Clinical Research Article

Thyroid Function During Pregnancy in A Multiethnic Population in Norway

Line Sletner,[1,2] Anne Karen Jenum,[3] Elisabeth Qvigstad,[4,5] and Sara Salehi Hammerstad[6,7]

[1]Department of Pediatric and Adolescents Medicine, Akershus University Hospital, PB 1000, 1478 Lørenskog, Norway; [2]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Norway; [3]General Practice Research Unit (AFE), Department of General Practice, Institute of Health and Society, Faculty of Medicine, University of Oslo, PB 1130 Blindern, 0318, Oslo, Norway; [4]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Aker, PB 4950, 0424 Oslo, Norway; [5]Institute of Clinical Medicine, University of Oslo, Norway; [6]Department of Pediatric, Oslo University Hospital, Ullevål, PB 4950, 0424, Oslo, Norway; and [7]Specialist Center Pilestredet Park, Pilestredet Park 12.A 0176 Oslo, Norway

ORCiD number: 0000-0001-7619-8701 (S. S. Hammerstad).

Abbreviations: ATA, American Thyroid Association; BMI, body mass index; FT4, free thyroxine; GW, gestational week; TSH, thyrotropin; TPO Abs, thyroid peroxidase antibodies; UIC, urinary iodine concentration.

Abstract

Context: Ethnic differences in thyroid function during pregnancy have been reported. However, it is unclear if this is equally valid across ethnic groups within multiethnic populations.

Objective: We aimed to assess ethnic differences in thyrotropin (TSH) and free thyroxine (FT4), and the prevalence of thyroid dysfunction and thyroid autoimmunity during pregnancy.

Methods: In a population-based cohort of 785 pregnant women in Oslo, Norway, TSH, FT4, and thyroid peroxidase antibodies (TPO Abs) were measured twice: at gestational week (GW) 15 and 28, and urine iodine concentration at GW 15. Associations were assessed using multivariate linear regression.

Results: We found ethnic differences in TSH levels at both time points, but not for fT4. South Asians had 0.42 mU/L (95% CI, 0.20-0.64) higher TSH than Europeans in GW 15. This difference persisted after adjusting for covariates (including TPO Ab positivity and iodine status), and increased further as pregnancy progressed. In contrast, East Asians had the lowest TSH. No new cases of overt hypothyroidism were detected in early pregnancy, but subclinical hypothyroidism was found in 6.6% among all, highest in South Asians (14.2%). Hyperthyroidism early in pregnancy was observed in 3.7% (almost all subclinical), highest in East Asians (11.9%). The prevalence of TPO Ab positivity was 4%, highest in South Asians (8%).

Conclusion: In a multiethnic population of presumably healthy women, we found ethnic variations in TSH but not FT4 levels throughout pregnancy. South Asians had higher TSH and more subclinical hypothyroidism, not explained by their higher prevalence of TPO Ab positivity. Larger studies are needed to define ethnic- and trimester-specific reference ranges in pregnancy.

Key Words: thyroid and pregnancy, thyroid epidemiology, subclinical hypothyroidism, ethnic differences, hyperthyroidism

Thyroid function is essential for fetal developmental, in particular during the first and second trimester. Thyroid hormone production and iodine uptake changes during pregnancy, induced by hormonal changes and increased metabolic demands. Thyrotropin (TSH) measurement is the principal test to diagnose thyroid disorders during pregnancy, but particularly the upper reference values have been highly debated. Besides methodological variations in thyroid function tests and reference values, differences between countries have been observed [1], both during and outside pregnancy [2]. The American Thyroid Association (ATA) guidelines recommend population-based trimester-specific reference ranges for serum TSH based on samples from healthy, iodine-sufficient pregnant women with a singleton pregnancy, and negative thyroid peroxidase antibody (TPO Ab) status from the local population [1]. If such data are not available, the ATA suggests that an upper reference level of 4.0 mU/L may be used [1]. The previous trimester-specific upper reference levels were lower [3], and were found to overdiagnose subclinical hypothyroidism.

Ethnic differences in TSH levels have been observed within some populations. Thus, to which degree local population-based reference ranges can be generalized to all ethnic groups in today's multiethnic societies is not clear.

The aim of this study was to assess ethnic differences in TSH and free thyroxin (FT4) values, and changes during pregnancy, and the prevalence of thyroid dysfunction and thyroid autoimmunity in a multiethnic population-based cohort in Oslo, Norway.

Materials and Methods

Design, Setting, and Study Population

We used data from the STORK Groruddalen study, a population-based cohort of healthy women with multiethnic background, residing in Groruddalen, Oslo, Norway, where 75% to 85% of pregnant women attend child health clinics for antenatal care. Women were enrolled in the study between May 2008 and May 2010. All data were collected at 3 child health clinics. To facilitate inclusion of ethnic minority women, all information material was translated into Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu, and Vietnamese. Women were included if they 1) lived in the district, 2) planned to give birth at 1 of the 2 study hospitals, 3) were less than 20 weeks' pregnant, 4) could communicate in Norwegian or any of the specified languages, and 5) were able to provide written consent to participate. Women with prepregnancy diabetes or other diseases necessitating intensive hospital follow-up during pregnancy were excluded. All women were interviewed during gestational week (GW) 15 (visit 1) and 28 (visit 2) by certified staff, assisted by translators when needed. Information from questionnaires including medication use, clinical data, as well as fasting serum and urine samples were collected.

In total, 59% of the 823 included women were of ethnic minority background. Participation was based on informed, written consent. The participation rate was 74% (range, 64%-83% for ethnic groups). Participating women were found to be representative for the main ethnic groups. The Regional Committee for Medical and Health Research Ethics South East Norway (Reference No. 2007/894) approved the study protocol.

Laboratory Measurements Related to Thyroid Function

Serum samples from same participants were collected in GW 15 and GW 28, and morning urine in GW 15 after an overnight fast, and biobanked at –80 °C. Women could participate during only one pregnancy. As we were assessing thyroid function in the second trimester, we did not exclude pregnancies that were the result of in vitro fertilization (n = 13). During data collection, serum TSH was analyzed consecutively at Akershus University Hospital and women with TSH greater than 3.5 mU/L were recommended to consult their general practitioner, supplied with information about test results, and suggested follow-up, according to protocol.

