Pregnancy outcomes are not altered by variation in thyroid function within the normal range in women free of thyroid disease

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Abstract

Objective: In the recently revised guidelines on the management of thyroid dysfunction during pregnancy, treatment with thyroid hormone (LT4) is not recommended in women without thyroid autoimmunity (TAI) and TSH levels in the range 2.5–4.0 mIU/L, and in a recent study in that particular group of pregnant women, more complications were observed when a treatment with LT4 was given. The objective of the study was therefore to investigate whether variation in thyroid function within the normal (non-pregnant) range in women free of thyroid disease was associated with altered pregnancy outcomes?

Design: Cross-sectional data analysis of 1321 pregnant women nested within an ongoing prospective collection of pregnant women's data in a single centre in Brussels, Belgium.

Methods: Thyroid peroxidase antibodies (TPO-abs), thyroid-stimulating hormone (TSH), free T4 (FT4) and ferritin levels were measured and baseline characteristics were recorded. Women taking LT4, with TAI and thyroid function outside the normal non-pregnant range were excluded. Pregnancy outcomes and baseline characteristics were correlated with all TSH and FT4 levels within the normal range and compared between two groups (TSH cut-off < and ≥2.5 mIU/L).

Results: Tobacco use was associated with higher serum TSH levels (OR: 1.38; CI 95%: 1.08–1.74; $P=0.009$). FT4 levels were inversely correlated with age and BMI ($\rho=-0.096$ and -0.089 ; $P<0.001$ and 0.001 respectively) and positively correlated with ferritin levels ($\rho=0.097$; $P<0.001$). Postpartum haemorrhage (>500 mL) was inversely associated with serum FT4 levels (OR: 0.35; CI 95%: 0.13–0.96; $P=0.040$). Also 10% of women free of thyroid disease had serum TSH levels ≥2.5 mIU/L.

Conclusions: Variation in thyroid function during the first trimester within the normal (non-pregnant) range in women free of thyroid disease was not associated with altered pregnancy outcomes. These results add evidence to the recommendation against LT4 treatment in pregnant women with high normal TSH levels and without TPO antibodies.

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Introduction

The impact of subclinical thyroid dysfunction (SCH) and/or thyroid autoimmunity (TAI) on pregnancy outcomes such as miscarriage, preterm delivery, low birth

weight, pre-eclampsia and gestational diabetes remains controversial (1, 2, 3). One of the reasons for that may be the heterogeneity in the definition of SCH and how TAI is

detected. In older studies, as cut-off, the upper limit of the assay of non-pregnant women was used (4.0–5.0 mIU/L) and since 2012, the Endocrine Society proposed a fixed cut-off of 2.5 mIU/L, when no institutional one was available (4). In the recent guidelines of the American Thyroid Association (ATA), it is proposed to decrease the upper limit of the assay for non-pregnant women by 0.5 mIU/L when no institutional cut-off is available (in daily practice often ~4.0 mIU/L), and treatment with thyroid hormone (LT4) is not recommended in women without thyroid autoimmunity and TSH levels in the range 2.5–4.0 mIU/L (5). In a recent study, it has been shown that treatment with LT4 in pregnant women with serum TSH levels in the range 2.5–5.0 mIU/L led to a higher prevalence of pre-eclampsia and preterm deliveries (5, 6). In another study in pregnant women with SCH and TAI, it was shown that in the group with TSH levels between 2.5 and 5.0 mIU/L, LT4 did not decrease the rate of preterm deliveries while it was the case when TSH was >5.0 mIU/L (7). In a study by Negro and coworkers, LT4 did not decrease the miscarriage rate in pregnant women with TAI and TSH levels <2.5 mIU/L as compared with placebo (8). In contrast, in another study, a lower miscarriage rate was observed in pregnant women with TAI treated with LT4 and aiming to obtain TSH levels <2.5 mIU/L as compared with the group in which the TSH target was ≥ 2.5 mIU/L (9). In the study by Benhadi and coworkers, in pregnant women without overt thyroid dysfunction, the risk of child loss decreased with lower levels of maternal TSH (10). Finally, Negro and coworkers reported a lower first trimester miscarriage rate in pregnant women without TAI and TSH levels <2.5 mIU/L compared with that in women with TSH levels between 2.5 and 5.0 mIU/L (11).

