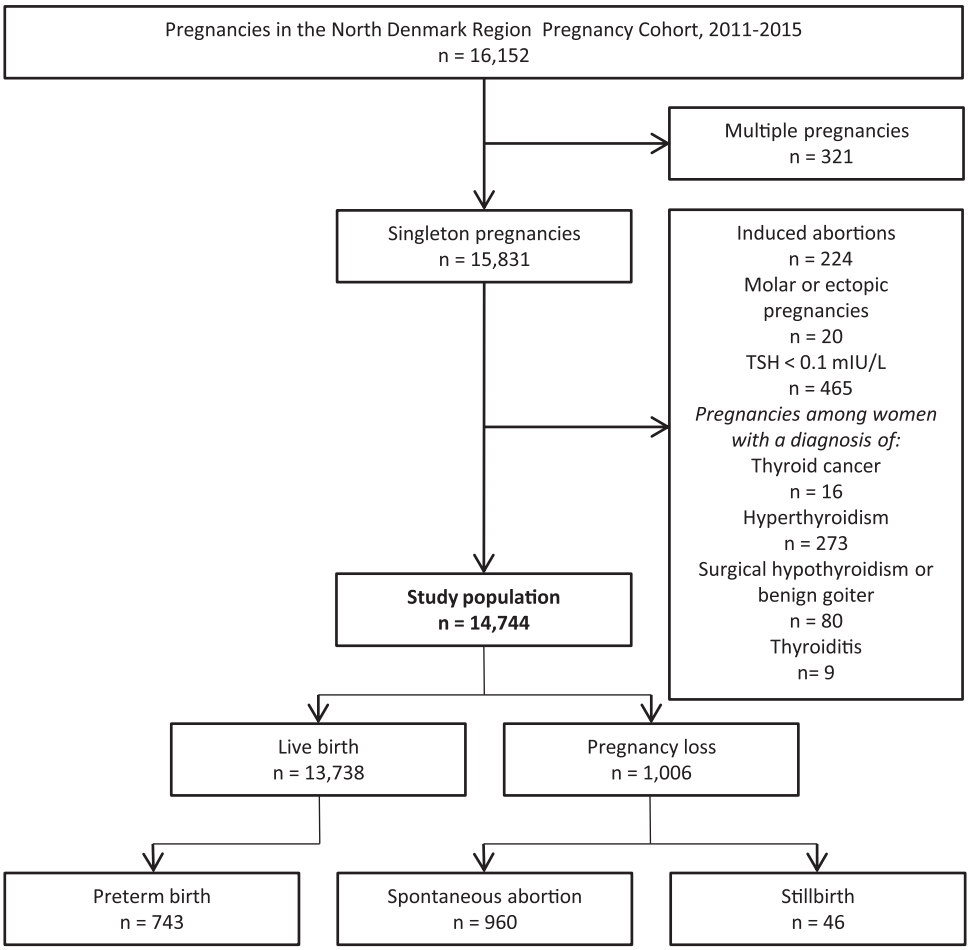

FIGURE 1 Flowchart illustrating the selection of pregnancies from the North Denmark Region Pregnancy Cohort included in the study

by at least one redeemed prescription in the 3-months period before the date of blood sampling in early pregnancy.[19] A total of 6 women with no known thyroid disease at the time of blood sampling in early pregnancy initiated treatment with LT4 later in the pregnancy under study and all terminated the pregnancy with live birth, however, this number was too small to consider any effect of treatment in the analyses.