For the present study, we performed new analyses of TSH and FT4 from biobanked sera from the same participants (GW 15 and GW 28) at the Central Laboratory,

Oslo University Hospital, Rikshospitalet, in 2016, using electrochemiluminescence Roche Modular E170 (Roche diagnostics, Switzerland) [4, 5] (reference ranges for TSH 0.5-3.6 mU/L, FT4 8-21 pmol/L, coefficient of variation 6%). Urinary iodine concentration (UIC) measurements (micromole per liter, µmol/L) (GW 15) were performed using an in-house colorimetric method at The Hormone Laboratory, Oslo University Hospital. The UIC results were later transformed to microgram per liter (µg/L). Collection of urine samples was established a few months after study start, therefore, urine samples are missing for the first 111 participants. TPO Abs from both visits were measured at Akershus University Hospital using chemiluminescent immunoassay (Access immunoassay, Beckman Coulter) for TPO Abs (reference range < 9 kU/L, coefficient of variation 6%).

Outcome Measures

Serum TSH and FT4 from both visits, and their changes, were our primary outcomes. Secondary outcomes were thyroid dysfunction, using categories primarily based on TSH, and taking both the ATA and European Thyroid Association guidelines into account. "Optimal values" were defined as TSH 0.1 to 2.5 mU/L, "suboptimal values" as TSH 2.6 to 4.0 mU/L, "subclinical hypothyroidism" as TSH 4.1 to 10 mU/L, and FT4 within reference ranges, "overt hypothyroidism" as TSH greater than 10 mU/L and FT4 less than 8 pmol/L, and "hyperthyroidism" as TSH less than 0.1 mU/L (including both overt and subclinical hyperthyroidism). TPO Abs greater than 60 kU/L was considered positive. Our last secondary outcome was mean, median (2.5th and 97.5th percentiles) for TSH and FT4 at both visits (GW 15 and 28) in iodine-sufficient women with singleton pregnancies, no known thyroid disease, and negative TPO Abs from the largest ethnic groups.

Main Exposure Variable

Ethnic origin was defined by the participant's country of birth, or the participant's mother's country of birth, if the participant's mother was born outside Europe. Ethnicity was further categorized as Europe, South Asia (primarily Pakistan and Sri Lanka), East Asia (primarily Vietnam, the Philippines, and Thailand), Middle East/North Africa (primarily Iraq, Turkey, Afghanistan, and Morocco), and sub-Saharan Africa (primarily Somalia, Eritrea, and Ethiopia).

Covariates

Gestational age was primarily derived from the first day of the mother's last menstrual period, but ultrasound-derived gestational age was used in 7% of pregnancies. Parity was

categorized as nulliparous (no previous pregnancy lasting > 22 weeks), uniparous (one previous pregnancy) or multiparous (2 or more previous pregnancies). For the statistical analyses, the last 2 categories were merged. Maternal socioeconomic position, a score derived from a principal components analysis, was normally distributed (mean = 0, median = 0.1, SD = 1; range, –2.91 to 2.59). The individual level data; education, occupational class and employment status, and household variables; own or renting tenure and rooms per person contributing most to the score. Prepregnancy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared [kg/m^2]) was calculated from self-reported weight before pregnancy and height measured at inclusion. Information about severe pregnancy-induced nausea was collected in GW 28, and categorized by the interviewing midwife as yes or no based on the frequency of vomiting, impact, and duration of symptoms. UIC in spot urine, often used as an assessment of iodine status of population levels, was measured in GW 15 and for this study dichotomized as severe insufficiency (< 50 µg/L) or not.

Statistics

Statistical analyses were performed using IBM SPSS Statistics, version 25 for Windows. Descriptive statistics are described as appropriate. We were primarily interested in the direct effect of ethnicity. By definition there are no real confounders to the association between ethnicity and thyroid function because few factors can affect ethnicity. However, we adjusted for variables that may be associated with selection bias and were related both to ethnicity and thyroid function (gestational age at inclusion, age, parity, socioeconomic position, prepregnant BMI, and severe pregnancy-induced nausea), and hence could mediate the effects between ethnicity and thyroid function.

To explore ethnic differences in TSH and FT4 levels, and their changes, we used general linear (regression) models, using either TSH or FT4 levels at each time point, or the calculated change from visit 1 to visit 2 (Δ) as outcomes. We first performed univariate analyses, thereafter included all covariates (Model 1). For the analyses of TSH/FT4 at visit 1, we have also explored the additional impact of TPO Abs (Model 2) and severe iodine insufficiency (UIC < 50 µg/L) (Model 3) on the ethnic differences.

Results

Characteristics of the Study Sample

Of the 823 women included in the STORK Groruddalen study, we excluded those of Central/South American origin because of the low number (n = 12) and those with missing

TSH values at enrollment (n = 26); leaving a sample of 785 women for descriptive analyses (Supplementary Figure S1) [6].

Women with European, South Asian, and Middle Eastern ethnic origin represented the largest groups. The study participant characteristics for the largest ethnic groups are presented in Table 1. Furthermore, 14 of 785 (1.8%) had known thyroid disease (13 on levothyroxine [1.7%] and 1 on carbimazole ([0.1%]), leaving 771 women for further analysis (see Supplementary Figure S1) [6].

Thyrotropin and Free Thyroxine Levels in Early Pregnancy

Crude levels for TSH, FT4, and GW at visit 1 (mean GW 15.4 [SD = 3.4]), and visit 2 (mean GW 28.8 [SD = 1.4]) are presented in Supplementary Table S1 [6]. In the 771 women without known thyroid disease, mean TSH values were higher for South Asians and lower for East Asians compared with Europeans (Table 2, univariate analyses), with a difference of about 1 mU/L between the two. Women from the Middle East and South Saharan Africa had similar levels as Europeans. The ethnic differences in TSH persisted after adjusting for GW, age, parity, socioeconomic position, prepregnant BMI, and nausea (Model 1), as well as after additional adjustments for TPO Ab positivity (Model 2) and iodine status (Model 3). For East Asians the difference persisted in Models 1 and 2, but was only borderline significant in Model 3. In contrast, no significant ethnic differences in FT4 were observed before or after similar adjustments (Table 3). In final models we explored interactions between ethnicity and covariates, and none were significant (all $P > .05$).