In order to avoid conflicting results between studies, due to the use of different TSH cut-offs; an interesting approach is to investigate associations between an outcome and TSH in a linear relationship (12). In a recent study in China, preconception high normal TSH levels within the non-pregnant normal range (2.5–4.3 mIU/L) were associated with an increased risk of adverse pregnancy outcomes, but TSH was measured 6 months before conception and no information on the presence of TAI was available (13). The presence of TAI is known to be an independent risk factor associated with pregnancy complications (1, 14).

Therefore and in order to investigate only the impact of serum TSH levels within the normal range, we excluded women with TSH levels outside the normal range, with TAI and treated with LT4.

The aims of the study were to investigate: (i) whether variation in serum TSH/FT4 levels within the normal (non-pregnant) range in women free of thyroid disease were associated with altered pregnancy outcomes, (ii) whether baseline characteristics and pregnancy outcome data were different between women with serum TSH levels < and ≥ 2.5 mIU/L and (iii) what the distribution of serum TSH levels were in women free of thyroid disease.

Subjects and methods

Overall study design

The obstetrical clinic of the CHU St-Pierre is a downtown public university (tertiary referral) maternity in Brussels, Belgium. In our centre, the first antenatal consultation is systematically completed with a biological analysis including TSH, free T4 (FT4), thyroid peroxidase antibodies (TPO-abs) and ferritin measurement and obstetrical data (history and follow-up) are noted in a specific database (Cognos).

We report here on data of a cross-sectional analysis of pregnant women (period 2013–2014) that was nested within the ongoing prospective collection of women's obstetrical parameters and biological data. Finally and after exclusion of twin and assisted pregnancies ($n=98$), women with TAI ($n=122$), increased and decreased serum TSH levels ($n=144$) and started on LT4 ($n=92$), 1321 women were included for comparison/correlation of thyroid parameters with baseline characteristics and pregnancy outcome data. For the limits of serum TSH levels, the non-pregnant values were used. The upper limit of our assay is 4.0 mIU/L for non-pregnant women, a cut-off that is in line with the proposal of the recent ATA guidelines, in which it is mentioned 'to decrease the upper limit of the assay for non-pregnant women by 0.5 mIU/L when no institutional cut-off is available and that for the typical patient in early pregnancy, this corresponds to a TSH upper reference limit of 4.0 mIU/L' (5). For the lower limit, we used 0.3 mIU/L, since we also wanted to exclude women with suppressed TSH levels.

In Fig. 1, we illustrate more in detail the inclusion/exclusion criteria with a flowchart.

For the pregnancy outcomes, only data were recorded from women who had successful ongoing pregnancies. Furthermore, miscarriage was not taken into account in our study, since it is a heterogeneous outcome, easily underestimated (including biochemical and clinical miscarriage), associated with many other variables besides

Figure 1

Flowchart illustrating the selection of the finally included women in the study.

TSH (15) and finally, it is strongly associated with the presence of TAI than with thyroid dysfunction (1, 14).

Gestational age determination was based on ultrasound findings. Intrauterine growth restriction (IUGR) was defined as a baby <10th percentile weight for gestational age and gender (16). Gestational diabetes (GDM) was present when fasting glycaemia was ≥ 92 mg/dL or when during the second trimester, women had a positive 75 g oral glucose tolerance test (OGTT); i.e. 1 h post prandial glycaemia (≥ 180 mg/dL) or at 2 h ≥ 153 mg/dL (17). Pre-eclampsia was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg and with a proteinuria > 0.3 g/24 h after 20 weeks of amenorrhea (18).

In the two study groups (TSH < and ≥ 2.5 mIU/L), parameters were expressed as continuous values for TSH, FT4, ferritin, BMI, age, parity, gestational age, first prenatal visit, pregnancy length, birth weight and postpartum haemorrhage. As categorical data were expressed: iron deficiency (ferritin: < 15 μ g/L), obesity (BMI: ≥ 30 kg/m²), older age (≥ 35 years), tobacco use (yes/no), high parity (≥ 3 children), history of ≥ 2 miscarriages, GDM, preeclampsia,

IUGR, preterm birth (<37 weeks), low birth weight (<2.5 kg) and important postpartum haemorrhage (≥ 500 mL).