The outcome of pregnancy was defined from information in the Medical Birth Register (MBR)[20] and the DNHR, as previously described[13] (Supporting Information: Table S1). From the MBR information on all live- and stillbirths was obtained, while information from the DNHR was used to identify pregnancies with a diagnosis of spontaneous abortion, induced abortion, and molar or ectopic pregnancy. The primary outcome was pregnancy loss defined as spontaneous abortion and stillbirth. According to Danish guidelines,[21] spontaneous abortion was defined as pregnancy loss before the 23rd gestational week (22 completed weeks + 0 days), whereas stillbirth was defined as pregnancy loss from the 23rd gestational week and a registration of stillbirth. The secondary outcome was preterm birth, defined as delivery before the 38th week of gestation (37 completed weeks + 0 days) among all pregnancies carried to a live birth. Furthermore, outcome of caesarean section was evaluated in a sub-analysis. The primary exposure was maternal hypothyroidism defined by levels of TSH. In a sub-analysis, results were stratified according to maternal levels of fT4 to identify overt and subclinical thyroid abnormalities. Maternal fT4 was evaluated according to the method- and pregnancy-week specific reference ranges previously established within the cohort.[13] This sub-analysis was only performed among women with TSH above 4.0 mIU/L to ensure enough individuals in the stratified groups.

Categorical variables were described by the number (*n*) and the frequency (%), whereas continuous variables were described by median with a binomial based 95% confidence interval (95% CI). Differences in categorical and continuous variables between groups were assessed by the chi-squared test and Mann−Whitney *U* test, respectively. Logistic regression was used to assess the odds ratio (OR) with 95% CI for spontaneous abortion, preterm birth, and caesarean section in pregnancies exposed to maternal hypothyroidism or elevated levels of thyroid autoantibodies. Results of logistic regression were presented as crude estimates and adjusted for maternal age, parity, origin, and diabetes. Additionally, analyses among pregnancies carried to a live or stillbirth were adjusted for maternal pre-pregnancy BMI and smoking status. Maternal age, BMI, and TSH were included in

the models as continuous variables and all other variables as dichotomous categorical variables. The number of pregnancies with missing data on one or more variables was low (0.5%) and restricted to covariates of maternal origin, BMI, and smoking. Thus, imputation of missing data was not performed. Robust standard errors were added to account for dependency between pregnancies, and analyses were also restricted to the woman's first pregnancy (n = 13,091) in the study period in a sensitivity analysis. Statistical analyses were performed using STATA version 17.0 (StataCorp LLC).

The study was approved by the North Denmark Region Committee on Health Research Ethics (N-20150015) and registered according to the General Data Protection Regulation in the North Denmark Region (2015-34). The ethic committee granted an exemption from the requirement of informed consent.

3 | RESULTS

Altogether 14,744 pregnancies were studied, and outcomes were 13,738 (93.2%) live births, 960 (6.5%) spontaneous abortions, and 46 (0.3%) stillbirths (Figure 1). Maternal hypothyroidism (TSH above 6.0 mIU/L corresponding to the 99.16th percentile in the study cohort) was found in 0.8% (n = 123) of the pregnancies (Table 1), whereas in 10.5% (n = 1548) of the pregnancies the woman was positive for TPO-Ab and in 13.2% (n = 1948) for Tg-Ab (Table 2). In exposed pregnancies maternal age, and parity was higher, and known hypothyroidism as well as diabetes were more frequently seen, whereas smoking was less frequent (Tables 1 and 2). Furthermore, maternal hypothyroidism was more frequent among obese women (Table 1), and non-Danish origin was more frequent with exposure to TPO- and Tg-Ab (Table 2).

TABLE 1 Maternal characteristics by thyroid function exposure groups in the main analysis (TSH > 6.0 mIU/L) and in the sub-analysis (TSH > 4.0 mIU/L and thyroid autoantibody positive)