Changes in Thyrotropin and Free Thyroxine Levels From Gestational Weeks 15 to 28

Figure 1 displays mean TSH and FT4 adjusted for covariates in general linear regression models (Model 2, including TPO Abs) from GW 15 and GW 28 in those with available TSH and FT4 data at both time points and after excluding women with known thyroid disease at any visit (n = 698). Mean TSH increased and mean FT4 declined from GW 15 to GW 28. However, compared with Europeans, South Asians and women from sub-Saharan Africa had a larger increase in TSH levels (Supplementary Table S2A) [6]. Hence, the difference between South Asians and Europeans was larger in the third trimester than in the second trimester. In contrast, East Asian women had the lowest TSH at both visits and a larger reduction in FT4 from inclusion to GW

28, but only after adjusting for covariates (Supplementary Table S2B) [6].

Thyroid Dysfunction During Pregnancy

Other than the 13 (1.7%) women treated with levothyroxine, no new cases of overt hypothyroidism were found in early pregnancy (GW 15) (Table 4). However, 6.6% had subclinical hypothyroidism (TSH 4.1-10 mU/L and FT4 within reference ranges). Eight women had FT4 levels less than 11 pmol/L, but none of these had TSH greater than 4 mU/L (data not shown).

South Asians presented with the highest prevalence of subclinical hypothyroidism (14.2%), whereas this was found in only 4.1% of the Europeans.

Twenty-four percent of women with TSH levels of 2.6 to 4 mU/L during GW 15 developed subclinical hypothyroidism at GW 28, but none developed overt hypothyroidism (Supplementary Table S3) [6]. Fifteen percent of women with untreated subclinical hypothyroidism in GW 15 presented with TSH greater than 10 mU/L or were treated with levothyroxine during GW 28.

Hyperthyroidism (TSH < 0.1 mU/L) was seen in 3.7%, whereas only one woman presented with overt hyperthyroidism (FT4 > 24 pmol/L). East Asians had the highest prevalence of hyperthyroidism (11.9%). The majority of those with hyperthyroidism during GW 15 (78.6%) had normal TSH values during GW 28. Only one woman had TSH less than 0.01 mU/L in GW 15 but presented with overt hyperthyroidism during GW 28 (Supplementary Table S3) [6].

In total 31 women (3.9%) had TPO Abs greater than or equal to 60 kU/L early in their pregnancy (Table 4). South Asians had the highest prevalence of TPO Ab positivity (8% compared to 3% for Europeans).

Total Cohort and Ethnic-Specific Reference Ranges

Table 5 displays the crude and adjusted mean (95% CI), and (2.5th and 97.5th percentiles) and distribution for TSH and FT4 at visits 1 and 2, after excluding women with known thyroid disease (self-reported use of levothyroxine or antithyroid medication), twin pregnancies, autoimmunity (TPO Abs > 60 kU/L), and severe iodine deficiency (UIC < 50 μg/L); overall (n = 526), and separately for the 3 largest ethnic groups. South Asians had the highest median and 97.5th percentile levels for TSH. Compared with Europeans, the distribution of TSH in South Asians generally skewed to the right, particularly in GW 28 (Figure 2). No ethnic differences in FT4 levels or its distribution were found.

Table 1. Characteristics of study sample (n = 785) at enrollment (visit 1) by ethnic origin. Numbers are mean (SD) or No. (%)

	No.	Europe(n = 363)	South Asia(n = 197)	East Asia(n = 42)	Middle East/N Africa(n = 127)	SS Africa(n = 56)
Gestational wk at enrollment	785	14.7 (2.5)	15.7 (4.0)	16.1 (4.3)	15.6 (3.3)	17.0 (4.5)
Age, y	785	30.6 (4.5)	28.7 (4.5)	31.1 (4.8)	29.5 (5.5)	28.3 (5.2)
Maternal education	779					
Primary school or less		15 (4.2%)	35 (17.9%)	7 (16.7%)	46 (36.8%)	24 (42.9%)
Completed high school		112 (31.1%)	99 (50.5%)	19 (45.2%)	55 (44.0%)	24 (42.9%)
Completed college/university		233 (64.7%)	62 (31.6%)	16 (38.1%)	24 (19.2%)	8 (14.3%)
Socioeconomic score[a]	781	0.46 (0.88)	-0.18 (0.78)	0.13 (0.73)	–0.60 (0.90)	–1.00 (1.01)
Time of residence in Norway, y	768					
Born in Norway		286 (82.2%)	41 (20.5%)	1 (2.4%)	7 (5.6%)	1 (1.8%)
≥ 20		1 (0.3%)	23 (11.7%)	11 (26.2%)	14 (11.2%)	1 (1.8%)
5-19		30 (8.6%)	86 (43.7%)	17 (40.5%)	70 (56.0%)	29 (51.8%)
< 5		25 (7.2%)	47 (23.9%)	12 (28.6%)	34 (27.2%)	25 (44.6%)
Smoking						
Daily smoking before pregnancy	778	76 (21.2%)	1 (0.5%)	4 (9.5%)	8 (6.3%)	2 (3.6%)
Daily smoking at enrollment	778	20 (5.5%)	0	1 (2.3%)	1 (0.8%)	1 (1.7%)
Any smoking in pregnancy[b]	784	35 (9.6%)	1 (0.5%)	1 (2.4%)	4 (3.2%)	2 (3.6%)
Parity	785					
Nulliparous		196 (54.0%)	84 (42.6%)	17 (40.5%)	44 (34.6%)	24 (42.9%)
Para 1		129 (35.5%)	62 (31.5%)	17 (40.5%)	44 (34.6%)	12 (21.4%)
Para 2+		38 (10.5%)	51 (25.9%)	8 (19.0%)	20 (35.7%)	20 (35.7%)
Height, cm	785	167.1 (5.8)	160.1 (5.7)	157.6 (6.5)	161.3 (5.3)	163.2 (5.8)
Prepregnant BMI	773	24.5 (4.8)	23.8 (4.2)	22.3 (3.5)	26.0 (5.1)	25.5 (5.4)
Prepregnant BMI category	773					
Underweight, < 18.5		14 (3.9%)	16 (8.3%)	4 (9.5%)	5 (4.0%)	3 (5.5%)
Normal weight, 18.5-24.9		212 (59.4%)	114 (59.1%)	30 (71.4%)	60 (47.6%)	24 (43.6%)
Overweight, 25-29.9		87 (24.4%)	44 (22.8%)	6 (14.3%)	34 (27.0%)	17 (30.9%)
Obesity, ≥ 30		44 (12.3%)	19 (9.8%)	2 (4.8%)	27 (21.4%)	11 (20.0%)
BMI at enrollment	784	25.2 (4.7)	24.4 (4.2)	22.9 (3.6)	26.9 (5.4)	26.4 (5.2)
Severe pregnancy-induced nausea[c]	716	29 (8.7%)	54 (29.3%)	11 (29.7%)	22 (19.3%)	13 (28.3%)
Urine iodine concentration < 50 μg/L[d]	657	36 (12.6%)	25 (14.6%)	5 (13.2%)	23 (20.9%)	5 (9.4%)