The study was approved by the institutional review board (AK/15-11-114/4568).

Serum assay

All provisions were implemented by the laboratory of hormonology of our institution. Serum TSH, FT4 and TPO-abs levels were measured using the Chemiluminescence Centaur XP Siemens Immunoanalyzer. The (non-pregnant) reference values were 0.3–4.0 mIU/L, 13.64 ± 1.80 pmol/L (0.8–2.0 ng/dL) and < 60 kIU/L for TSH, FT4 and TPO-Abs respectively. Ferritin reference values are 15–300 μ g/L. The total imprecision CVs were 6.9, 4.2, 7.6 and 3.7% for TSH, FT4, TPO-abs and ferritin respectively. For conversion of FT4, 1 ng/dL = 12.9 pmol/L.

Statistical analysis

Data were stored in a Microsoft Excel database and for the pregnancy outcomes in an adapted database

Figure 2

Histogram of frequency distribution of serum TSH levels during the first trimester.

(Cognos). Statistical analyses were performed using Stata 11.2 software (Lakeway Drive, Texas, USA). Continuous data were expressed as median (IQR) when not normally distributed and as mean $\pm$ s.d. for normally distributed data. Categorical data were presented as number (percentage) of cases. Differences between groups (TSH < and ≥ 2.5 mIU/L) were analyzed by Fisher's exact tests for categorical data and by the Mann-Whitney *U* test for continuous data. Correlations between continuous variables were quantified using Spearman's ρ correlation coefficient.

The impact of the independent variables (with TSH and FT4 as continuous data) on the dependent categorical variables (demographic and pregnancy outcome data) were explored by a logistic regression and when an association was present in the univariable analysis, this was then further corrected for confounders in a multivariable model for the pregnancy outcomes (main aim of the study).

All statistical tests were considered significant whenever $P < 0.05$.

Results

Figure 2 shows a histogram of frequency distribution of serum TSH levels during the first trimester.

Ninety percent of women had TSH levels <2.5 IU/L and 10% between 2.5 and 4.0 IU/L. Among women with TSH levels ≥ 2.5 IU/L, 90% had TSH levels <3.25 IU/L.

Table 1 shows thyroid function, iron status and demographic characteristics in all women and according to the thyroid function status.

Serum TSH and FT4 levels from all women included were 1.47 ± 0.73 IU/L and 13.64 ± 1.80 pmol/L respectively. By definition, mean serum TSH levels were lower in the TSH <2.5 group as compared with those in the TSH ≥ 2.5 group (1.31 ± 0.55 vs 2.98 ± 0.40 ; $P < 0.001$).

Mean age was higher in the TSH <2.5 group as compared to that in the TSH ≥ 2.5 group (30.0 ± 5.8 vs 28.73 ± 4.9 years; $P = 0.001$), but when age was expressed as 'older age'; i.e. ≥ 35 years, there was no difference between the groups. Iron status, BMI levels, the prevalence of obesity and smokers were comparable between both study groups.

Table 2 shows obstetric and pregnancy outcome data in all women and according to the thyroid function status.

Parity was higher in TSH <2.5 group as compared with that in the TSH ≥ 2.5 group (median (IQR), 1 (0–2) vs 1 (0–1); $P = 0.001$); but when expressed as 'high parity' (≥ 3 births), no difference was present (13.4% in the TSH <2.5 and 9.1% in the TSH ≥ 2.5 group; $P = 0.165$).

All other outcome measures were comparable between both study groups.

Table 3 shows the Spearman's ρ of the correlations between serum TSH, FT4 levels and iron levels, demographic and pregnancy outcome data.

Serum TSH levels were inversely correlated with FT4 ($r = -0.150$; $P < 0.001$) and age ($r = -0.066$; $P = 0.017$).

Table 1 Baseline and demographic characteristics in all patients and according to the thyroid function status.