	TSH ≤ 6.0 mIU/L		TSH > 6.0 mIU/L		TSH ≤ 4.0 mIU/L		TSH > 4.0 mIU/L[a]	
	n	Freq (%)	*n*	Freq (%)	*n*	Freq (%)	*n*	Freq (%)
All pregnancies	**14,621**		**123**		**14,374**		**287**	
Age								
<35 years	12,182	83.3	93	75.6	11,976	83.3	226	78.8
≥35 years	2439	16.7	30	24.4	2398	16.7	61	21.2
Parity								
Nulliparous	6822	46.7	44	35.8	6687	46.5	120	41.8
Multiparous	7799	53.3	79	64.2	7687	53.5	167	58.2
Origin[b]								
Born in Denmark	12,974	88.9	110	89.4	12,753	88.9	260	90.9
Not born in Denmark	1617	11.1	13	10.6	1592	11.1	26	9.1
Diabetes in pregnancy								
No	13,326	91.1	101	82.1	13,104	91.2	249	86.8
Yes	1295	8.9	22	17.9	1270	8.8	38	13.2
Known hypothyroidism in pregnancy								
No	14,499	99.2	99	80.5	14,273	99.3	246	85.7
Yes	122	0.8	24	19.5	101	0.7	41	14.3
All births	**13,669**		**115**		**13,444**		**269**	
Pre-pregnancy BMI[b]								
<30 kg/m^2	11,481	83.9	78	68.4	11,236	83.9	203	76.0
≥30 kg/m^2	2192	16.1	36	31.6	2150	16.1	64	24.0
Smoking in pregnancy[b]								
No	12,021	88.4	104	91.2	11,811	88.3	250	93.6
Yes	1581	11.6	10	8.8	1567	11.7	17	6.4

Abbreviations: BMI, body mass index; freq, frequency.

[a]TSH > 4.0 mIU/L and thyroid autoantibody positive (TPO-Ab > 60 U/ml and/or Tg-Ab > 33 U/ml).

[b]Missing values not included: origin (n = 30), BMI (n = 60), and smoking (n = 68).

TABLE 2 Maternal characteristics by thyroid autoantibody exposure groups

	TPO-Ab negative[a]		TPO-Ab positive[a]		Tg-Ab negative[b]		Tg-Ab positive[b]	
	n	Freq (%)	*n*	Freq (%)	*n*	Freq (%)	*n*	Freq (%)
All pregnancies	**13,196**		**1548**		**12,796**		**1948**	
Age								
<35 years	11,068	83.9	1207	78.0	10,730	83.9	1545	79.3
≥35 years	2128	16.1	341	22.0	2066	16.1	403	20.7
Parity								
Nulliparous	6185	46.9	681	44.0	6027	47.1	839	43.1
Multiparous	7011	53.1	867	56.0	6769	52.9	1109	56.9
Origin[c]								
Born in Denmark	11,739	89.1	1345	87.2	11,419	89.4	1665	85.7
Not born in Denmark	1432	10.9	198	12.8	1352	10.6	278	14.3
Diabetes in pregnancy								
No	12,041	91.3	1386	89.5	11,690	91.4	1737	89.2
Yes	1155	8.7	162	10.5	1106	8.6	211	10.8
Known hypothyroidism in pregnancy								
No	13,155	99.7	1443	93.2	12,743	99.6	1855	95.2
Yes	41	0.3	105	6.8	53	0.4	93	4.8
All births	**12,344**		**1440**		**11,963**		**1821**	
Pre-pregnancy BMI[c]								
<30 kg/m^2	10,317	83.9	1179	82.3	9985	83.8	1511	83.4
≥30 kg/m^2	1975	16.1	253	17.7	1927	16.2	301	16.6
Smoking in pregnancy[c]								
No	10,832	88.2	1293	90.4	10,428	87.6	1697	93.8
Yes	1453	11.8	138	9.6	1479	12.4	112	6.2

Abbreviations: BMI, body mass index; freq, frequency.

[a]Cut-off: 60 U/ml.

[b]Cut-off: 33 U/ml.

[c]Missing values not included: origin (*n* = 30), BMI (*n* = 60), and smoking (*n* = 68).