Abbreviations: BMI, body mass index; N Africa, North Africa; SS Africa, sub-Saharan Africa.

[a]Factor extracted from a principal components analysis of 11 different sociodemographic variables. The score was normally distributed (mean = 0, median = 0.1, SD = 1 range, –2.91 to 2.59). See "Materials and Methods."

[b]Reported either daily or occasional smoking at enrollment or at visit 2 (28 weeks' gestation)

[c]Reported severe vomiting and/or nausea with large impact on daily function. See "Materials and Methods."

[d]From morning spot urine at enrollment.

Table 2. Association between ethnicity and other background factors, and thyrotropin levels in early pregnancy (n = 771 [657 with known urine iodine status])

	Univariate		Model 1		Model 2		Model 3	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Ethnicity								
Europe	Reference		Reference		Reference		Reference	
South Asia	0.42 (0.20 to 0.64)	<.001	0.47 (0.21 to 0.73)	<.001	0.44 (0.19 to 0.69)	<.001	0.53 (0.25 to 0.80)	<.001
East Asia	−0.55 (−0.96 to −0.14)	.009	−0.53 (−1.00 to −0.07)	.02	−0.49 (−0.93 to −0.05)	.03	−0.44 (−0.91 to 0.02)	.06
Middle East	0.03 (−0.23 to 0.28)	.8	0.03 (−0.28 to 0.33)	.9	0.04 (−0.26 to 0.33)	.8	0.05 (−0.27 to 0.37)	.8
SS Africa	0.05 (−0.32 to 0.41)	.8	−0.12 (−0.57 to 0.33)	.6	−0.08 (−0.51 to 0.36)	.7	−0.14 (−0.59 to 0.32)	.6
Gestational wk	0.03 (0.01 to 0.06)	.02	0.03 (0.004 to 0.06)	.03	0.04 (0.01 to 0.07)	.01	0.04 (0.01 to 0.07)	.02
Age, y	−0.03 (−0.04 to −0.01)	.009	−0.01 (−0.03 to 0.02)	.6	−0.01 (−0.03 to 0.02)	.6	0.003 (−0.02 to 0.03)	.8
Parity								
Nulliparous	Reference		Reference		Reference		Reference	
Parous	−0.36 (−0.54 to −0.18)	<.001	−0.35 (−0.57 to −0.14)	.001	−0.39 (−0.60 to −0.18)	<.001	−0.25 (−0.68 to −0.22)	<.001
Socioeconomic score	−0.03 (−0.13 to 0.06)	.5	−0.03 (−0.15 to 0.09)	.6	−0.04 (−0.16 to 0.08)	.5	−0.06 (−0.19 to 0.06)	.3
Prepregnant BMI								
Normal, 18.5-24.9	Reference		Reference		Reference		Reference	
Underweight, < 18.5	0.35 (−0.05 to 0.76)	.09	0.31 (−0.13 to 0.75)	.2	0.26 (−0.16 to 0.69)	.2	0.17 (−0.28 to 0.62)	.5
Overweight, 25–29.9	0.15 (−0.07 to 0.37)	.2	0.19 (−0.05 to 0.42)	.1	0.16 (−0.07 to 0.38)	.2	0.18 (−0.07 to 0.43)	.2
Obesity, ≥ 30	0.004 (−0.28 to 0.28)	1	0.08 (−0.24 to 0.38)	.6	0.01 (−0.29 to 0.30)	1	0.04 (−0.28 to 0.36)	.8
Severe nausea	−0.02 (−0.28 to 0.23)	.9	−0.06 (−0.32 to 0.19)	.6	−0.04 (−0.29 to 0.21)	0.7	0.04 (−0.23 to 0.31)	.8
TPO Abs > 60 kU/L	1.30 (0.81 to 1.79)	<.001	1.42 (0.91 to 1.93)	<.001	1.42 (0.91 to 1.93)	<.001	1.55 (1.00 to 2.10)	<.001
Urine iodine < 50 µg/L	0.23 (−0.05 to 0.52)	.1					0.18 (−0.12 to 0.47)	.2

Model 1: adjusted for maternal background factors. Model 2: adjusted for maternal background factors and TPO Ab positivity. Model 3: additionally adjusted for iodine status. Significant differences (*P* < .05) are presented in bold.

Abbreviations: BMI, body mass index; SS Africa, sub-Saharan Africa; TPO Abs, thyroid peroxidase antibodies.