Characteristics	TSH (mIU/L)			P level
	0.3–4.0	<2.5	≥ 2.5	
Number of patients (n (%))	1321 (100)	1189 (90)	132 (10)	
TSH (mIU/L, mean $\pm$ s.d.)	1.47 ± 0.73	1.31 ± 0.55	2.98 ± 0.40	<0.001
FT4 (pmol/L, mean $\pm$ s.d.)	13.64 ± 1.80	13.64 ± 1.80	13.13 ± 1.67	0.001
Age (years, mean $\pm$ s.d.)	29.9 ± 5.8	30.0 ± 5.8	28.7 ± 4.9	0.014
Older age* (n (%))	306 (23)	283 (24)	23 (17)	0.099
BMI (kg/m ² , mean $\pm$ s.d.)	25.8 ± 4.9	25.8 ± 4.9	25.7 ± 4.4	0.816
Obesity** (n (%))	221 (17)	202 (17)	19 (14)	0.700
Ferritin (μ g/L, median (IQR))	20 (12–36)	20 (12–37)	17 (11–34)	0.193
Iron deficiency†, n (%)	463 (35)	410 (34)	53 (40)	0.195
Smoking (yes, n (%))	126 (9.5)	108 (9.1)	18 (13.4)	0.091

*Age ≥ 35 years; **BMI ≥ 30 kg/m²; †ferritin <15 μ g/L.

Table 2 Obstetric and pregnancy outcome data in all women and according to the thyroid function status.

	Serum TSH (mIU/L)		P level
	0.3–4.0	≥2.5	
No. of patients, n (%)	1321 (100)	1189 (90)	132 (10)
Parity (n; median (IQR))	1 (0–2)	1 (0–2)	1 (0–1)
High parity rate (≥3, n (%))	171 (13.0)	159 (13.4)	12 (9.1)
First trimester MC (>2, n (%))	28 (2.1)	27 (2.3)	1 (0.8)
First prenatal visit (weeks)	11 (9–14)	11 (9–14)	11 (9–16)
First prenatal visit ≥12 weeks, n (%)	539 (41)	476 (40)	63 (47)
GDM, n (%)	245 (19)	220 (19)	25 (19)
Pre-eclampsia, n (%)	70 (5.3)	63 (5.3)	7 (5.3)
IUGR, n (%)	38 (2.9)	35 (2.9)	3 (2.3)
Pregnancy length (weeks, median (IQR))	39.6 (38.5–40.5)	39.6 (38.5–40.5)	39.6 (39.0–40.5)
Preterm birth (<37 weeks, n (%))	67 (5.1)	58 (4.8)	9 (6.8)
Birth weight (kg)	3.3±0.5	3.3±0.5	3.3±0.6
Low birth weight (<2.5kg, n (%))	66 (5.0)	58 (4.8)	9 (6.8)
Postpartum haemorrhage (mL, median (IQR))	300 (200–448)	300 (200–400)	300 (250–500)
Postpartum haemorrhage (≥500mL, n (%))	284 (22)	251 (21)	33 (25)

GDM, gestational diabetes mellitus; IUGR, intra-uterine growth retardation.

Table 3 Spearman's ρ coefficients of correlations between serum TSH, FT4 levels and continuous demographic and pregnancy outcome data.

	ρ	P
TSH (mIU/L) levels correlated with		
FT4 (pmol/L)	−0.150	<0.001
Age (years)	−0.066	0.017
BMI (kg/m ²)	−0.011	0.703
Ferritin (μg/L)	−0.053	0.054
First prenatal visit (weeks)	0.119	<0.001
History of miscarriages (n)	0.005	0.857
Pregnancy length (weeks)	0.016	0.571
Birth weight (kg)	−0.003	0.903
Postpartum haemorrhage (mL)	−0.017	0.547
FT4 (pmol/L) levels correlated with		
TSH (mIU/L)	−0.150	<0.001
Age (years)	−0.096	<0.001
BMI (kg/m ²)	−0.089	0.001
Ferritin (μg/L)	0.097	<0.001
First prenatal visit (weeks)	−0.169	<0.001
History of miscarriages (n)	−0.010	0.714
Pregnancy length (weeks)	−0.001	0.966
Birth weight (kg)	−0.040	0.181
Postpartum haemorrhage (mL)	−0.070	0.012