For the primary outcomes of spontaneous abortion or stillbirth, maternal median TSH in early pregnancy was higher and fT4 lower as compared to live births ($p \leq .03$) (Supporting Information: Table S2). When outcome analyses were performed (Table 3), maternal TSH above 6.0 mIU/L was not a risk factor for spontaneous abortion neither in crude nor in adjusted analyses with an OR of 1.0 (Table 3). Considering pregnancies exposed to maternal TSH above 10 mIU/L (*n* = 40), the frequency of spontaneous abortion was high, and the adjusted OR, although nonsignificant, was 2.0 (Table 3). When restricting to pregnancies with no treated gestational hypothyroidism, the findings were corroborated (Table 3). Notably, maternal hypothyroidism was unidentified and untreated in all pregnancies with an outcome of spontaneous abortion (Table 3). One-third (31.3%) of the women with TSH above 6.0 mIU/L in early pregnancy were diagnosed with hypothyroidism in the years following pregnancy as compared to 0.8% of the women with TSH below 6.0 mIU/L ($p < 0.001$). In all outcomes of stillbirth, maternal TSH was below 6.0 mIU/L. Thyroid autoimmunity defined by TPO-Ab or Tg-Ab positivity was not a risk factor for spontaneous abortion (Table 3) or stillbirth (TPO-Ab: adjusted OR 0.9 (95% CI: 0.3–2.5); Tg-Ab: adjusted OR 0.9 (95% CI: 0.3–2.3)).

For the secondary outcomes of preterm birth (*n* = 743), there was no apparent difference in maternal median TSH, fT4, or the presence of thyroid autoantibodies (Suporting Information: Table S3). However, known maternal hypothyroidism, diabetes and smoking was more frequent among preterm births and similar was the frequency of deliveries by caesarean section (Suporting Information: Table S3). When outcome analyses were performed (Table 4), the frequency of preterm birth was higher among pregnancies exposed to maternal hypothyroidism, especially when maternal TSH was above 10 mIU/L,

TABLE 3 Frequency and odds ratio of spontaneous abortion by maternal level of TSH and thyroid autoantibody status in the early pregnancy among all pregnancies (n = 14,744) and restricted to pregnancies with no treated gestational hypothyroidism (n = 14,598)

	All pregnancies								Pregnancies with no treated gestational hypothyroidism							
	All	Spontaneous abortion							All	Spontaneous abortion						
Exposure	*n*	*n*	Freq (%)[a]	95% CI	OR	95% CI	aOR[b]	95% CI	*n*	*n*	Freq(%)[a]	95% CI	OR	95% CI	aOR[b]	95% CI
TSH ≤ 6.0 mIU/L	14,621	952	6.5	6.1–6.9	Ref.	-	Ref.	-	14,499	946	6.5	6.1–6.9	Ref.	-	Ref.	-
TSH > 6.0 mIU/L	123	8	6.5	2.8–12.4	1.0	0.5–2.0	1.0	0.5–1.9	99	8	8.1	3.5–15.3	1.3	0.6–2.6	1.2	0.6–2.5
TSH ≤ 10 mIU/L	14,704	955	6.5	6.1–6.9	Ref.	-	Ref.	-	14,566	949	6.5	6.1–6.9	Ref.	-	Ref.	-
TSH > 10 mIU/L	40	5	12.5	4.2–26.8	2.1	0.8–5.1	2.0	0.8–5.1	32	5	15.6	5.3–32.8	2.7	1.1–6.7	2.6	1.0–6.9
TPO-Ab negative[c]	13,196	852	6.5	6.0–6.9	Ref.	-	Ref.	-	13,155	851	6.5	6.1–6.9	Ref.	-	Ref.	-
TPO-Ab positive[c]	1548	108	7.0	5.8–8.4	1.1	0.9–1.3	1.0	0.8–1.3	1443	103	7.1	5.9–8.6	1.1	0.9–1.4	1.1	0.9–1.3
Tg-Ab negative[d]	12,796	833	6.5	6.1–7.0	Ref.	-	Ref.	-	12,743	830	6.5	6.1–7.0	Ref.	-	Ref.	-
Tg-Ab positive[d]	1948	127	6.5	5.5–7.7	1.0	0.8–1.2	1.0	0.8–1.2	1855	124	6.7	5.6–7.9	1.0	0.8–1.3	1.0	0.8–1.2

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; freq, frequency; OR, odds ratio; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

[a]Frequency within the exposure group.

[b]Adjusted model included maternal age (continuous variable), and the categorical variables: parity, origin, and diabetes.