Table 3. Association between ethnicity and other background factors, and free thyroxine levels in early pregnancy (n = 771 [657 with known urine iodine status])

	Univariate		Model 1		Model 2		Model 3	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Ethnicity								
Europe	Reference		Reference		Reference		Reference	
South Asia	0.15 (−0.25 to 0.55)	.5	0.19 (−0.24 to 0.62)	.4	0.23 (−0.19 to 0.66)	.3	0.19 (−0.27 to 0.65)	.4
East Asia	0.18 (−0.56 to 0.92)	.6	0.51 (−0.24 to 1.27)	.2	0.48 (−0.27 to 1.22)	.2	0.54 (−0.24 to 1.32)	.2
Middle East	0.07 (−0.40 to 0.53)	.8	0.41 (−0.09 to 0.92)	.1	0.42 (−0.08 to 0.92)	.1	0.44 (−0.10 to 0.97)	.1
SS Africa	−0.71 (−1.37 to −0.06)	.03	−0.004 (−0.75 to 0.74)	1	−0.04 (−0.77 to 0.70)	.9	−0.03 (−0.79 to 0.73)	.9
Gestational wk	−0.22 (−0.27 to −0.18)	<.001	−0.21 (−0.26 to −0.17)	<.001	−0.22 (−0.27 to −0.17)	<.001	−0.21 (−0.26 to −0.16)	<.001
Age, y	−0.08 (−0.12 to −0.05)	<.001	−0.09 (−0.13 to −0.05)	<.001	−0.09 (−0.13 to −0.05)	<.001	−0.10 (−0.14 to −0.06)	<.001
Parity								
Nulliparous	Reference		Reference		Reference		Reference	
Parous	−0.13 (−0.45 to 0.20)	.4	0.27 (−0.09 to 0.62)	.1	0.29 (−0.06 to 0.65)	.1	0.34 (−0.04 to 0.73)	.08
Socioeconomic score	0.13 (−0.04 to 0.30)	.1	0.32 (0.12 to 0.51)	.002	0.33 (0.13 to 0.52)	.001	0.35 (0.14 to 0.56)	.001
Prepregnant BMI								
Normal, 18.5-24.9	Reference		Reference		Reference		Reference	
Underweight, < 18.5	1.25 (0.53 to 1.98)	.001	0.76 (0.03 to 1.49)	.03	0.80 (0.08 to 1.53)	.03	0.70 (−0.06 to 1.45)	.07
Overweight, 25-29.9	−0.16 (−0.41 to 0.38)	.9	−0.08 (−0.46 to 0.31)	.7	−0.05 (−0.43 to 0.34)	.8	−0.10 (−0.52 to 0.31)	.6
Obesity, ≥ 30	−0.30 (−0.79 to 0.21)	.3	−0.03 (−0.53 to 0.47)	.9	−0.002 (−0.50 to 0.50)	1	−0.13 (−0.66 to 0.40)	.6
Severe nausea	0.40 (−0.03 to 0.84)	.07	0.25 (−0.17 to 0.68)	.2	0.24 (−0.19 to 0.66)	.3	0.25 (−0.20 to 0.70)	.3
TPO Abs > 60 kU/L	−0.68 (−1.58 to 0.22)	.1			−1.48 (−2.34 to −0.62)	.001	−1.62 (−2.54 to −0.70)	.001
Urine iodine<50 µg/L	−0.31 (−0.82 to 0.20)	.2					−0.34 (−0.83 to 0.15)	.2

Model 1: adjusted for maternal background factors. Model 2: adjusted for maternal background factors and TPO Ab positivity. Model 3: additionally adjusted for iodine status. Significant differences (*P* < .05) are presented in bold.

Abbreviations: BMI, body mass index; SS Africa, sub-Saharan Africa; TPO Abs, thyroid peroxidase antibodies.

Discussion

This is one of few population-based studies of healthy pregnant women to explore thyroid function and thyroid autoimmunity in different ethnic groups in a multiethnic European population. In early pregnancy, ethnic differences were observed for TSH, but not for FT4. Compared with ethnic Europeans, South Asian women had higher mean TSH values,

Figure 1. Changes in thyrotropin (TSH; mU/L) and free thyroxine (FT4; pmol/L) during pregnancy (n = 698). Numbers are estimated marginal means at visit 1 (gestational week 15.4) and visit 2 (gestational week 28.8) from separate general linear models, adjusted for covariates.

with a TSH distribution curve skewed to the right, and this difference increased as pregnancy progressed. South Asians also had a higher prevalence of subclinical hypothyroidism using ATA guidelines with a cutoff of TSH 4 mU/L and also a higher prevalence of TPO Ab positivity. In contrast, East Asian women had lower TSH levels than Europeans.

However, no significant differences in the distribution of FT4 were seen. Few women had subclinical hyperthyroidism, and TSH levels mostly became normal during GW 28.

Several studies have presented trimester-specific reference values from different countries and continents, showing large variations in median, and lower to upper reference values (reviewed in [1]). There are, however, only a few multiethnic population studies from Europe [7, 8, 9], and the United States [2, 10, 11]. Of note, direct comparisons between studies are hampered by methodological issues such as differences in timing, analysis methods, and diagnostic criteria used. Furthermore, population characteristics and important covariates, including TPO Ab positivity and iodine status, may be missing or differ.

In line with our findings, ethnic differences in TSH but not FT4, during pregnancy have been found by some others. Multiethnic studies from the United States found that Black Americans had lower TSH values than European-origin populations during pregnancy [2, 10, 11]. This is in contrast to our findings of similar TSH values in early pregnancy in sub-Saharan African and European women. However, African women in our study are mostly migrants from the Horn of Africa (East Africa), whereas the majority of Black Americans have their ancestral origin from West Africa.