A positive correlation was present with the timing of the first prenatal visit ($r=0.119$; $P<0.001$). Serum FT4 levels were inversely correlated with age ($r=-0.096$; $P<0.001$), BMI ($r=-0.089$; $P=0.001$), the timing of the first prenatal visit ($r=-0.169$; $P<0.001$) and postpartum haemorrhage ($r=-0.070$; $P=0.012$). A positive correlation was present with ferritin levels ($r=0.097$; $P<0.001$).

Table 4 shows the results of the univariable logistic regression analysis with iron, demographic and pregnancy outcome data as categorical dependent variables and serum TSH, FT4 levels as continuous independent variables.

Tobacco use was associated with higher serum TSH levels (OR: 1.38 (95% CI: 1.08–1.74); $P=0.009$). A first prenatal visit >12 weeks of gestation was also associated with higher serum TSH levels (OR: 1.35 (95% CI: 1.15–1.56); $P<0.001$). No other pregnancy outcomes were associated with serum TSH levels. A first prenatal visit >12 weeks of gestation (OR: 0.38 (95% CI: 0.17–0.89); $P=0.025$) and post-partum haemorrhage >500mL (OR: 0.35 (95% CI: 0.13–0.96); $P=0.040$) were associated with lower serum FT4 levels. After correction in a multivariable model for other variables associated with post-partum haemorrhage >500mL (IUGR, ID, tobacco use, low birth weight, obesity and preterm birth); the significance with FT4 persisted (OR: 0.33 (95% CI: 0.11–0.98); $P=0.045$). The absence of associations between serum TSH and FT4 levels and pregnancy outcomes in the univariable model did not change in the multivariable model (data not shown).

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Table 4 Univariable logistic regression analysis with iron, demographic and pregnancy outcome data as categorical dependent variables and serum TSH, FT4 levels as continuous independent variables.

	TSH		FT4	
	OR (95% CI)	P	OR (95% CI)	P
Demographic/obstetric data				
Older maternal age (≥ 35 years)	0.89 (0.74–1.06)	0.201	0.84 (0.32–2.19)	0.733
Obesity (BMI ≥ 30 kg/m ²)	0.98 (0.80–1.20)	0.882	1.18 (0.40–3.41)	0.765
Iron deficiency (ferritin < 15 µg/L)	1.13 (0.96–1.32)	0.122	0.76 (0.32–1.77)	0.533
Tobacco use	1.38 (1.08–1.74)	0.009	1.32 (0.34–5.07)	0.685
High parity rate (≥ 3)	0.84 (0.66–1.05)	0.119	0.46 (0.13–1.55)	0.210
History of miscarriages (≥ 2)	0.89 (0.52–1.51)	0.679	6.93 (0.62–76.73)	0.136
First prenatal visit (≥ 12 weeks)	1.35 (1.15–1.56)	<0.001	0.38 (0.17–0.89)	0.025
Pregnancy outcome data				
Gestational diabetes	1.13 (0.94–1.36)	0.188	0.46 (0.16–1.32)	0.147
Pre-eclampsia	1.01 (0.72–1.40)	0.944	1.17 (0.19–6.88)	0.861
IUGR	0.68 (0.42–1.12)	0.119	1.20 (0.11–12.85)	0.880
Preterm birth (< 37 weeks)	1.05 (0.75–1.46)	0.762	0.89 (0.14–5.53)	0.900
Low birth weight (< 2.5 kg)	0.93 (0.66–1.31)	0.700	1.11 (0.18–6.89)	0.910
Postpartum haemorrhage (≥ 500 mL)	0.94 (0.78–1.12)	0.486	0.35 (0.13–0.96)	0.040*

Demographic and pregnancy outcomes data=categorical dependent data (Y); TSH and FT4 levels=continuous independent data (X).

* $P=0.045$ after correction for IUGR, ID, tobacco use, low birth weight, obesity and preterm birth.