[c]Cut-off: 60 U/ml.

[d]Cut-off: 33 U/ml.

TABLE 4 Frequency and odds ratio of preterm birth and caesarean section by the maternal level of TSH and thyroid autoantibody status in the early pregnancy among all pregnancies with an outcome of live birth (n = 13,738)

	Live births														
	All	Preterm birth							Caesarean section						
	n	*n*	Freq (%)[a]	95% CI	OR	95% CI	aOR[b]	95% CI	*n*	Freq (%)[a]	95% CI	OR	95% CI	aOR[b]	95% CI
TSH ≤ 6.0 mIU/L	13,623	734	5.4	5.0–5.8	Ref.	-	Ref.	-	2878	21.1	20.4–21.8	Ref.	-	Ref.	-
TSH > 6.0 mIU/L	115	9	7.8	3.6–14.3	1.5	0.7–3.0	1.5	0.7–2.9	27	23.5	16.1–32.3	1.1	0.7–1.8	0.9	0.6–1.5
TSH ≤ 10 mIU/L	13,703	739	5.4	5.0–5.8	Ref.	-	Ref.	-	2897	21.1	20.5–21.8	Ref.	-	Ref.	-
TSH > 10 mIU/L	35	4	11.4	3.2–26.7	2.3	0.8–6.4	2.7	0.9–7.6	8	22.9	10.4–40.1	1.1	0.5–2.4	1.0	0.5–2.2
TPO-Ab negative[c]	12,302	667	5.4	5.0–5.8	Ref.	-	Ref.	-	2596	21.1	20.4–21.8	Ref.	-	Ref.	-
TPO-Ab positive[c]	1436	76	5.3	4.2–6.6	1.0	0.8–1.2	1.0	0.8–1.3	309	21.5	19.4–23.7	1.0	0.9–1.2	1.0	0.8–1.1
Tg-Ab negative[d]	11,922	652	5.5	5.1–5.9	Ref.	-	Ref.	-	2538	21.3	20.6–22.0	Ref.	-	Ref.	-
Tg-Ab positive[d]	1816	91	5.0	4.1–6.1	0.9	0.7–1.1	0.9	0.7–1.2	367	20.2	18.4–22.1	0.9	0.8–1.1	0.9	0.8–1.0

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; freq, frequency; OR, odds ratio; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

[a]Frequency within the exposure group.

[b]Adjusted model included maternal age and pre-pregnancy BMI (continuous variables), and the categorical variables: parity, origin, diabetes, and smoking.

[c]Cut-off: 60 U/ml.

[d]Cut-off: 33 U/ml.

but the adjusted estimates did not reach statistical significance. Maternal hypothyroidism was often known and treated among pregnancies with an outcome of preterm birth (55.6%). Considering the sub-analysis of all deliveries by caesarean sections ($n = 2905$), maternal hypothyroidism was not a significant risk factor (Table 4). Among pregnant women with previously diagnosed hypothyroidism, the frequency of caesarean section was 25.7% as compared to 21.1% among women with no known thyroid disease ($p = 0.2$). Thyroid autoimmunity defined by TPO-Ab or Tg-Ab positivity showed no association with either preterm birth or caesarean section (Table 4).

The sub-analysis using a lower cut-off of TSH (4.0 mIU/L) in combination with thyroid antibody positivity showed no association between this exposure and outcomes of spontaneous abortion, preterm birth, or caesarean section (Table 5). Similarly, no significant associations were seen when stratified by overt and subclinical abnormalities according to maternal level of fT4 (Table 5).

Sensitivity analyses showed consistent findings when restricting analyses to the first pregnancy in the study period (Supporting Information: Table S4). Furthermore, the risk estimates were similar when adjusting analyses of maternal thyroid autoimmunity for the level of maternal TSH (Supporting Information: Table S5), and when a cut-off of 60 U/ml for Tg-Ab was used for identification of Tg-Ab positive pregnant women (Supporting Information: Table S6).