Two Dutch multiethnic studies found that Dutch women had the highest TSH levels and Moroccans the lowest,
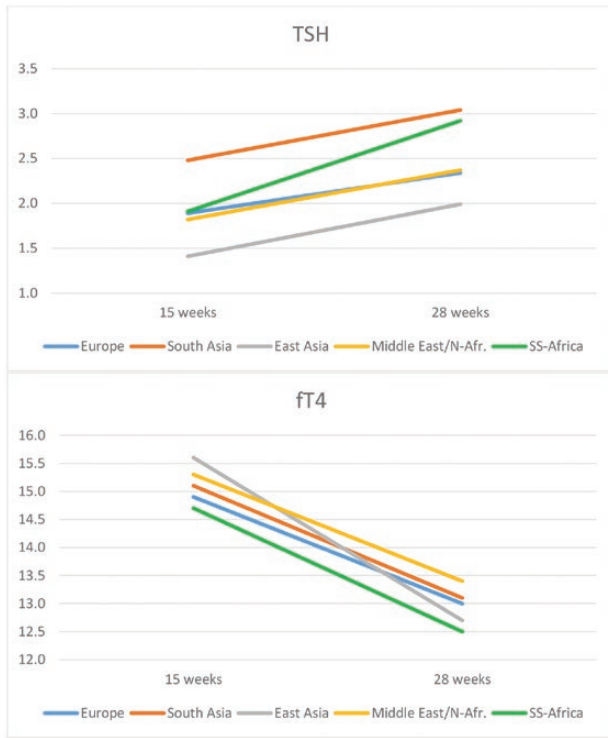
Table 4. Proportion of women in different clinical thyrotropin categories, in total sample and by ethnic origin, and thyroid peroxidase antibody positivity in total sample

	Total(n = 785)	TPO Abs> 60 kU/L	Europe(n = 363)	South Asia(n = 197)	East Asia(n = 42)	Middle East(n = 127)	SS Africa(n = 56)
TSH 0.1-2.5 mU/L	555 (70.7%)	9 (1.6%)	274 (75.5%)	118 (59.9%)	33 (78.6%)	91 (71.7%)	39 (69.9%)
TSH 2.6-4.0 mU/L	135 (17.2%)	7 (5.2%)	64 (17.6%)	36 (18.3%)	3 (7.1%)	23 (18.1%)	9 (16.1%)
Subclinical hypothyroidism TSH 4.1-10.0 mU/L	52 (6.6%)	9 (17.3%)	15 (4.1%)	28 (14.2%)	0	6 (4.7%)	3 (5.4%)
Overt hypothyroidism TSH > 10 mU/L	0 (0%)	0	0	0	0	0	0
Hyperthyroidism TSH < 0.1 mU/L	29 (3.7%)	1 (3.4%)	6 (1.7%)	8 (4.1%)	5 (11.9%)	7 (5.5%)	0
Treated with levothyroxine	13 (1.7%)	5 (38.5%)	4 (1.1%)	7 (3.6%)	0	0	3 (5.4%)
Treated with carbamizole	1 (0.1%)	0	0	0	1 (2.4%)	0	0
Positive TPO Abs (> 60 kU/L)		31 (3.9%)	11 (3%)	16 (8%)	0	4 (3%)	0

Abbreviations: BMI, body mass index; SS Africa, sub-Saharan Africa; TPO Abs, thyroid peroxidase antibodies; TSH, thyrotropin.

Table 5. Crude and fully adjusted mean (95% CI) thyrotropin and free thyroxine values and crude 2.5th and 97.5th percentiles at visit 1 and visit 2, in total sample and 3 largest ethnic groups. Includes women with singleton pregnancy, with no known thyroid disease, negative antithyroid peroxidase antibodies (< 60 kU/L) and no severe iodine deficiency (urine iodine ≥ 50 µg/L)

	Total		Europe		South Asia		Middle East/North African	
	Mean (95% CI)	(2.5th, 97.5th perc.)	Mean (95% CI)	(2.5th, 97.5th perc.)	Mean (95% CI)	(2.5th, 97.5th perc.)	Mean (95% CI)	(2.5th, 97.5th perc.)
Visit 1	n = 526		n = 239		n = 128		n = 82	
TSH, mU/L								
Crude	1.8 (1.7-1.9)	(0.04, 5.2)	1.8 (1.6-1.9)	(0.1, 5.0)	2.2 (2.0-2.5)	(0.01, 5.9)	1.7 (1.4-2.0)	(0.04, 4.0)
Adjusted[a]	1.9 (1.7-2.1)		1.9 (1.6-2.1)		2.4 (2.1-2.6)		1.8 (1.5-2.2)	
fT4, pmol/L								
Crude	14.9 (14.6-15.1)	(11.0, 20.0)	14.9 (14.6-15.2)	(11.0, 19.0)	15.0 (14.6-15.4)	(11.0, 23.3)	15.1 (14.6-15.6)	(12.0, 19.0)
Adjusted[a]	15.2 (14.8-15.5)		14.9 (14.5-15.3)		15.2 (14.7-15.6)		15.3 (14.7-15.9)	
Visit 2	n = 482		n = 224		n = 117		n = 75	
TSH, mU/L								
Crude	2.3 (2.2-2.5)	(0.5, 5.6)	2.1 (2.0-2.3)	(0.6, 5.5)	2.8 (2.5-3.0)	(0.2, 7.0)	2.2 (2.4-3.2)	(0.1, 4.8)
Adjusted[a]	2.6 (2.4-2.8)		2.4 (2.1-2.6)		3.0 (2.7-3.3)		2.4 (2.1-2.8)	
fT4, pmol/L								
Crude	12.9 (12.7-13.1)	(9.7, 17.0)	12.8 (12.6-13.0)	(10.0, 16.0)	13.1 (12.8-13.4)	(9.7, 17.0)	13.4 (13.0-13.7)	(10.0, 17.1)
Adjusted[a]	12.9 (12.7-13.2)		13.0 (12.6-13.3)		13.1 (12.7-13.4)		13.4 (12.9-13.8)	

Abbreviations: BMI, body mass index; fT4, free thyroxine; perc., percentile; SS Africa, sub-Saharan Africa; TSH, thyrotropin.