IUGR, intra-uterine growth restriction; OR, odds ratio.

Discussion

The presence of TAI is the most important cause of high serum TSH levels and SCH, and therefore, we excluded in this study women with TAI in order to investigate the impact of variation on serum TSH levels within the normal (non-pregnant) range on pregnancy outcomes (19, 20). Serum TSH levels were strongly correlated with FT4 levels, conforming the reliability of FT4 during the first trimester of pregnancy, as it has also been shown in the study by Korevaar and coworkers, in which pregnancy outcomes were better correlated with FT4 than with total T4 (21). Due to the exclusion of women with TAI, a left-shifted TSH distribution was observed with 90% of women having TSH levels < 2.5 mIU/L. Despite the absence of positive TPO-abs, 10% of women had serum TSH levels in the upper range of normality (≥ 2.5 mIU/L) and although the precise reasons for that remain speculative, some hypotheses can be made based on our results. In two studies, performed in the same area in Brussels as our study was, it was shown that thyroglobulin antibodies may be present, even in the absence of TPO-abs (22, 23). In that by Unuane and coworkers, it was shown that women with Tg-abs had higher mean serum TSH levels as compared with women without antibodies or with TPO-abs (22). We did not measure Tg-abs in our study, since for reimbursement reasons in the Belgian social security system, it is not allowed to measure both antibodies at the same day. The importance of Tg-abs in some patients is also noticed now in the recent ATA

guidelines, but at the same time, it is mentioned that the systematic measurement is not recommended (5). Besides the presence of Tg-abs, iron deficiency has also been associated with higher serum TSH levels and SCH (independently from that of TAI) in two studies (24, 25). In the present study, there was also a trend for a higher prevalence of iron deficiency in women with higher serum TSH levels, and (low) FT4 and iron (deficiency) were weakly correlated. Obesity is known to be associated with higher serum TSH levels, probably mediated via a leptin pathway (26). In our study, an inverse correlation between BMI and FT4 levels was present. One theory suggests an increased deiodinase activity that leads to a high conversion rate of T4 to T3 (26). Also in another study higher BMI levels (> 25 kg/m²) were associated with higher prevalence of hypothyroidism during pregnancy, a finding we did not confirm (27). Smoking and smoking cessation have been associated with a lower and a higher prevalence of thyroid antibodies respectively (28). Besides the impact on the immune system, smoking has also been associated with a dose-dependent decrease of serum TSH, induced by activation of the sympathetic nervous system (increasing FT3 and FT4 levels). However, in iodine-deficient regions (such as Belgium with a median (IQR) urinary iodine of 117 (70–189) µg/L in pregnant women), slightly greater thyroid sizes were observed caused by competitive inhibition of thyroidal iodide uptake by thiocyanate (28, 29). The prevalence of smokers was comparable between women with a low and high normal TSH levels, but smoking was associated with higher serum TSH levels. We cannot

provide the precise underlying mechanisms explaining this association because we excluded women with TAI and did not report on smoking cessation. Age was slightly inversely correlated with serum TSH and strongly with FT4 levels. In literature, older age has been associated with more thyroid dysfunction in one study, but in two others, there was no impact of older age on serum TSH levels or the prevalence of SCH (19, 27, 30). In our study, age was inversely correlated with serum TSH and especially with FT4 levels, but no associations between age and important pregnancy outcomes were present. Parity was inversely correlated with serum TSH and although causality cannot be proven, women with lower TSH levels might have become more easily pregnant. However, when parity was defined as high parity (≥ 3), no association with TSH/FT4 was present, in analogy with a large Danish cohort study (27). We did not measure hCG levels in our study, although it is known to be an important confounding factor in the interpretation of serum TSH levels, especially during the first trimester (19, 31). As surrogate marker of hCG, we included the timing of the first prenatal visit and in analogy with the peak hCG levels that decrease after the first trimester of pregnancy, a first prenatal visit after the 12th week of gestation was correlated with higher serum TSH and lower FT4 levels.