4 | DISCUSSION

In a large cohort of nearly 15,000 pregnancies with retrospective biochemical assessment of maternal thyroid function parameters, 0.8% of the women had early pregnancy TSH above 6.0 mIU/L, whereas 0.3% had TSH above 10 mIU/L. Considering maternal hypothyroidism in early pregnancy in relation to outcomes of pregnancy, results of the present study substantiated a high frequency of spontaneous abortion and preterm birth when maternal hypothyroidism was marked with TSH was above 10 mIU/L. On the other hand, maternal hypothyroidism defined by a TSH cut-off of 6.0 mIU/L and the presence of thyroid autoantibodies per se did not increase the risk of adverse pregnancy outcomes.

Hypothyroidism in pregnant women has long been a matter of clinical and scientific concern. Historically, concerns were raised from the description of cretinism in areas with severe iodine deficiency and a causal role of maternal thyroid function was established.[6] Since then, the clinical recommendations on diagnosis and treatment of maternal overt hypothyroidism are indisputable, however, universal screening for overt hypothyroidism is hitherto not implemented.[5] In contrast, a substantial focus on subclinical hypothyroidism and isolated low fT4 has emerged.[6] Considering such smaller abnormalities in maternal thyroid function, results of observational studies are divergent and in contrast to large RCTs.[6] The discrepancy and the lack of treatment effect in the RCTs is debated, however, with a predominant focus on the timing of intervention (treatment) and on the assessment of outcomes in the child (e.g., age at intelligence testing).[5,22,23] One may also speculate on the definition of

TABLE 5 Frequency and odds ratio of outcomes of spontaneous abortion, preterm birth, and caesarean section when stratified by maternal TSH as well as overt and subclinical abnormalities in early pregnancy

	All pregnancies						Live births									
	All	Spontaneous abortion					All	Preterm birth				Caesarean section				
	n	*n*	Freq (%)[a]	95% CI	aOR[b]	95% CI	*n*	*n*	Freq(%)[a]	95% CI	aOR[c]	95% CI	*n*	Freq(%)[a]	95% CI	aOR[c]	95% CI
TSH ≤ 4.0 mIU/L	14,374	930	6.5	6.1–6.9	Ref.	-	13,399	720	5.4	5.0–5.8	Ref.	-	2828	21.1	20.4–21.8	Ref.	-
TSH > 4.0 mIU/L[d]	287	18	6.3	3.8–9.7	0.9	0.6–1.5	269	17	6.3	3.7–9.9	1.2	0.7–2.0	60	22.3	17.5–27.8	1.0	0.7–1.3
Overt[e]	89	9	10.1	4.7–18.3	1.4	0.7–2.9	80	4	5.0	1.4–12.3	1.0	0.3–2.7	18	22.5	13.9–33.2	1.0	0.6-1.6
Subclinical[f]	198	9	4.5	2.1–8.5	0.7	0.3–1.3	189	13	6.9	3.7–11.5	1.3	0.8–2.4	42	22.2	16.5–28.8	1.0	0.7–1.4

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; freq, frequency; TSH, thyroid stimulating hormone.

[a]Frequency within the exposure group.

[b]Adjusted model included maternal age (continuous variable), and the categorical variables: parity, origin, and diabetes.

[c]Adjusted model included maternal age and pre-pregnancy BMI (continuous variables), and the categorical variables: parity, origin, diabetes and smoking.

[d]TSH > 4.0 mIU/L and thyroid autoantibody positive (TPO-Ab > 60 U/ml and/or Tg-Ab > 33 U/ml).

[e]Abnormal TSH and free T4 below the pregnancy week and method-specific lower reference limit.