[a]Adjusted for gestational week, age, parity, socioeconomic position, prepregnant BMI, and pregnancy-induced nausea.
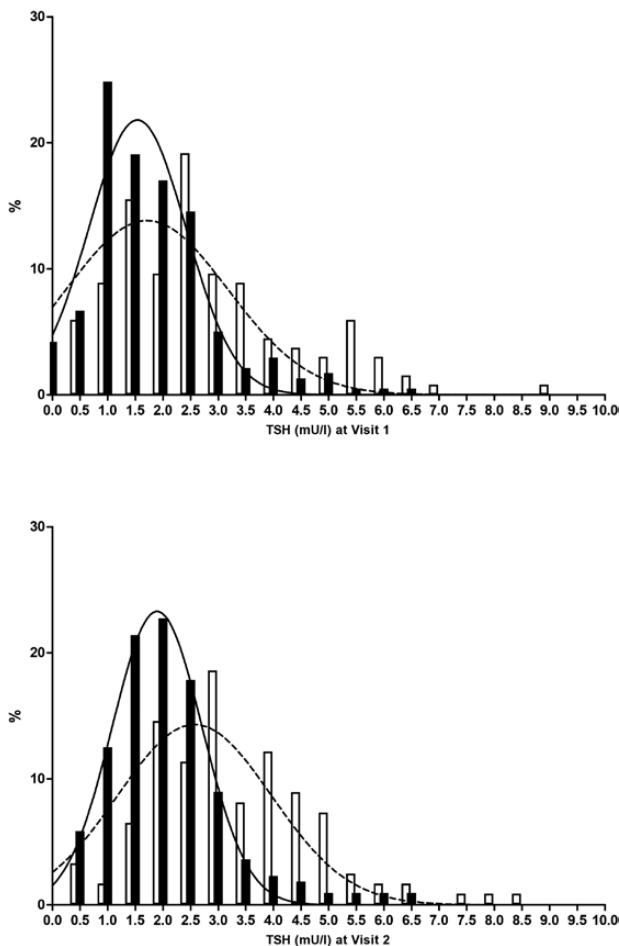
Figure 2. The distribution (%) of thyrotropin (TSH) at visit 1 (gestational week 15.4) and visit 2 (gestational week 28.8) in European (black bars) and South Asian (white bars) women. Includes women with a singleton pregnancy, no known thyroid disease, negative thyroid peroxidase antibodies, and no severe iodine deficiency.

while Turkish women had the highest TSH values of all ethnic minority women [7, 8]. A Belgian study showed that ethnic sub-Saharan and North African women had a lower median TSH than White pregnant women [9]. Because the number of Moroccan and Turkish participants was low in our study, women from these 2 countries were categorized in the same group (Middle Easterners/North Africans). TSH in this group was similar to Europeans.

To the best of our knowledge, our study is the first to report results from different ethnic minority groups of Asian origin in Europe, showing striking differences between South and East Asians. Although other studies from the United States also included Asian women in the first and second trimester, they did not specify their ancestral origin. The population with South Asian ancestral origin in multiethnic samples from the Netherlands were mainly Surinamese Hindustanis (emigrating mainly from India to Suriname during the 19th century) and had similar values as Dutch women [8]. In contrast, the mean TSH values in

primarily first-generation South Asian immigrants in our study were higher than in Europeans at both time points. In corroboration with our results, a study from the United Kingdom reported that South Asians had an increased risk of raised TSH in early pregnancy [12].

The prevalence of subclinical hypothyroidism is reported to occur in about 2% to 2.5% of pregnant women, but was higher in our study, as also found in some other samples [12-16]. Generally, the median TSH in our study was higher than in, for example, the multiethnic study from the Netherlands [7], and this is probably largely related to differences in laboratory methods. However, this will not explain the ethnic differences within our cohort. While 6.6% of all women in our study presented with subclinical hypothyroidism, 14.2% of South Asians had TSH levels in the range of 4 to 10 mU/L compared to 4.1% of Europeans. In contrast, East Asians had consistently the lowest TSH values and the highest proportion with hyperthyroidism, comparable to numbers reported by Price et al [17], and none presented with subclinical hypothyroidism early in pregnancy in our study. In general, very few cases of subclinical hyperthyroidism persisted at GW 28, compatible with human chorionic gonadotropin–related gestational thyrotoxicosis early in pregnancy, in accordance with other studies.

The overall prevalence of TPO Ab positivity in our study was similar to other multiethnic population studies [7, 8, 18, 19], but was lower in Middle Eastern women, similar to reports by others, and higher in South Asians [20-22]. Ethnic differences in TPO Ab positivity have also been found in large studies in pregnant women in the United States [10, 11], with the lowest prevalence in Black and highest in Asian, Hispanic, and White women. However, although we found that TPO Ab positivity was associated with higher TSH values, TPO Ab positivity did not explain the ethnic variation in TSH levels.

The proportion of women with severe iodine insufficiency was similar across ethnic groups, and did not explain the increased TSH in South Asians. Furthermore, the generally skewed TSH distribution indicates that the difference in this group is not driven by outliers (ie, some women with very high values).

Exploring a wide range of potential explanatory factors for the observed ethnic differences was beyond the scope of this study. However, other than genetic determinant factors and the amount and different type of human chorionic gonadotropin between groups [17, 23], the differences could partly be related to insulin resistance, as seen in South Asians [24], and nutritional factors such as iron deficiency [25]. Nevertheless, additional adjustments for ferritin (indicator of iron deficiency) or the homeostasis model assessment of insulin resistance had minimal impact on the ethnic differences in TSH (data not shown).

The ATA guidelines recommends that "when possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice," including only pregnant women with no known thyroid disease, optimal iodine intake, and negative TPO Ab status. Because we could control for all these factors, our geographically homogeneous population-based sample with TSH and FT4 measurements from 2 time points during pregnancy should be well suited to produce such reference ranges. However, as well as the reported ethnic differences in TSH, even within Asian subgroups, a large proportion in all ethnic groups had mild to moderate iodine deficiency according to the World Health Organization [26]. Excluding all these would reduce our sample size substantially. In fact, even after excluding only participants with known thyroid disease, TPO Ab positivity, and severe iodine insufficiency, the sample size was too small to produce robust reference ranges. This illustrates some of the challenges related to producing recommend reference ranges, as this would require large studies.