The prevalence of GDM was comparable between women with high and low normal TSH levels and no correlations with TSH and FT4 levels were present. Also in a recent Chinese study, GDM was only associated with SCH and TAI, but not with TSH/FT4 levels (32). The prevalence of pre-eclampsia in our cohort (5.4%) was in the range obtained in a large study cohort, with an overall incidence of hypertensive disorders of 6.2, 8.5 and 10.9% in women with subclinical hyperthyroidism, euthyroid women and SCH, respectively (33). In a study, higher FT4 levels in early pregnancy were associated with higher vascular resistance in the second and third trimesters in both the maternal and foetal placental compartment and that might have explained the association between FT4 and pre-eclampsia (34). In our study, FT4 levels and pre-eclampsia were not associated what in part might have been due to the exclusion of women with suppressed serum TSH levels. Both SCH and hyperthyroidism have been associated with IUGR, maybe due to the imbalance in thyroid hormones that are needed for normal foetal development (35, 36) and furthermore, might an impact of thyroid hormones on the placental haemodynamics have played a role in the development of IUGR (34). In our study, no association was observed between IUGR and TSH/FT4 levels. Preterm delivery has been associated with

the presence of SCH due to TAI, but not with SCH as such (1, 2). However, in a recent study, it was nicely shown that after correction for maternal age, BMI and preeclampsia, the association between thyroid dysfunction and preterm delivery was absent (37). In our study, preterm delivery was little more frequent in women with higher normal TSH levels, but without reaching statistical significance. We did not observe an association between (low) birth weight and TSH/FT4 levels, in agreement with most results in literature (2), although two studies associated it with overt hypothyroidism and high FT4 levels respectively (35, 38). Postpartum haemorrhage was inversely correlated with FT4 levels. There is a well-known association between thyroid dysfunction and an altered menstruation pattern and between hypothyroidism and an increased bleeding tendency in general; a mechanism that is probably mediated via an impact of thyroid hormones on the production of coagulation factors in the liver (20, 39).

Some weaknesses of our study were the absence of Tg-abs and hCG levels, two variables of which we explained the importance previously in the discussion and the fact that the ethnic backgrounds of the women were not included, a variable that might influence TSH levels (40).

Recent data have shown that LT4 treatment of pregnant women with TSH levels <4.0 mIU/L had a higher prevalence of preterm deliveries and pre-eclampsia as compared with women with TSH levels ≥ 4.0 mIU/L (6). The authors did not provide a clear explanation for their observations, what might have been due to the retrospective setting of the study. However, based on our study results, we believe that the lower serum TSH levels were not the main reason for their observations. Other explanations could have been a detrimental effect of TAI (no data were provided in their study) or an overtreatment with LT4 leading to peak concentrations of T4 and a negative impact on the placental physiology (4, 34).

Our data add evidence to the proposal of the revised guidelines on the management of thyroid dysfunction during pregnancy, in which it is recommended against LT4 treatment in pregnant women without TAI and high normal serum TSH levels (<4.0 mIU/L or $<$ upper limit of institutional cut-off) (5). Although this study was not designed to investigate the impact of TAI and higher serum TSH levels (>4.0 mIU/L) on pregnancy outcomes, the fact that their exclusion in the present study was associated with the absence of impaired pregnancy outcomes, highlights indirectly that these two factors are most probably the ones that can hamper successful ongoing pregnancies. Further studies should focus on the

impact of these factors on pregnancy outcomes, in order to determine the best candidates for LT4 treatment.

Conclusion

Variation in thyroid function within the normal (non-pregnant) range during the first trimester of pregnancy in women free of thyroid disease was not associated with altered pregnancy outcomes. Ten percent of women without TPO antibodies had TSH levels in the upper limit of normality, what might have been due to other pregnancy related conditions such as obesity or iron deficiency. Our results provide new evidence in favour of the recommendation against LT4 treatment in pregnant women with high normal TSH levels and no TPO antibodies.

Declaration of interest

Kris Poppe received lecture fees from the Merck company (Thyroid symposium) in 2014, the IBSA Institut Biochimique SA (satellite meeting of the European Thyroid Association) in 2016 and the Berlin-Chemie AG company (ETA educational thyroid meeting) in 2017.

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