[f]Abnormal TSH irrespective of maternal free T4 in early pregnancy.

exposure.[6,12] Thus, the identification of subclinical hypothyroidism and isolated low fT4 varies considerably between studies regarding the biochemical methods and the definition of abnormal thyroid function.[24,25] Furthermore, reports in pregnant and nonpregnant populations have raised a concern about the indirect methods for assessment of free thyroid hormone concentrations.[24,26–28]

We recently highlighted a focus on the persistency of biochemical abnormalities in early pregnant women.[12] In most studies, the definition of exposure to abnormal maternal thyroid function and randomisation to treatment is made from a single blood sample. However, substantial biological variation occurs in thyroid function tests,[29,30] and in a large cohort of Danish pregnant women, we found that maternal TSH in early pregnancy should be above 6.0 mIU/L to ensure that the classification of hypothyroidism was consistent in a repeated blood sample.[12] These findings led us to speculate whether the inclusion of non-persistent thyroid function abnormalities may have contributed to the divergent literature regarding subclinical hypothyroidism and isolated low fT4 in maternal thyroid function.[12] Following these lines of thought, it was an a priori decision to identify pregnancies exposed to persistent maternal hypothyroidism in the present study using the chosen TSH cut-offs. Our study design with linkage between the biochemical measurements of maternal thyroid function in early pregnancy blood samples and information in nationwide health registers provided unique opportunities to identify pregnancies exposed to unidentified maternal hypothyroidism since the women were followed for later onset of thyroid disease. This follow-up substantiated the cut-off of 6.0 mIU/L to identify persistent hypothyroidism in early pregnancy since the frequency of later diagnosed hypothyroidism was above 30% as compared to less than 1% among pregnancies with TSH below 6.0 mIU/L. Our previous investigation raised a concern about non-persistent thyroid function abnormalities when using a TSH cut-off lower than 6.0 mIU/L, particularly among thyroid autoantibody negative pregnant women.[12] In women of reproductive age, hypothyroidism is predominantly of autoimmune origin,[14] and we speculate on the underlying mechanisms of slightly elevated TSH in thyroid autoantibody negative women and whether this relates to actual thyroid disease.[6,9] Thus, when considering a lower TSH cut-off of 4.0 mIU/L in the present study we included the criteria of TPO- and/or Tg-Ab positivity to identify persistent abnormalities, and results corroborated the main findings using af TSH cut-off of 6.0 mIU/L. Based on our previous investigations within the cohort and other recent reports,[24,31] we did not study associations with isolated abnormalities in maternal fT4. Concern has been raised about the validity of free thyroid hormone measurements in pregnancy using automatic immunoassays (indirect methods) and thereby the definition of exposure,[6] and our focus was on marked and persistent autoimmune hypothyroidism in early pregnant women.

Criteria for the definition of overt hypothyroidism in pregnant women differs across studies.[9,25] In a large meta-analysis of 43 studies with data on overt hypothyroidism, the prevalence ranged from 0% to 13.1% and the overall pooled prevalence of overt hypothyroidism among studies using population-based trimester-specific reference ranges was 0.5%.[25] Considering unidentified overt maternal hypothyroidism that would be detected by universal screening, the prevalence is estimated to be around 0.3%, but with study differences regarding the definition.[9] When a TSH cut-off of 10 mIU/L was applied in our cohort of 14,744 pregnancies, we found 32 cases of undetected and untreated maternal hypothyroidism. Haddow et al. similarly identified pregnant women with untreated hypothyroidism and found 48 cases among 25,216 pregnancies.[7] From these figures it appears that even if the study cohort is large, the expected prevalence of undetected marked maternal hypothyroidism with TSH above 10 mIU/L is less than 0.5% and the number of exposed pregnancies will be small. It was a fact, also in our study, that numbers were small in some of the analyses for example for the rare outcome of stillbirth. However, exposure to persistent and marked hypothyroidism is clinically important and broadening of the exposure definition to increase numbers in the exposed groups may water down the results, thus, it is in our view not an appropriate method. Individual participant-data meta-analyses with combined assessment of different pregnancy cohorts will increase the number of exposed individuals. However, such recent large studies did not report results of overt hypothyroidism and pregnancy outcomes.[32–34]