Further, our understanding of the complex relationships between maternal thyroid function and fetal outcomes is still limited. A recent meta-analysis reported of an inverse, dose-response association between maternal TSH and FT4 and lower birth weight [27]. Another meta-analysis from 2019 showed that subclinical hypothyroidism, isolated hypothyroxinemia, and TPO Ab positivity were significantly associated with higher risk of preterm birth [19]. Hence, whether the increased TSH levels in South Asian mothers can have clinical consequences is unknown.

This study has several strengths: the multiethnic population-based cohort design, high participation rates, and a large proportion of ethnic minorities being representative of the main ethnic groups of pregnant women in Oslo. Furthermore, analyses were conducted with reliable methods, and we had access to a range of potentially confounding or mediating factors and minor loss to follow-up.

However, there are also limitations to report. Women were recruited consecutively when attending antenatal care, thus GW at inclusion differed somewhat. We did not measure thyrotropin receptor Abs or antithyroglobulin Abs. Our result may also be affected by heterogeneity within the relatively broad ethnic groups and low number of participants, particularly from East Asia and South Sahara Africa.

Conclusions

This multiethnic cohort demonstrates the classic physiological changes in thyroid hormone levels with an increase in TSH and a decrease in FT4 during pregnancy. Importantly, we found significant ethnic variations, most pronounced in South Asian women who demonstrated higher TSH levels throughout pregnancy, a higher prevalence of TPO Abs, and subclinical hypothyroidism. FT4 was not subjected to variation between ethnic groups.

Although it is recommended to use trimester-specific and ethnic-specific TSH ranges during pregnancy, larger epidemiological studies are needed to define how this should be applied to multiethnic populations.

Acknowledgments

Additional Information

Correspondence: Sara Salehi Hammerstad, MD, PhD, Department of Pediatrics, Oslo University Hospital, Ullevål, PB 4950, 0424, Oslo, Norway; or Specialist Center Pilestredet Park, Pilestredet Park 12.A 0176 Oslo, Norway. Email: hammerstad.sara@gmail.com; s.s.hammerstad@medisin.uio.no.

Disclosures: The authors have nothing to disclose.

Data Availability: Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid.* 2017;**27**(3):315-389.
2. Walker JA, Illions EH, Huddleston JF, Smallridge RC. Racial comparisons of thyroid function and autoimmunity during pregnancy and the postpartum period. *Obstet Gynecol.* 2005;**106**(6):1365-1371.
3. Stagnaro-Green A, Abalovich M, Alexander E, et al; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid.* 2011;**21**(10):1081-1125.
4. RRID:AB_2801661.
5. RRID:AB_2877702.
6. Sletner L, Jenum AK, Qvigstad E, Hammerstad SS. Thyroid function during pregnancy in a multiethnic population in Norway. figshare. Deposited February 21, 2021. https://figshare.com/articles/figure/Thyroid_function_during_pregnancy_in_a_multiethnic_population_in_Norway/14069582

7. Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, van der Wal MF, Bonsel GJ. Ethnic differences in TSH but not in free T4 concentrations or TPO antibodies during pregnancy. *Clin Endocrinol (Oxf)*. 2007;**66**(6):765-770.

8. Korevaar TIM, Medici M, de Rijke YB, et al. Ethnic differences in maternal thyroid parameters during pregnancy: the Generation R study. *J Clin Endocrinol Metab*. 2013;**98**(9):3678-3686.

9. Korevaar TI, Chaker L, Medici M, et al. Maternal total T4 during the first half of pregnancy: physiologic aspects and the risk of adverse outcomes in comparison with free T4. *Clin Endocrinol*. 2016;**85**(5):757-763.

10. La'ulu SL, Roberts WL. Second-trimester reference intervals for thyroid tests: the role of ethnicity. *Clin Chem*. 2007;**53**(9):1658-1664.

11. La'ulu SL, Roberts WL. Ethnic differences in first-trimester thyroid reference intervals. *Clin Chem*. 2011;**57**(6):913-915.

12. Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007;**92**(1):203-207.

13. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005;**105**(2):239-245.

14. Li S, Gao X, Wei Y, Zhu G, Yang C. The relationship between iron deficiency and thyroid function in Chinese women during early pregnancy. *J Nutr Sci Vitaminol (Tokyo)*. 2016;**62**(6):397-401.

15. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol*. 2007;**109**(5):1129-1135.

16. Abalovich M, Mitelberg L, Allami C, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. *Gynecol Endocrinol*. 2007;**23**(5):279-283.

17. Price A, Obel O, Cresswell J, et al. Comparison of thyroid function in pregnant and non-pregnant Asian and western Caucasian women. *Clin Chim Acta*. 2001;**308**(1-2):91-98.

18. Stricker R, Echenard M, Eberhart R, et al. Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. *Eur J Endocrinol*. 2007;**157**(4):509-514.

19. Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth; Korevaar TIM, Derakhshan A, Taylor PN, et al. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. *JAMA*. 2019;**322**(7):632-641.

20. Rajput R, Yadav T, Seth S, Nanda S. Prevalence of thyroid peroxidase antibody and pregnancy outcome in euthyroid autoimmune positive pregnant women from a tertiary care center in Haryana. *Indian J Endocrinol Metab*. 2017;**21**(4):577-580.

21. Pearce EN, Oken E, Gillman MW, et al. Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. *Endocr Pract*. 2008;**14**(1):33-39.

22. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol*. 2004;**150**(6):751-755.

23. Veltri F, Poppe K. Variables contributing to thyroid (dys)function in pregnant women: more than thyroid antibodies? *Eur Thyroid J*. 2018;**7**(3):120-128.

24. Vyakaranam S, Vanaparthy S, Nori S, Palarapu S, Bhongir AV. Study of insulin resistance in subclinical hypothyroidism. *Int J Health Sci Res*. 2014;**4**(9):147-153.

25. Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. *Thyroid*. 2002;**12**(10):867-878.

26. World Health Organization. *Urinary iodine concentrations for determining iodine status in populations*. WHO; 2013. https://www.who.int/vmnis/indicators/urinaryiodine/en/

27. Derakhshan A, Peeters RP, Taylor PN, et al. Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2020;**8**(6):501-510.