Our findings in the present study indicate adverse outcomes of pregnancy when maternal TSH is above 10 mIU/L and either undetected and untreated or known and inadequately treated. Notably, the association observed for spontaneous abortion strengthen when considering only undetected maternal hypothyroidism which may suggest that correction of the hypothyroidism could play a role in modifying the risk. This specific association with marked untreated maternal hypothyroidism is in line with previous investigations on child neurodevelopmental outcomes. Haddow et al. found that untreated maternal hypothyroidism associated with lower intelligence quotient (IQ) in the child, whereas IQ was normal when maternal hypothyroidism had been treated.[7] Andersen et al. found that undetected maternal TSH above 10 mIU/L in early pregnancy associated with lower IQ in the offspring, whereas child IQ was normal when maternal TSH was in the range from 5 to 10 mIU/L.[8] Considering outcomes of pregnancy loss, Taylor et al. evaluated the risk of spontaneous abortion among LT4 treated pregnant women, and TSH above 10 mIU/L revealed the highest risk of spontaneous abortion pointing towards a concern of inadequately treated maternal hypothyroidism.[35] Stillbirth is a serious, but rare, outcome of pregnancy and large cohorts are needed to study the outcome when the exposure is similarly rare. Allan et al.[36] studied 9403 pregnant women in the second trimester and concluded that maternal TSH above 6.0 mIU/L was a risk factor for foetal death, however, their stratified analyses on levels of maternal TSH reveal that the highest frequency of foetal death was seen when maternal TSH was above 10 mIU/L. In addition to pregnancy loss, we studied the risk of preterm birth, and our results for this outcome of pregnancy similarly pointed towards a risk associated with maternal TSH above 10 mIU/L. We additionally evaluated the outcome of caesarean section and found no association between maternal hypothyroidism and outcomes of caesarean section neither when

maternal hypothyroidism was known (pre-existing) nor when it was defined from biochemical measurement in early pregnancy. Previous investigations reported that pre-exiting maternal hypothyroidism increased the risk of caesarean section and suggested that this increased risk may be due to associated pregnancy complication.[37,38] However, indications for caesarean section are heterogenous and deemed important to extend the findings on this specific outcome in women with hypothyroidism and to investigate the association with other adverse outcomes of pregnancy.

We studied a large and unselected cohort of Danish pregnant women, however, the exposure investigated was relatively rare making the number of exposed cases limited in some of the analyses. Thus, the sample size may have influenced the findings and did not allow for stratified analyses by maternal TSH in the range from 4 to 10 mIU/L. We a priori defined exposure based on our previous findings within the cohort and with the aim of identifying persistent hypothyroidism in early pregnant women. Considering assay differences, the cut-off investigated may not directly apply to other TSH methods. The rate of participation in the prenatal screening programme for chromosomal anomalies is high[39] and selection bias attributable to lack of participation is considered low. Women with known thyroid disease in pregnancy and outcomes of the pregnancy were identified from the Danish nationwide registers and the validity is considered high.[17,18] It should be acknowledged that only clinically recognized pregnancy outcomes were studied and a woman was only included if a blood sample had been drawn in early pregnancy as part of the prenatal screening programme, thus, our study population did not include pregnancies with very early losses. The biochemical analyses were performed retrospectively and not related to any clinical practice related to the pregnancy. The samples were stored until biochemical analyses, and thyroid function parameters and thyroid autoantibodies are considered stable for long-term frozen storage.[40]

5 | CONCLUSION

This large study focused on persistent maternal hypothyroidism and adverse outcomes of pregnancy. The frequency of spontaneous abortion and preterm birth was high when maternal hypothyroidism was overt and marked with TSH was above 10 mIU/L in an early pregnancy blood sample. In contrast, thyroid autoimmunity per se was not a risk factor for adverse outcomes of pregnancy. Results emphasize a clinical and scientific focus on the detection and treatment of marked overt hypothyroidism in pregnancy and substantiate that the severity of maternal hypothyroidism as reflected by the level of TSH in early pregnancy is important. The findings inform the debate on universal screening to detect marked maternal hypothyroidism in pregnancy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data cannot be shared due to regulatory restrictions that apply to the availability of data generated and analysed during this study to preserve patient confidentiality and according to the GDPR regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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